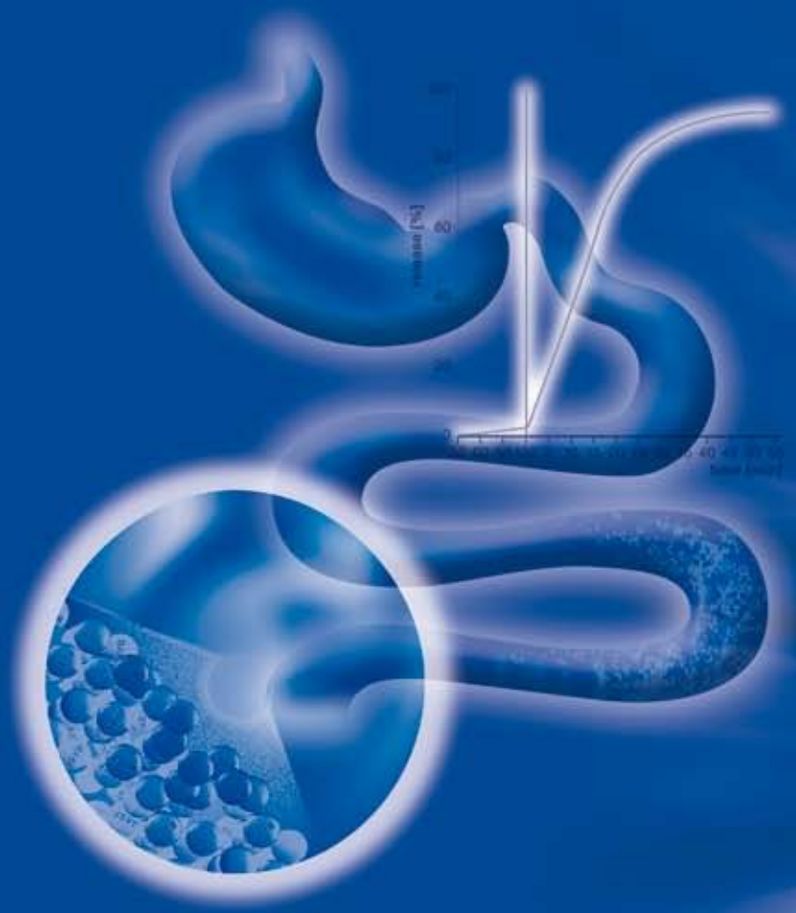

This book is intended for all persons in pharmaceutical technology working with solid drug forms.

The properties of the seven Kollicoat® grades as coating and controlled release agents are described in some detail. Numerous applications are described in conjunction with a number of different active ingredients and formulations. An alphabetical index at the end of the book serves as an aid in finding the appropriate application.

In a separate chapter, the various problems and their causes that can occur during coating processing are described in detail.

Volker Bühler **Kollicoat® Grades** –
Functional Polymers for the Pharmaceutical Industry

MEMP060602e-00

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Kollicoat® Grades

Functional Polymers for the Pharmaceutical Industry

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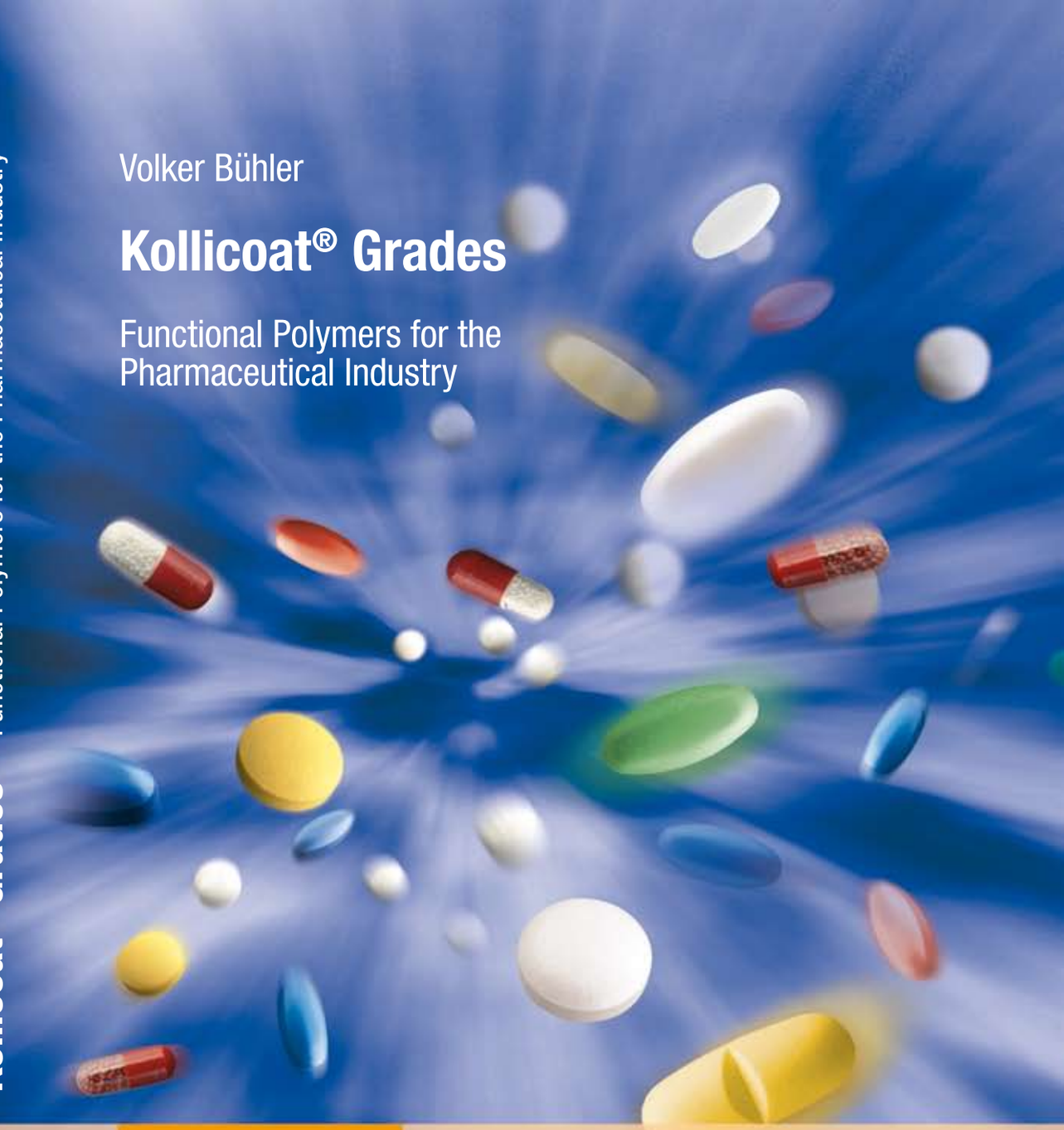
Kollicoat® Grades

Functional Polymers for the Pharmaceutical Industry



BASF
The Chemical Company

Volker Bühler

Kollicoat grades

Functional polymers for the pharmaceutical industry

BASF Aktiengesellschaft
Pharma Solutions
67056 Ludwigshafen, Germany

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Januar 2007

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Trademark	Company	Mentioned in chapter
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Driacoater®	Driam	2.3.2.3 (2x), 2.3.2.6 (2x), 2.4.3.2 (2x)
Sepispers®	Seppic	2.4.2
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Labrasol®	Gattefossé	2.5.2
Aerosil®	Degussa	2.5.3.3, 3.3.2.3, 4.3.2.2 (2x), 4.3.2.3 (2x), 4.3.2.4 (2x), 4.3.3.2, 5.3.2.4, 5.3.2.5, 5.3.3.2 (2x), 5.3.3.3 (2x), 5.3.5
Aeromatic Strea-1™	Niro	3.3.3.2 (2x), 4.3.2.2, 4.3.2.3, 4.3.2.4, 4.3.2.5, 4.3.4.2 (2x), 4.3.4.4 (2x), 4.3.4.5 (2x), 4.3.6.2, 4.3.6.3, 5.3.2.1 (2x), 5.3.2.3 (2x), 5.3.3.2, 5.3.4.2 (2x)
Methocel®	Colorcon	4.3.2.1
Aquacoat®	FMC	4.3.5.1
Karion®	Merck	4.3.6.2, 4.3.6.3
Pharsil®	Wacker Chemie	5.3.1, 5.3.2.1

Contents

Preface

BASF offers a full range of aqueous film coating materials covering a broad pharmaceutical application spectrum ranging from instant release (e.g., moisture protection, taste masking) to modified release (e.g., enteric- and sustained release) coatings under the brand name Kollicoat. This book provides a comprehensive description of the properties and applications of the different Kollicoat grades.

Chapter 1 gives a brief introduction to the different Kollicoat product grades, especially to their classification/composition and fields of application. Each of the following 4 chapters reviews one of the four available Kollicoat product groups.

The Kollicoat IR film formers are water-soluble and are based on PEG-PVA copolymers and various additives. They can be used as instant release coatings (e.g., taste masking, moisture-and oxygen protection), as binders for wet granulation, as hydrophilic pore formers in sustained release coatings and as stabilisers in suspensions. The two Kollicoat MAE grades (based on methacrylic acid-ethyl acrylate copolymers) are for enteric coatings and are available as an aqueous dispersion or powder respectively.
Kollicoat SR 30D is an aqueous dispersion of poly(vinyl acetate). It is used primarily for sustained release coatings, but can also be used as a granulation fluid for matrix tablets. Kollicoat EMM 30D is an aqueous dispersion of ethyl acrylate-methyl methacrylate copolymer and is used as a sustained release coating or granulation material. The chapters on the different Kollicoat grades are similarly structured and thus make for ease of reading. They list in great detail the chemical structure/composition, product specifications, extensive product properties [e.g., solubility, dissolution behaviour, dispersibility, viscosity, hygroscopicity, powder properties (particle size, bulk density)], film properties (mechanical properties, dissolution, tackiness, permeability), stability on storage and detailed formulation and process examples (e.g. preparation of coating formulations, coating equipment process parameters (small scale and scale-up), and product characterization).

In chapter 6, valuable practical advice for film coating with the Kollicoat excipients is provided. The effect of coating process parameters (e.g., air temperature and volume, spray rates/pressure, nozzle settings, etc.) and formulation variables (e.g., viscosity/solid content of spray formulation, effect of plasticizers, pigments, etc.) and their adjustments to achieve the desired product properties or to solve processing and product problems are described in detail. Finally, chapter 7 gives an overview of toxicological studies, pharmacopoeial monographs and the registration status of the Kollicoat grades.

This book provides scientists with a clear and extensive guide on the use of the Kollicoat grades for both instant and modified release applications. Numerous examples with detailed formulation and process information aid the formulator in his task of quickly developing high-quality pharmaceutical dosage forms.

Prof. Dr. R. Bodmeier
College of Pharmacy
Freie Universität Berlin

1. Introduction and product overview

The Kollicoat range of products comprises seven modern high-quality film-forming agents that are used in the pharmaceutical industry for the production of medicinal products. They can be divided into four groups, each of which has a different chemical structure designed for the applications intended. With the exception of the Kollicoat MAE grades, they are all neutral, based on various homo-, co- or graft polymers. The Kollicoat MAE grades are ionic co-polymers. An overview of the basic chemical structures involved is given in Table 1 below.
The names given to the individual products do not always have a common origin. In the case of the Kollicoat IR and SR grades, the designations "IR"(Instant Release) and "SR" (Sustained Release) refer to specific applications. In the case of the acrylate copolymers Kollicoat MAE and EMM, the letters refer to the specific monomers used.

Table 1: Kollicoat product groups and their chemical structures

Product group	Basic chemical structure	Monomers
Kollicoat IR	Graft polymer, neutral	Ethylene oxide, vinyl acetate, saponified
Kollicoat MAE	Copolymer, ionic	Ethyl acrylate, methacrylic acid
Kollicoat SR	Homopolymer, neutral	Vinyl acetate
Kollicoat EMM	Copolymer, neutral	Ethyl acetate, methyl methacrylate

The Kollicoat grades have a very wide range of applications. These range from simple water-soluble tablet coatings, gastric juice-resistant films, sustained-release matrix forms to film-formers in sprays. Table 2 gives a rough overview of the most important applications. Additional details and examples of formulations are given in the appropriate chapters dealing with the specific Kollicoat types.

Table 2: Main application areas of the Kollicoat grades

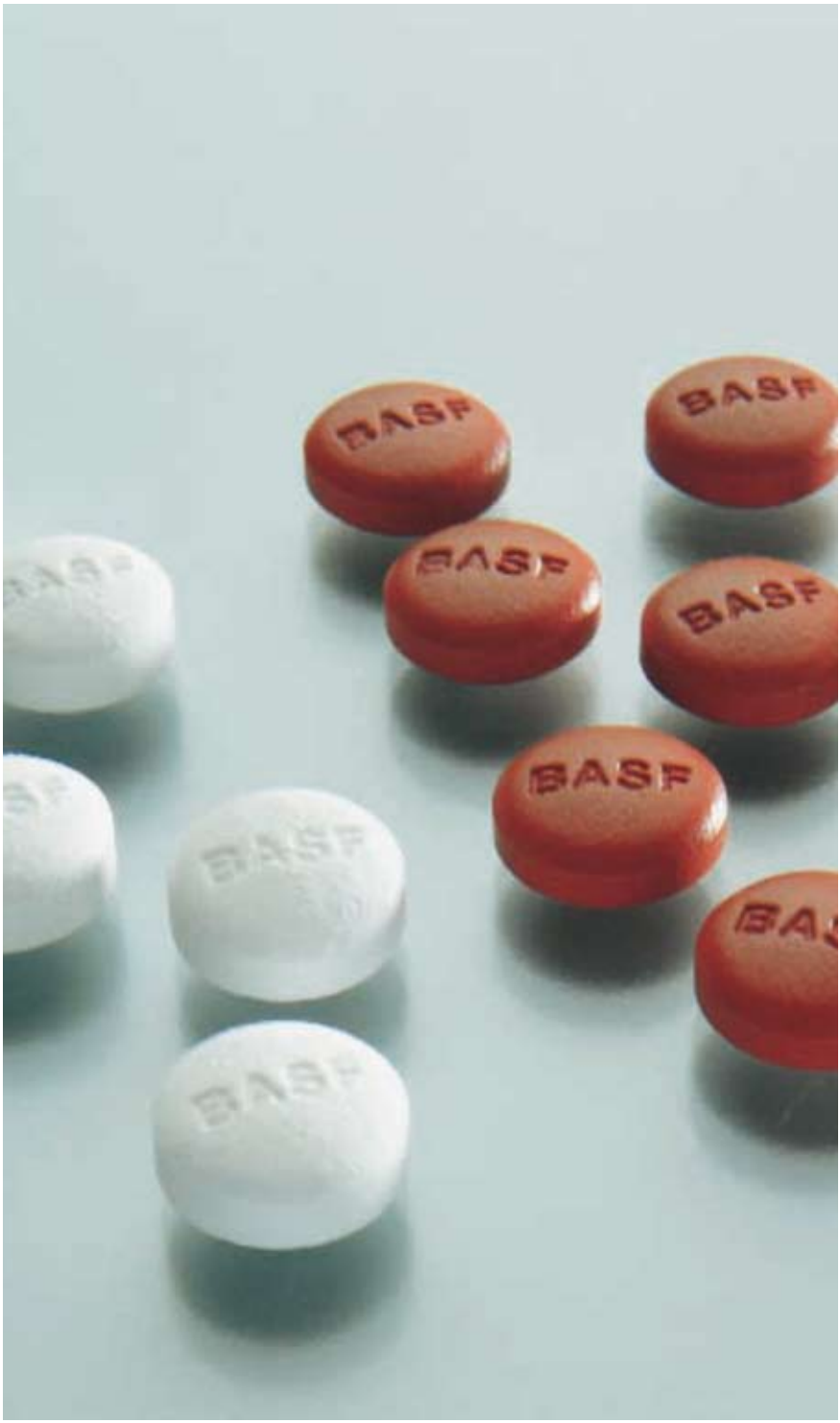
Product group	Principal application areas
Kollicoat IR	White or coloured, water-soluble and protective tablet coatings
Kollicoat MAE	Enteric coatings for tablets, capsules and crystals/ granules
Kollicoat SR	Sustained release polymer for tablets, sustained release coatings for pellets, taste masking in tablets
Kollicoat EMM	Sustained release coatings for pellets, sustained release polymer for tablets

The various Kollicoat grades available are adapted to the application in question. Some are available as powdered polymer, others as blends and others as aqueous dispersions. As all the products are intended for processing in water, only those types are in powder form that can be readily dissolved or suspended in water. Ready-made suspensions facilitate use in the production of pharmaceuticals. Powdered forms on the other hand can be stored longer. Table 3 provides an overview of the available types.

Table 3: The seven available Kollicoat grades

Product	**Powder polymer**	**Coating blend in powdered form**	**Aqueous dispersion**
Kollicoat IR	+		
Kollicoat IR White		+	
Kollicoat Protect		+	
Kollicoat MAE 30 DP			+
Kollicoat MAE 100P	+		
Kollicoat SR 30 D			+
Kollicoat EMM 30 D			+

The applications for the various Kollicoat grades are described in this book using formulations that have been developed in the Application Laboratories of BASF AG or in cooperation with these laboratories.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2. Kollicoat IR grades

2.1 Product range, structure, packaging

2.1.1 Product range

The Kollicoat IR product range comprises three individual types differing mainly in composition. Kollicoat IR is a pure polymer; Kollicoat IR White is a ready-made mixture for direct use based on Kollicoat IR; and Kollicoat Protect is a mixture of Kollicoat IR and a further well-known polymer as film-forming agent. All three products are listed in Table 4 with their BASF article and substance (PBG) numbers.

Manufacture of all three products is according to cGMP.

Table 4: Kollicoat IR grades

Product	BASF article number	PBG number
Kollicoat IR	55554797 (20 kg)	10219929
Kollicoat IR White	56653329 (30 kg)	10581609
Kollicoat Protect	56654018 (20 kg)	10581610

2.1.2 Chemical structure and composition

Kollicoat IR

Kollicoat IR powder comprises polyethylene glycol and polyvinyl alcohol bound in the ratio of 25:75. A polyethylene glycol chain forms a base onto which side chains of polyvinyl alcohol are grafted. The mean molecular weight is approximately 45,000. The precise structure is shown in Fig. 1. Kollicoat IR is manufactured in Ludwigshafen, Germany. The polyvinyl alcohol side chains are produced by grafting the vinyl acetate monomer onto the polyethylene glycol chain, which is then saponified. The product is subsequently spray-dried, 0.3 % silica gel being added as a flowability agent.

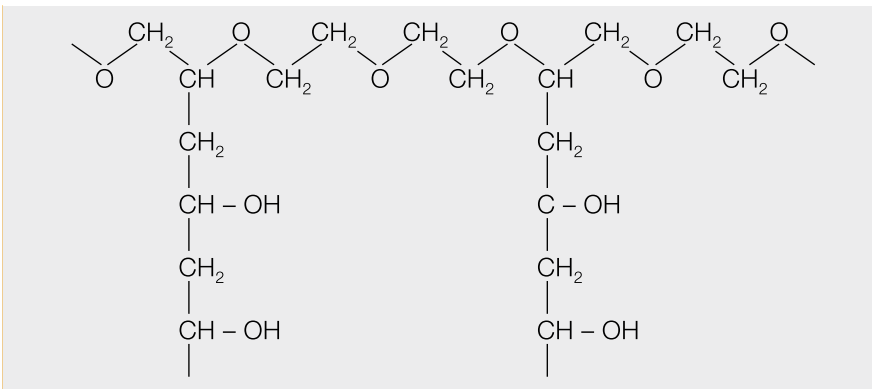


Fig. 1: Chemical structure of Kollicoat IR

Kollicoat IR White

Kollicoat IR White is a ready-mix powder comprising the two film-forming agents Kollicoat IR and copovidone [3], the pigments titanium dioxide and kaolin and the stabiliser sodium lauryl sulphate. It is available for direct use as a white soluble tablet or capsule coating. White coatings play a more important role that would appear at first glance. In 2004 in Germany, for example, they had a market share of approximately 40 %.
The precise composition of Kollicoat IR White is shown in Table 5. Due to the use of innovative technology, the insoluble components titanium dioxide and kaolin are embedded in the polymer matrix in such a way that, when the powder is subjected to mechanical stress, they neither separate physically nor do they agglomerate.

Table 5: Composition of Kollicoat IR White

Components	**Content**	
Kollicoat IR	61.2 %	(45 – 74 %)
Copovidone (Kollidon VA64)	6.8 %	(5 – 10 %)
Titanium dioxide	14.0 %	(10 – 20 %)
Kaolin	16.0 %	(10 – 20 %)
Sodium lauryl sulphate	2.0 %	(1 – 5 %)

Kollicoat Protect

Kollicoat Protect is a mixture of Kollicoat IR and polyvinyl alcohol, the latter having a mean molecular weight of approximately 30,000 (Table 6). Both components are mixed in solution form during manufacture and dried in such a way that a powder mix consisting of uniform particles is formed that does not allow the components to separate when subjected to mechanical stress.

Table 6: Composition of Kollicoat Protect

Components	**Content**
Polyethylene glycol-polyvinyl alcohol graft polymer (Kollicoat IR)	60 % (55 – 65 %)
Polyvinyl alcohol	40 % (35 – 45 %)
Silicon dioxide	0.3 % (0.1 – 0.3 %)

2.1.3 Packaging

The three Kollicoat IR grades are packaged in polyethylene inliners in blue plastic drums. Filling is dependent on the bulk density of the product. Details are given in Table 7.

Table 7: Packaging of the Kollicoat IR grades

Product	Container	Packaging number (external)	Unit
Kollicoat IR	60-L plastic drum with PE inliner	67696064	20 kg
Kollicoat IR White	120-L plastic drum with PE inliner	67696124	30 kg
Kollicoat Protect	120-L plastic drum with PE inliner	67696124	20 kg

2.2 Product properties

2.2.1 Description

As they are manufactured according to cGMP, all three types of the Kollicoat IR range are high-quality pharmaceutical grades. They are free-flowing, white-to-light yellow powders. On dissolution or suspension in water and subsequent drying on a glass plate, they leave a flexible film.

The melting point of Kollicoat IR is approximately 209 °C.

2.2.2 Specifications

Kollicoat IR is a relatively new pharmaceutical excipient and has not yet been listed in any of the pharmacopoeias as a monograph. However, all three Kollicoat IR grades are tested using the general methods described in the European Pharmacopoeia (Ph.Eur.) or by methods developed by BASF AG for this specific purpose. These methods can be made available on request. Table 8 lists the current valid parameters, limits and methods. The actual specifications are listed in the current Technical Data Sheets for the relevant products.

All the components used in the manufacture of Kollicoat IR, Kollicoat IR White and Kollicoat Protect correspond to the monographs of current pharmacopoeias Ph.Eur., USP and JP.

Table 8: Specifications of Kollicoat IR grades

Parameter	Kollicoat IR	Kollicoat IR White	Kollicoat Protect	Method
Identity	Corresponds	Corresponds	Corresponds	See below
Loss on drying	Max. 5.0 %	Max. 5.0 %	Max. 5.0 %	Ph.Eur.
pH	5,0 – 8,0	5.0 – 8.5	5.0 – 8.0	20 % in water
Viscosity	Max. 250 mPa.s	Max. 250 mPa.s	150 – 450 mPa.s	20 % in water
Ester value	10 - 75	--	--	Ph.Eur.
Heavy metals	Max. 20 mg/kg	--	Max. 20 mg/kg	Ph.Eur.
Sulphate ash	Max. 3.0 %	--	Max. 3.0 %	Ph.Eur.
Acetate, total	Max. 1.5 %	Max. 1.5 %	Max. 1.5 %	GC
Vinyl acetate	Max. 100 mg/kg	Max. 100 mg/kg	Max. 100 mg/kg	GC
Agglomerates	--	Max. 2 % > 100 µm	--	See below
Insoluble particles	--	--	Max. 0.5 % >100 µm	See below
Organic volatile impurities	Corresponds	--	--	USP
Residual solvents:				
Methanol	Max. 3,000 mg/kg	Max. 3,000 mg/kg	Max. 3,000 mg/kg	GC
Ethylene glycol	Max. 620 mg/kg	Max. 620 mg/kg	Max. 620 mg/kg	GC
1,4-Dioxane	Max. 100 mg/kg	Max. 380 mg/kg	Max. 380 mg/kg	GC
Methyl acetate	Max. 1,000 mg/kg	Max. 1,000 mg/kg	Max. 1,000 mg/kg	GC
Microbiological status	Corresponds to categories 2 and 3A	Corresponds to category 3A	Corresponds to categories 2 and 3A	Ph.Eur.

The identity of the three Kollicoat IR grades is determined by comparing their infrared spectra with that of the reference substance.

The viscosity of a solution containing 20 g of product in 80 ml water is measured at 23 °C and 100 rpm in a Brookfield viscosimeter according to EN ISO 2555.

The content of agglomerates in Kollicoat IR White in water is determined using the following method:
20 g of product are suspended in 80 ml water under stirring at room temperature. The suspension thus obtained is passed through a 100-µm sieve and the residue on the sieve weighed.

The content of insoluble particles in Kollicoat Protect in water is determined using the following method:
15 g of Kollicoat Protect are dissolved in 85 ml water under stirring at room temperature. The solution thus obtained is passed through a 100-µm sieve and the residue weighed.

2.2.3 Solubility, dissolution behaviour, dispersibility

2.2.3.1 Solubility and dissolution behaviour of Kollicoat IR

Kollicoat IR is characterized by its exceptional solubility in water as well as by its speed of dissolution (see chapter 2.2.8.3). These are major advantages compared with other film-forming agents for soluble tablet coatings (e.g. hypromellose 2910). The rapid dissolution is particularly aided by the low viscosity. Aqueous solutions of weakly acidic or alkaline pH with a concentration of up to 50 % can be obtained. Table 9 gives an overview of the solubility in various media.

Table 9: Solubility of Kollicoat IR

Solvent	Concentration
Water	up to 50 %
Weak acids	over 40 %
Weak bases	over 40 %
Ethanol + water 1:1	up to 25 %
Ethanol, 96 %	practically insoluble
Non-polar solvents	insoluble

2.2.3.2 Dispersibility of Kollicoat IR White

Due to the content of pigments (see Table 5), the ready-mix of Kollicoat IR White does not produce a clear solution; a suspension is always formed with water and all other solvents. However, its dispersibility is excellent; under stirring, a homogeneous suspension is formed without the formation of lumps. The stirring speed, however, should not be too fast; this prevents the formation of foam. The four photos in Fig. 2 show the individual stages of the process:

1. Water prior to addition – stirred, but not too rapidly, with a magnetic stirrer.
2. Actual addition of substance.
3. Towards the end of addition.
4. Homogeneous suspension of Kollicoat IR White.

Using this method and due to the low viscosity, ready-made suspensions with a solid content of up to 30 % can be prepared for direct use in the preparation of white tablet coatings. The size of the suspended particles in such dispersions is under 5 µm.

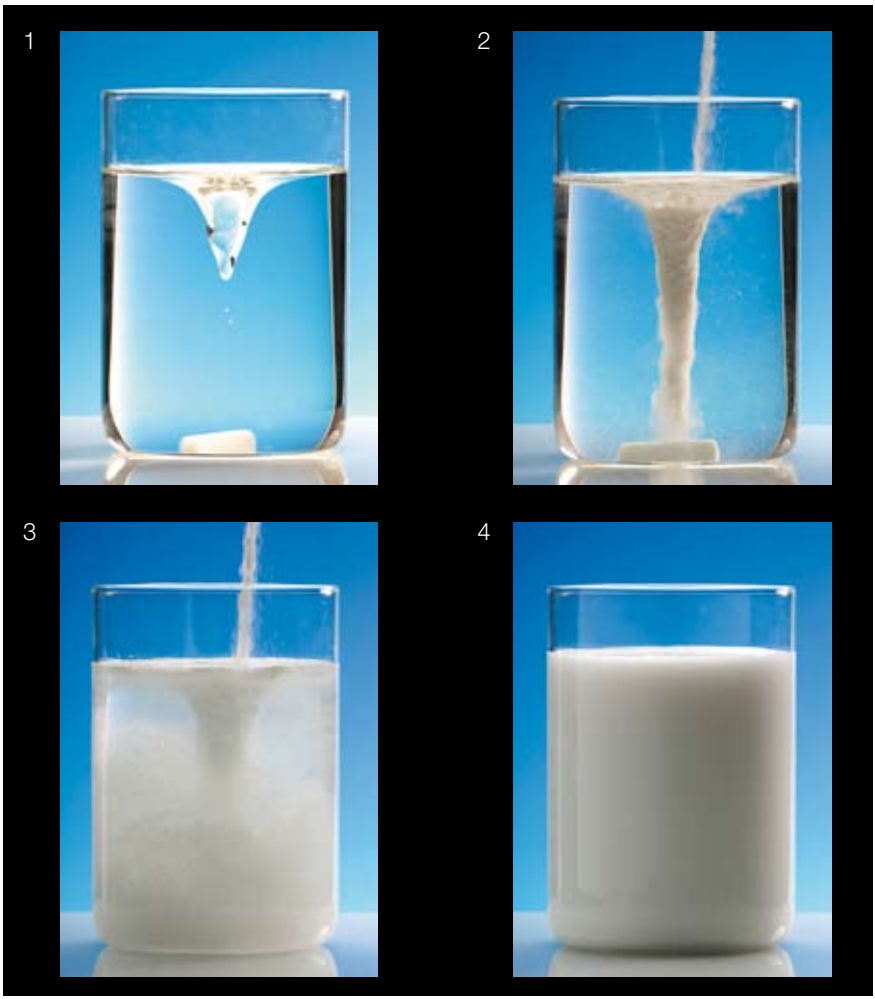


Fig. 2 Dispersion of Kollicoat IR White in water.

1 Slightly stirred water using a magnetic stirrer prior to addition.
2 Start of addition of Kollicoat IR White.
3 During the addition of Kollicoat IR White.
4 Final homogeneous suspension.

2.2.3.3 Solubility and dissolution behaviour of Kollicoat Protect

As with Kollicoat IR, Kollicoat Protect is characterized by excellent water solubility and high dissolution speed. Dissolution is particularly enhanced by the low viscosity; clear solutions with concentrations up to 30 % can be prepared.

In order to prevent foaming during dissolution, the stirring speed should not be too high; alternatively, an anti-foaming agent such as e.g. 0.1 % simethicon emulsion can be added. The following method can be recommended: Slowly add 15 g of product over a period of 2 minutes to 85 ml of water and stir with a paddle stirrer. Allow the stirrer to function for a further 5 minutes; neither coarse particles nor foam are formed.

2.2.4 Viscosity

2.2.4.1 Viscosity of aqueous solutions of Kollicoat IR

One of the major application advantages of Kollicoat IR compared to other polymers in the water-soluble coating of tablets is its low viscosity in water. This reduces the time and the costs of the film-coating process considerably (see chapter 2.3.2.7, Table 29). At room temperature and up to a concentration of 25 %, the viscosity is under 250 mPa·s, the level that is regarded as the upper level for spraying tablets. At higher concentrations, the viscosity increases quite rapidly, as shown in Fig. 3.

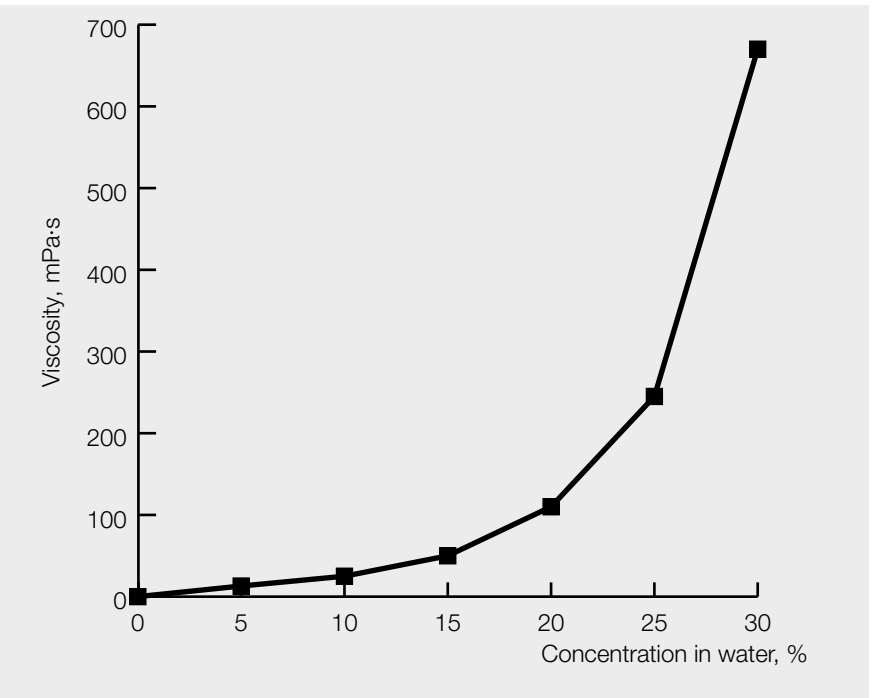


Fig. 3: Viscosity of aqueous Kollicoat IR solutions as a function of concentration (room temperature)

In comparing the viscosity of solutions of Kollicoat IR with other polymers frequently used for tablets with soluble coatings, e.g. hypromellose (HPMC), it can be seen that Kollicoat IR has enormous advantages. Fig. 4 shows such a comparison with Kollicoat IR using a 20 % solution of two different types of hypromellose (HPMC 2910). The differences mean that tablets can be coated with a much higher concentrated spray suspension of Kollicoat IR, which reduces processing time considerably.

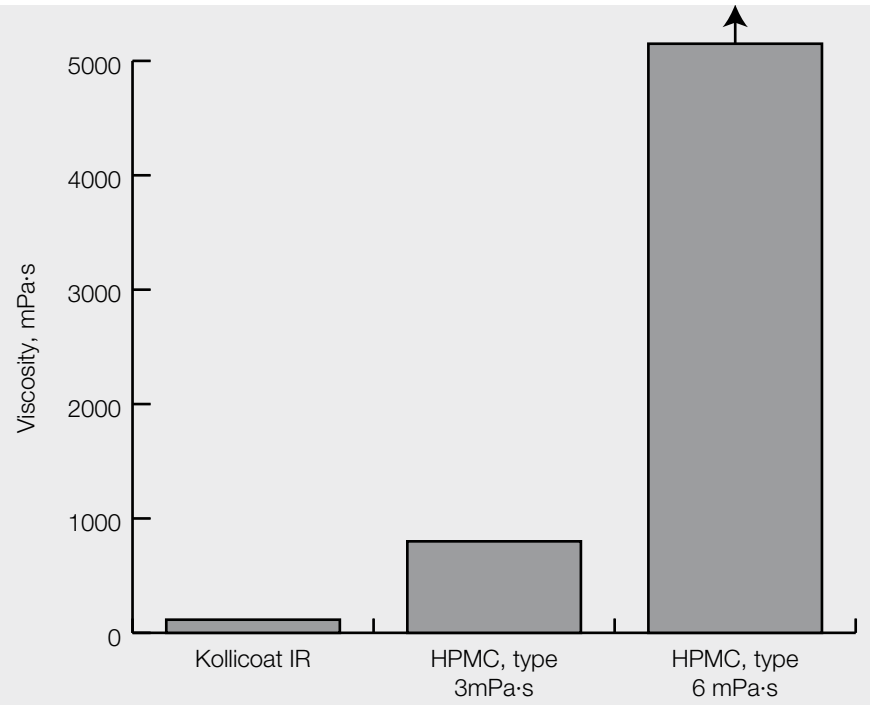


Fig. 4: Comparison of the viscosities of Kollicoat IR and hypromellose (20 % in water, room temperature).

As is the case with practically all polymers, the viscosity of Kollicoat IR is influenced by the temperature. The viscosity decreases with increasing temperature; this effect can in fact be utilized to increase the concentration when coating tablets. Fig. 5 demonstrates this effect. It can be seen that by increasing the temperature from 25 to 50 °C, the viscosity of a 20 % aqueous solution is reduced by half.

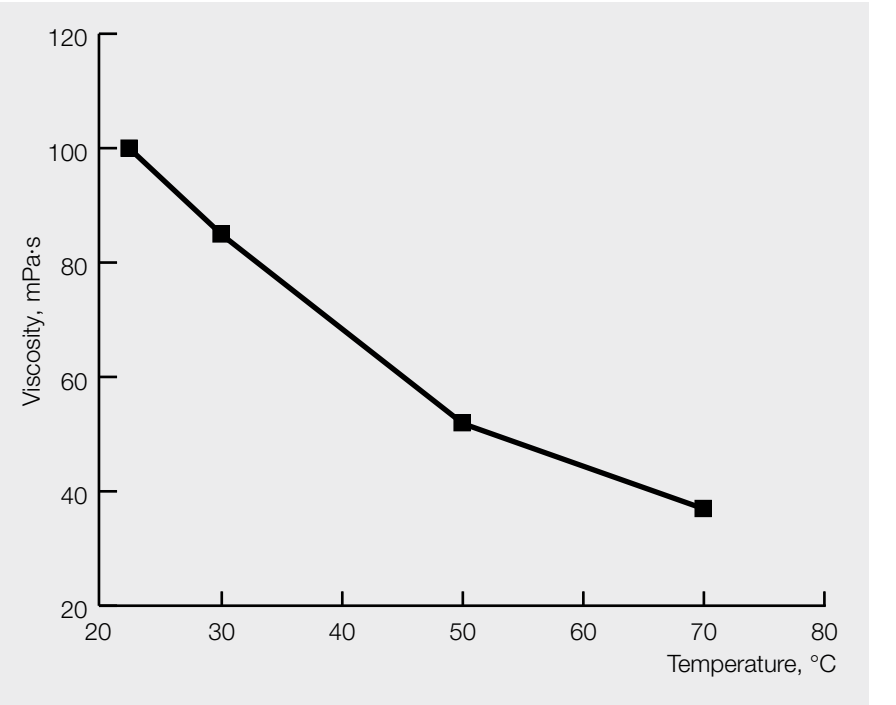


Fig. 5: Influence of temperature on the viscosity of a 20 % aqueous solution of Kollicoat IR

Talcum powder is the most frequently used anti-adhesive agent in tablet coatings. For this reason, the influence of this excipient on the viscosity of solutions of Kollicoat IR and hypromellose (HPMC) was investigated. Table 10 shows the results obtained from 20 % polymer and various concentrations of added talcum based on that of the polymer. In the case of Kollicoat IR, the absolute viscosity and its increase on the addition of talcum were considerably lower than those of hypromellose.

Table 10: Influence of the addition of talcum on the viscosity of spray suspensions of 20 % aqueous solutions of Kollicoat IR- and hypromellose (mPa·s at room temperature, Brookfield method)

Addition of talcum (based on polymer concentration)	**Kollicoat IR**	**HPMC 2910 type 3 mPa·s**	**HPMC 2910 type 6 mPa·s**
0 %	93	659	4460
10 %	106	800	5490
25 %	133	1140	7980
50 %	244	2830	18600

2.2.4.2 Viscosity of aqueous suspensions of Kollicoat IR White

When Kollicoat IR White is stirred into water, a suspension is obtained. At room temperature, analogue to Kollicoat IR, this has a low viscosity. Thus, in preparing an aqueous 25 % suspension, a viscosity of only approx. 150 mPa·s is obtained (Fig. 6).

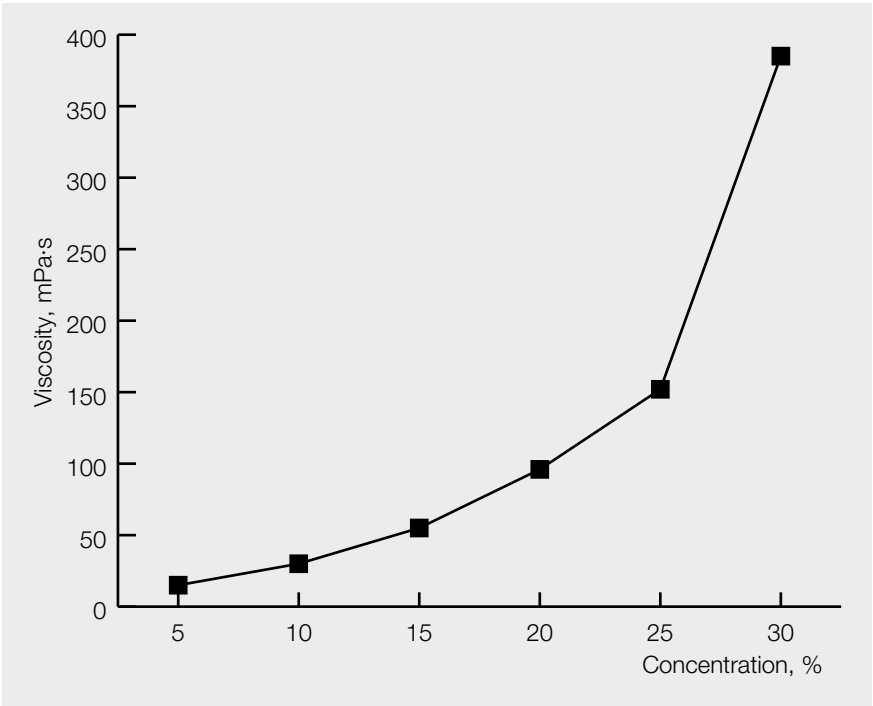


Fig. 6: Viscosity of aqueous suspensions of Kollicoat IR White as a function of concentration (room temperature)

As can be seen from Fig. 7, the influence of temperature on viscosity is not quite as strong as in the case of Kollicoat IR (cf. Fig. 5). To decrease the viscosity of a 20 % aqueous suspension by half, the temperature would have to be increased from 25 to approximately 70 °C. In the case of a 25 % suspension, the influence of temperature on the viscosity is somewhat stronger.

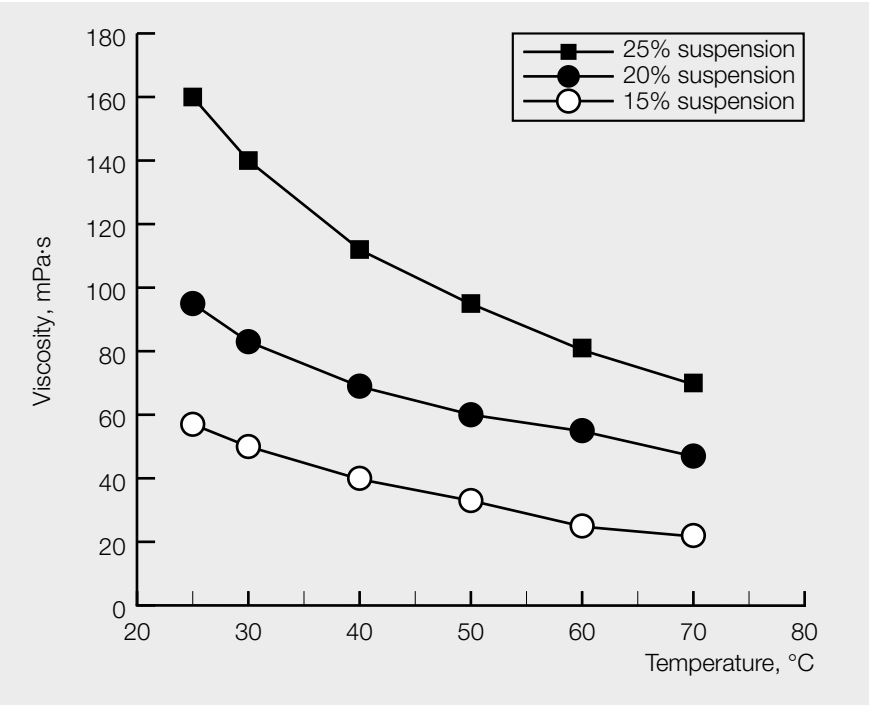


Fig. 7: Influence of temperature on the viscosity of a suspension of Kollicoat IR White in water.

2.2.4.3 Viscosity of aqueous solutions of Kollicoat Protect

The viscosities of aqueous solutions of Kollicoat Protect are not quite as low as those of Kollicoat IR. An aqueous solution with a concentration of 20 % Kollicoat Protect has a viscosity of approx. 230 mPa·s at room temperature. The viscosity of a 15 % solution is under 100 mPa·s. Fig 8 shows the viscosities of aqueous solutions with concentrations between 5 and 20 %.

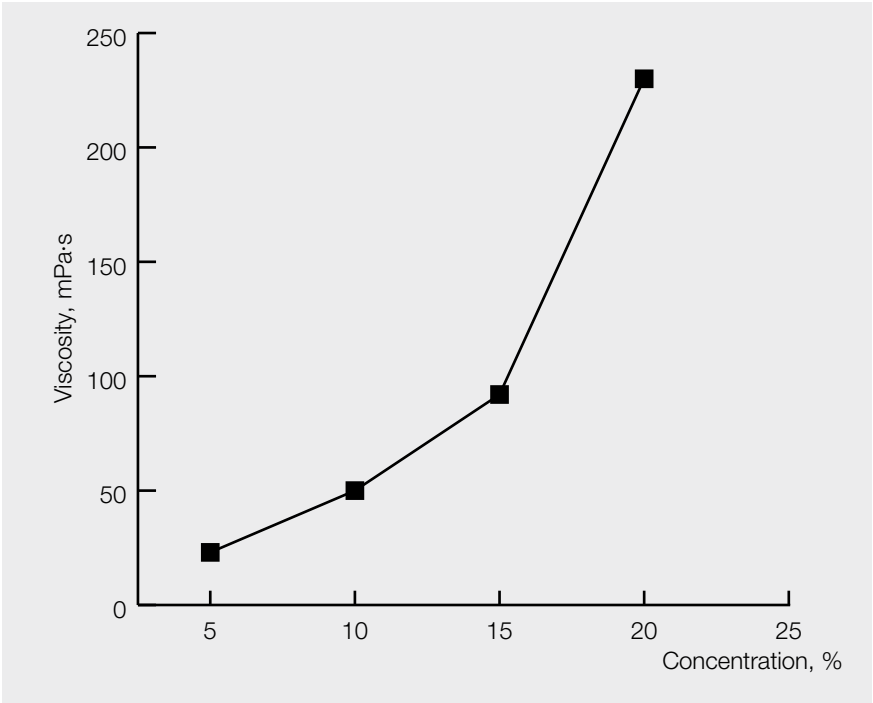


Fig. 8: Viscosity of aqueous solutions of Kollicoat Protect as a function of concentration (room temperature)

Fig. 9 shows the influence of temperature on the viscosity of 15 and 20 % aqueous solutions of Kollicoat Protect. By increasing the temperature from 25 to 45 °C, the viscosity of these solutions is reduced by half. This can well be important in tablet coating; the concentration of the spray suspension can be maintained at a high level, thus saving time and cost.

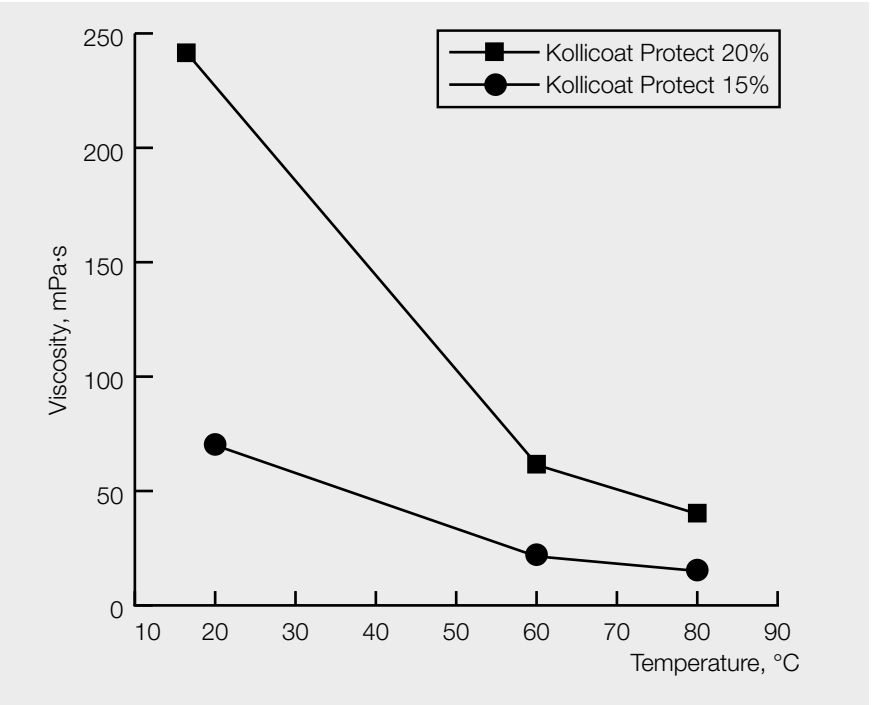


Fig. 9: Influence of temperature on the viscosity of a 15 and 20 % aqueous solution of Kollicoat Protect.

The addition of larger quantities of pigment or talcum powder may also affect the viscosity of spray suspensions of Kollicoat Protect. This was investigated using three different spray suspensions with a total solid content of 20 % at room temperature. The suspensions contained different levels of talcum, titanium dioxide and kaolin. On comparing Table 11 with Fig. 8, it can be seen that the increase in viscosity brought about by the pigment and the talcum is relatively small, the viscosity being determined mainly by the polymer content.

Table 11: Viscosity of different spray suspensions of Kollicoat Protect (20 % solid content, room temperature).

	Kollicoat Protect/talcum/ titanium oxide 12 %/5 %/3 %	**Kollicoat Protect/kaolin/ titanium oxide 12 %/5 %/3 %**	**Kollicoat Protect/kaolin/ titanium oxide 8 %/8 %/4 %**
Viscosity	82 mPa·s	82 mPa·s	57 mPa·s

2.2.5 Hygroscopicity

All three types of Kollicoat IR have a relatively low degree of hygroscopicity. Fig. 10 shows that the polymer Kollicoat IR absorbs just over 20 % water at a relative humidity of 80 % after 14 days. Due to their composition, both other types are less hygroscopic.

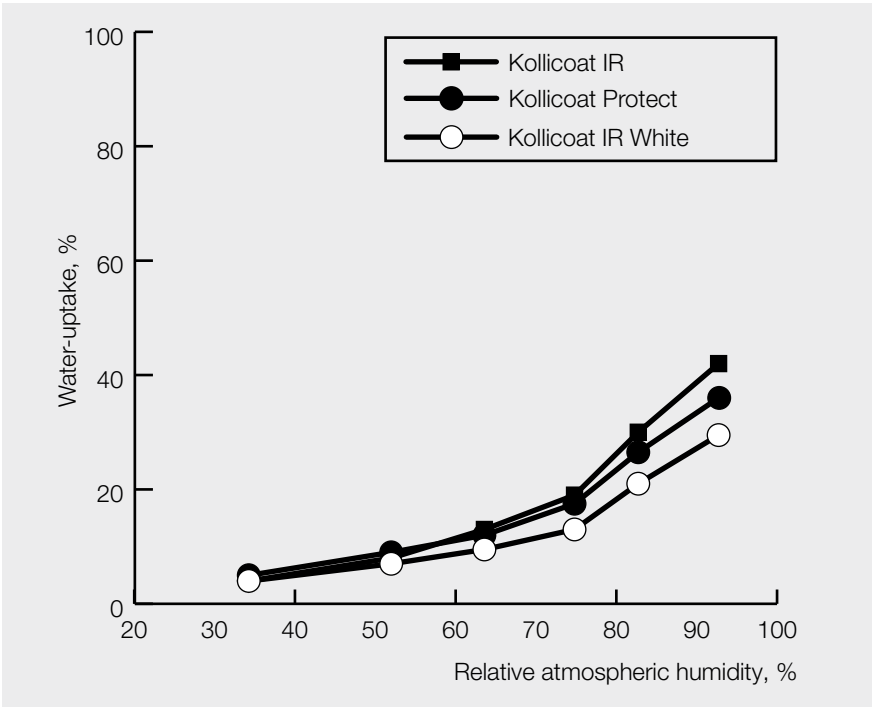


Fig. 10: Water uptake of the Kollicoat IR grades as a function of relative humidity after 14 days (room temperature).

2.2.6 Bulk density, particle size, particle structure

The bulk density of the Kollicoat IR grades is of little importance in tablet coatings as these are always dissolved or suspended in water.
The bulk density is relatively low in both Kollicoat IR and Kollicoat Protect.
The particle sizes of Kollicoat IR and Kollicoat Protect are also practically of no relevance as both products dissolve readily in water independent of their particle sizes.
In the case of Kollicoat IR White in contrast, the particle size is of relevance as it has an influence on dispersibility in water and on its ability to be used as a spray. For this reason, agglomeration is a specification parameter (see chapter 2.2.2). Subsequent to processing in water the particle size is generally under 5 µm. Table 12 summarizes bulk density and mean particle size of the Kollicoat IR grades.

Table 12: Bulk density and mean particle size of the Kollicoat IR grades (typical values/results from individual batches).

	Kollicoat IR	**Kollicoat IR White**	**Kollicoat Protect**
Bulk density	0.3 – 0.45 g/ml	approx. 0.3 g/ml	approx. 0.2 g/ml
Mean particle size	approx. 120 µm	approx. 200 µm	approx. 125 µm

The uniform structure of the particles of Kollicoat IR White (Fig. 11) clearly shows that this is not a simple physical mixture but rather that the pigments kaolin and titanium dioxide are enclosed within the polymers Kollicoat IR and Kollidon VA64.

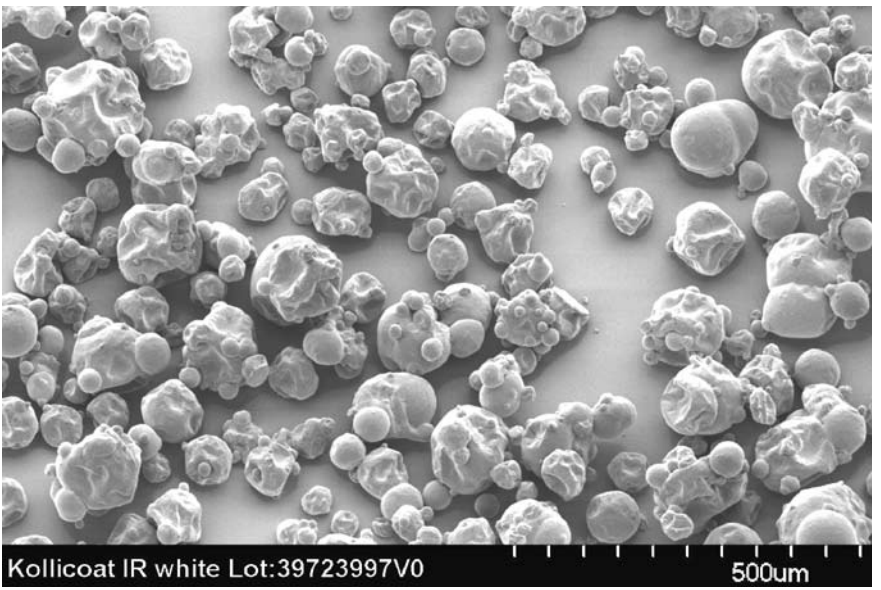


Fig. 11: Particle structure of Kollicoat IR White

2.2.7 Surface tension

Kollicoat IR, due to its chemical structure, has a certain surfactant effect; it thus decreases the surface tension of aqueous solutions. This improves the wettability of tablet surfaces, which in turn can be of advantage if they contain lipophilic or hydrophobic active ingredients.
This property can also be observed in Kollicoat IR White and Kollicoat Protect. Table 13 shows the surface tension of several solutions and suspensions of the Kollicoat IR grades in comparison with water.

Table 13: Surface tension of solutions and suspensions of Kollicoat IR grades compared with water.

	Surface tension
Water	61.6 mN/m
Kollicoat IR, 5 % in water	47.5 mN/m
Kollicoat IR, 20 % in water	41.4 mN/m
Kollicoat IR White, 20 % in water	39.5 mN/m
Kollicoat Protect, 15 % in water	42.3 mN/m

2.2.8 Film-forming properties of Kollicoat IR

2.2.8.1 Film formation

Kollicoat IR forms clear, colourless, glossy films. If an aqueous solution of at least 25 % Kollicoat IR is placed on a PE film and the water allowed to evaporate at room temperature or by warming, a flexible film is obtained on drying. The minimum film-forming temperature (MFT) is below 20 °C.

2.2.8.2 Flexibility, plasticity, elongation at break

The flexibility and plasticity of Kollicoat IR are exceptionally high in comparison with other film-forming agents used in tablets. To confirm this, the elongation at break of films of Kollicoat IR and hypromellose (HPMC 2910) were compared at room temperature and at relative humidities of 33, 54, and 75 %. Fig. 12 shows the results of this comparison. Even at a relative humidity of 75 %, the elongation at break of a Kollicoat IR film proved to be much greater than in the case of hypromellose films.

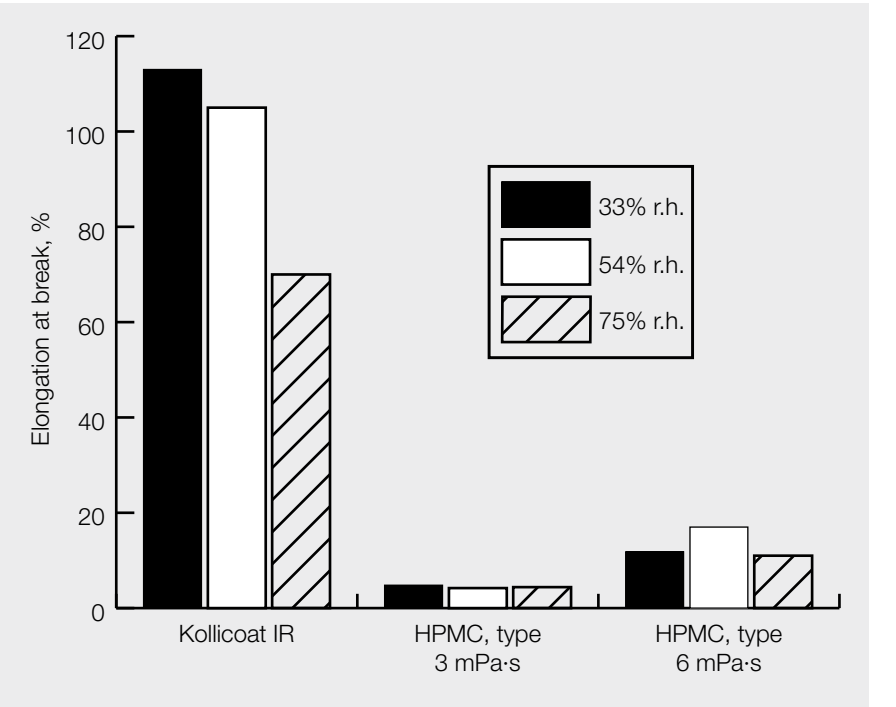


Fig. 12: Elongation at break of films of Kollicoat IR and hypromellose at different relative humidities (room temperature).

The high elongation at break of Kollicoat IR has the advantage that, when formulating tablet coatings, a plasticizer is never required. In addition, the flexibility does not change during storage.

However, the flexibility of tablet coatings is always subject to negative influence by other additives such as talcum, insoluble pigments and aluminium colour lakes. In the case of Kollicoat IR, this influence is different for each excipient; this is demonstrated in Fig. 13 using samples containing 10 % additives. In this investigation, the greatest influence was exerted by indigotin colour lake, followed by titanium dioxide. Red iron oxide (10 %) had the least effect on the elongation at break of Kollicoat IR.

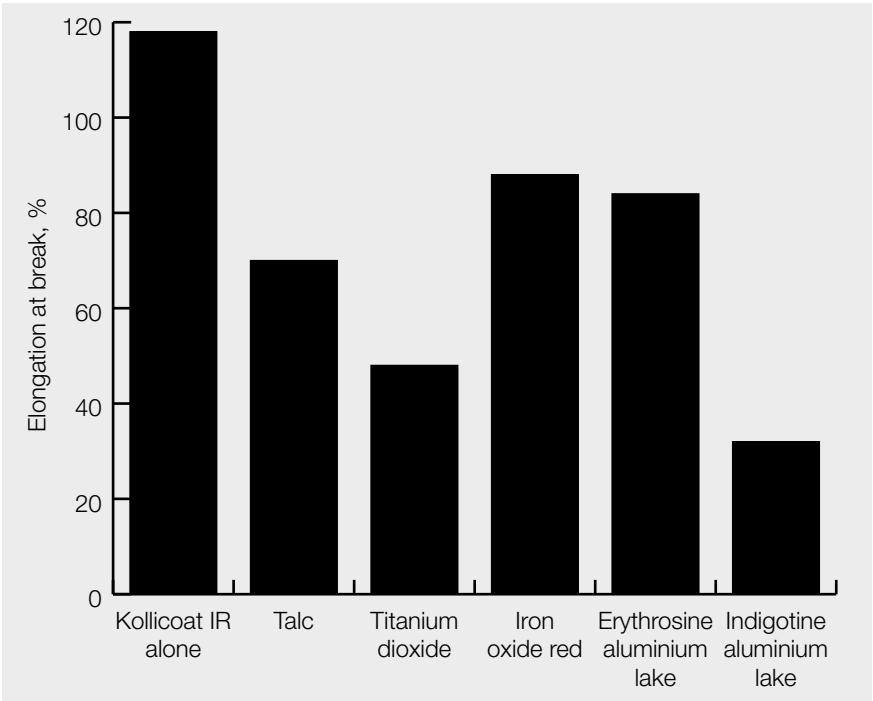


Fig. 13: Elongation at break of Kollicoat IR films containing 10 % of various excipients.

2.2.8.3 Dissolution behaviour of Kollicoat IR films

A further advantage of Kollicoat IR is that coatings dissolve rapidly; this is because not only the powder dissolves readily but also the film (see also chapter 2.2.3.1). To confirm this, isolated films of thickness approx.100 µm and free surface area 35 x 23 mm were clamped into a frame and suspended 3 cm under the surface of the liquid in a dissolution instrument equipped with a paddle stirrer. The stirrer was set at 50 rpm. The equipment complied with USP. The time taken for complete dissolution of the films at room temperature was measured. Fig. 4 shows the results of the comparison of films of Kollicoat IR and two water-soluble tablet coatings of conventional hypromellose types. It can be seen that the hypromellose dissolves considerably more slowly both in dilute hydrochloric acid and at pH 6.8.

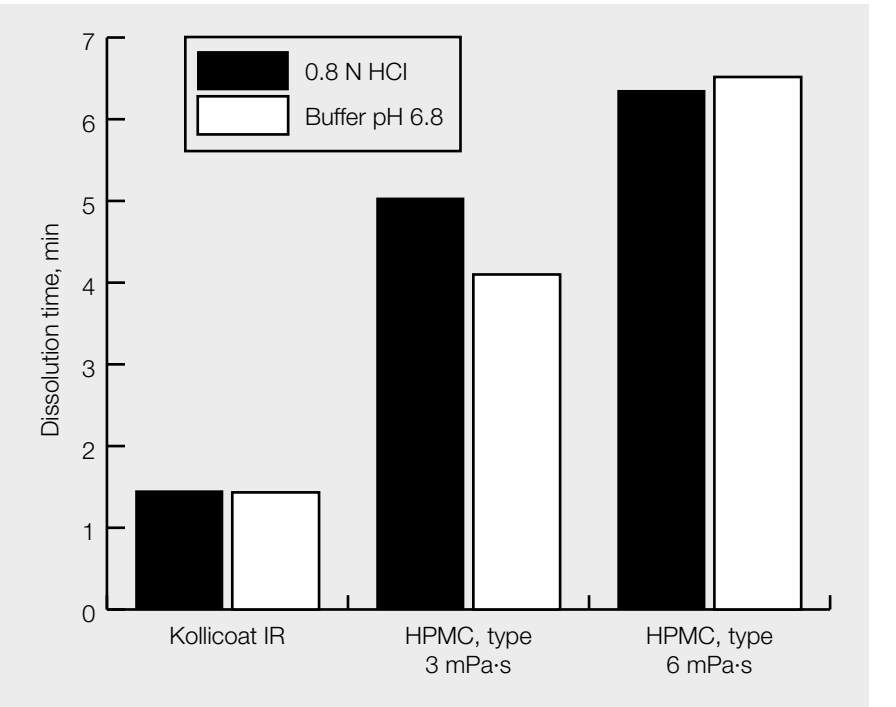


Fig. 14: Dissolution speed of films (100 µm) of Kollicoat IR and hypromellose (HPMC)

2.2.8.4 Tackiness and surface adhesion of Kollicoat IR films

Films containing Kollicoat IR do not have a tacky feel. To measure this, isolated films were stored for 12 hours at different relative humidities. Subsequently, the degree of tackiness was measured using the Hoessel method [1]. Long experience with this method has shown that the tackiness of films cannot be felt by the skin of the fingers if the Hoessel values are below 1.3. However, assessment can be carried out in this way if the Hoessel values are between 1.5 and approximately 5 as tackiness increases rapidly within this range. Table 14 lists the values measured with Kollicoat IR compared with film-forming agent copovidone (Kollidon VA64).

Kollicoat IR, due to its surfactant action, increases the wettability and hence possesses excellent adhesive properties on hydrophilic and lipophilic tablet surfaces.

Table 14: Tackiness of films made of Kollicoat IR, copovidone and hypromellose (Hoessel method)

	54 % rel. humidity, 23 °C	75 % rel. humidity, 30 °C	80 % rel. humidity, 20 °C
Kollicoat IR	0.75	1.0	1.25
Copovidone	--	4.0	--
HPMC 2910	--	0.3	--

2.2.8.5 Permeability of Kollicoat IR films to water and oxygen

As Kollicoat IR films possess low permeability to water and oxygen, they can also be used as protective films for tablets; this improves the stability of active ingredients that may be susceptible to hydrolysis or oxidation. Permeability to oxygen and water vapour is of the same magnitude as in the case of hypromellose.
Table 15 shows the permeability to oxygen of films made of Kollicoat IR and hypromellose 2910 at room temperature and at 55 % relative humidity.

Table 15: Permeability to oxygen of films made of Kollicoat IR and HPMC

	Permeability to oxygen (23 °C, 55 % rel. humidity)
Kollicoat IR	146 [g·100 µm/m^2·d]
HPMC, type 3 mPa.s	160 [g·100 µm/m^2·d]

To determine permeability to water, the films were prepared with the composition normally used in tablet coatings; this was to ensure the results obtained were as realistic as possible. Table 16 shows the results of four measurements each of Kollicoat IR and hypromellose (HPMC) at room temperature and 85 % relative humidity. In the case of hypromellose, macrogol was additionally added as a plasticizer as this is always necessary with this agent.

Table 16: Permeability to water vapour of films of Kollicoat IR and hypromellose (4 measurements)

	Permeability to water vapour (23 °C, 85 % rel. humidity)
Kollicoat IR+ talcum + pigments (64+18+18)	600 – 730 [g·100µm/m^2·d]
HPMC, type 3 mPa.s+ talcum + pigments + macrogol (50+20+20+10)	500 – 730 [g·100µm/m^2·d]

2.2.8.6 Light transmission of Kollicoat IR films

As some active ingredients tend to become less stable under the influence of light, it is of interest to be able to protect them from this by using a coating of lower light transmission. To confirm this possible application for Kollicoat IR, films of thickness 25 µm and containing 10 % added talcum or 30 % pigment were produced and their transmission compared to that of 5 mm thick brown glass. Fig. 15 shows that talcum reduces the transmission of Kollicoat IR only a little. However, a Kollicoat IR film containing 30 % red iron oxide transmits minimally only in the range 650 – 800 nm. The light transmission of the film containing iron oxide is much less than that of brown glass within this range; it therefore provides excellent protection against light. This shows that the high pigment capacity of Kollicoat IR is a major advantage for light-sensitive active ingredients.

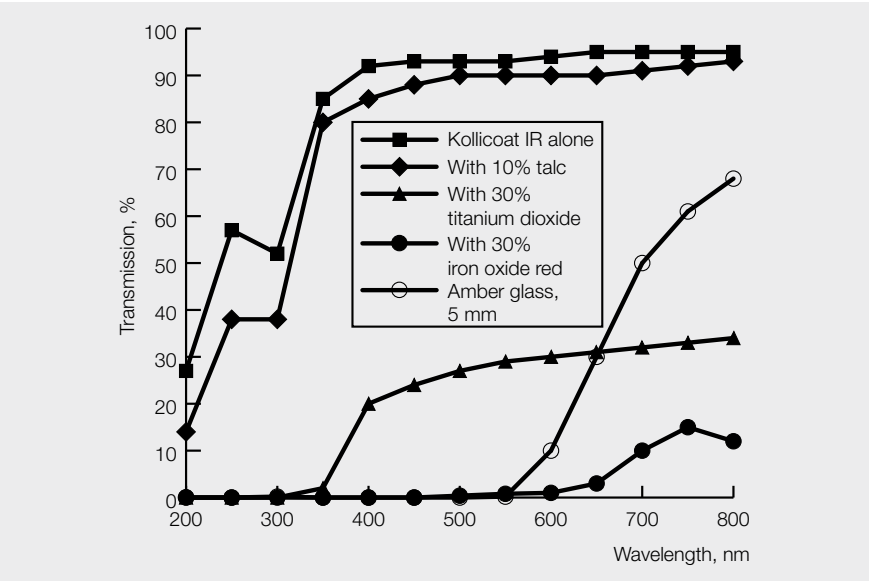


Fig. 15: Light transmission of Kollicoat IR films containing various pigments in comparison with brown glass (5 mm)

2.2.9 Film-forming properties of Kollicoat IR White

2.2.9.1 Film formation

Kollicoat IR White also forms glossy, flexible films; these are coloured white principally due to the titanium dioxide in the product. Film formation is enhanced by the synergistic effect of film-forming agents Kollicoat IR and Kollidon VA64. The gloss effect on the surface is also enhanced due to the presence of kaolin.
The minimum film formation temperature (MFT) in the case of Kollicoat IR White is below 20 °C, as in the case of Kollicoat IR.

2.2.9.2 Flexibility, elongation at break

The flexibility of Kollicoat IR White is extremely high in comparison with other commercially available ready-to-use mixtures for soluble tablet coatings.
At room temperature and 58 % relative humidity, elongation at break for a film of Kollicoat IR White without any further additives was measured as 41.4 %.

2.2.9.3 Tackiness and surface adhesion of Kollicoat IR White films

Films containing Kollicoat IR White do not have a tacky feel. However, they show excellent adhesion and spreading properties on hydrophilic and lipophilic tablet surfaces. This is based on the surfactant effect as well as on the excellent wettability of Kollicoat IR. See chapter 2.2.7 for further details on surface tension. This effect is additionally enhanced by sodium lauryl sulphate.

2.2.9.4 Dissolution behaviour of Kollicoat IR White films

Kollicoat IR White films dissolve readily in water and hydrochloric acid. If films are produced and tested as described in chapter 2.2.8.3, a film measuring 35 x 23 mm and 100 µm thick has a total dissolution time of less than two minutes both in 0.1N hydrochloric acid and in a phosphate buffer of pH 6.8 (see Table 17).

Table 17: Dissolution times of Kollicoat IR White films

	0.1 N hydrochloric acid pH 1	**Phosphate buffer pH 6.8**
Kollicoat IR White film Thickness: 100 µm, 35 x 23 mm	1‘ 32“	1‘35“

2.2.10 Film-forming properties of Kollicoat Protect

2.2.10.1 Film formation

Kollicoat Protect, which comprises the polymers Kollicoat IR and polyvinyl alcohol, also forms clear, colourless films in the same way as Kollicoat IR. To confirm this, place an aqueous solution of at least 20 % Kollicoat Protect onto a PE film and allow the water to evaporate at room temperature or by warming. On drying, a flexible film is obtained.
The minimum film-forming temperature (MFT) is far below 20 °C in this case.

2.2.10.2 Flexibility, elongation at break

Due to the presence of polyvinyl alcohol, the flexibility of Kollicoat Protect is considerably higher than that of Kollicoat IR; for this reason, a plasticizer is never required when using Kollicoat Protect for tablet coatings. The elongation at break was investigated using a practical formulation application.
A film comprising 60 % Kollicoat Protect, 25 % talcum and 15 % titanium dioxide was produced and the elongation at break measured and compared with that of pure product at room temperature and 58 % relative humidity. The results are shown in Table 18. Similar to Kollicoat IR, Kollicoat Protect shows less flexibility when it contains additives.

Table 18: Elongation at break of Kollicoat Protect films (room temperature, 58 % relative humidity)

Film	Elongation at break
Kollicoat Protect, without additives	260 %
Kollicoat Protect + talcum + titanium oxide (60+25+15)	58 %

2.2.10.3 Tackiness and surface adhesion of Kollicoat Protect films

Films containing Kollicoat Protect have no tacky feel. They demonstrate adhesion on all hydrophilic and lipophilic tablet surfaces, regardless of whether these are smooth or engraved. This is due to the surfactant effect and excellent wettability of Kollicoat IR (see also chapter 2.5.3.1, Fig. 22).

2.2.10.4 Dissolution behaviour of Kollicoat Protect films

Due to the excellent solubility in water of Kollicoat Protect films, they dissolve just as readily as Kollicoat IR or Kollicoat IR White.

2.2.11 Stability of Kollicoat IR grades

At room temperature, Kollicoat IR is stable for a period of at least 3 years and Kollicoat IR White and Kollicoat Protect for at least 3 years, provided they remain sealed in their original packs. In such cases the specifications as listed in chapter 2.2.2 are maintained.

One important parameter for certain applications can be the formation of peroxides, as is the case with a number of other polymers; this can have a negative effect on some active ingredients. For this reason, Kollicoat IR, which is also the main component of Kollicoat IR White and Kollicoat Protect, was investigated for the formation of peroxides over a period of 18 months at 25 and 40 °C and at 60 and 70 % relative humidity. The results in Table 19 show that there is practically no peroxide formation in the case of Kollicoat IR.

Table 19: Peroxide content of Kollicoat IR during storage

Storage period	**25 °C/60 % relative humidity**	**40 °C/75 % relative humidity**
0 months	1 ppm	1 ppm
3 months	1 ppm	1 ppm
6 months	1 ppm	1 ppm
12 months	3 ppm	1 ppm
18 months	4 ppm	1 ppm

2.3 Applications of Kollicoat IR

2.3.1 Application areas

Due to its excellent film-forming properties, enormous flexibility, low viscosity, good adhesion, excellent water solubility and rapid dissolution, Kollicoat IR has a wide range of application possibilities. These are summarized in Table 20.

Table 20: Application possibilities of Kollicoat IR

Dosage form	Function
Coated tablets and capsules	Film-forming agent in soluble coatings
Tablets and hard gelatine capsules, instant granules, effervescent tablets	Water-soluble binding agent for wet granulation
Sprays and transdermal systems	Washable, flexible film-forming agent
Sustained-release tablets and pellets	Pore-forming agent for adjusting active ingredient release
Suspensions	Stabilizer

In the following sections 2.3.2 – 2.3.4, the most important of these applications are described using formulation examples.

2.3.2 Film-forming agent in instant-release tablet coatings

2.3.2.1 Introduction

Generally, water-soluble tablet coatings are used for the following reasons:

- The colour produced can increase patient compliance and improve differentiation with respect to other tablets.
- A smooth, white or coloured coating can mask the taste and facilitate swallowing of the tablet.
- A smooth, white or coloured coating can improve the stability of the active ingredient by reducing contact with oxygen and moisture.

Kollicoat IR coatings can help achieve all of these goals.

Due to their high degree of flexibility, coating formulations based on Kollicoat IR do not require the addition of a plasticizer. In addition, the flexibility prevents the coating from cracking during storage, especially if the relative humidity varies. And, even if the cores contain a very efficient, swelling disintegrant, the Kollicoat IR coating remains intact.

If the active ingredient within the tablet core is sensitive to hydrolysis, a mixture of water and ethanol (e.g. in the ratio 1:1) can be used instead of just water for the spray suspension. In this way, the outlet air temperature is increased and the spraying process accelerated; it is also dryer and the moisture in the outlet air is reduced. However, it must be taken into account in this application that the viscosity of an ethanol/water mixture is higher that that of water alone; thus, the concentration of Kollicoat IR may have to be reduced somewhat.

2.3.2.2 Manufacture and application of the spray suspension

The manufacture of a spray suspension of Kollicoat IR for coating tablets and capsules is straightforward; it is also quicker than with most other film-forming agents. The suspension can be prepared using a number of methods; the recommended method is described below:
Suspend the pigments and talcum in part of the water and homogenize until fine and lump-free. Dissolve the Kollicoat IR in the rest of the water.
Add the homogenized pigment suspension to the Kollicoat IR solution. Pass the suspension through a sieve (e.g. 200 µm) in order to remove any pigment that may have agglomerated and that would block the spray nozzle.

Frequently, a simpler method is also possible: suspend the pigments in the total amount of water, homogenize and then stir in the Kollicoat IR, stirring for 5 min until dissolved.

Generally, the stirring speed should not be too high in order to prevent or minimize foaming.
Due to its surfactant properties, Kollicoat IR also acts as a protective colloid in the suspension, i.e. it prevents agglomeration of insoluble pigment particles, hence guaranteeing a homogeneous colour of the tablet surface.

As the viscosity of the spray suspension using Kollicoat IR as a film-forming agent is much lower than with other polymers (e.g. HPMC), a considerably increased concentration can be used. This reduces the production time for the coated tablets significantly so that manufacturing costs are also lower (see Table 29). The concentrations of Kollicoat IR in spray suspensions is normally within the range 15 – 25 %; this results in a solid content of 20 – 35 % depending on the amount of pigment employed.

Spray suspensions containing Kollicoat IR can be used in all conventional coating machines such as perforated-, fluidized bed-, immersion sword-, “Kugel”- and other coaters under the usual conditions for aqueous coating. The following settings, which have been proven in numerous runs, are recommended:

Inlet air temperature: 60 – 80 °C
Outlet air temperature: 30 – 50 °C
Spray pressure: 2 – 6 bar

Cleaning of the machines from spray suspension residues is also a simple procedure: cold or warm water is all that is required (see chapter 2.6).

2.3.2.3 Formulation of propranolol tablets with a red Kollicoat IR coating

In this case, tablet cores of the following composition were used: Propranolol-HCl (40 mg), Ludipress (97.5 mg), Kollidon VA64 (12.5 mg), microcrystalline cellulose (97.5 mg), magnesium stearate (2.5 mg).

The red spray suspension containing 16 % Kollicoat IR was prepared with the composition shown in Table 21. This suspension is basically designed for the film-coating of approximately 250 kg of cores (250 mg, 9 mm) but can also be used for other types of core.

Table 21: Typical red spray suspension with Kollicoat IR

	Weight (kg) for 250 kg of cores	**Content (%)**
Polymer solution:		
Kollicoat IR	6.08	16.0
Water	24.32	64.0
Pigment solution:		
Talcum	1.71	4.5
Titanium dioxide	1.14	3.0
Sicovit red iron oxide	0.57	1.5
Water	4.18	11.0
Total	38.0	100

- Dissolve the Kollicoat IR in water while stirring.
- Suspend the talcum and pigments in water under vigorous stirring and homogenise in a corundum disk mill.
- Stir the pigment suspension into the polymer solution to make the spray suspension.
- Continue to stir the spray suspension during the entire process.

The spray suspension was sprayed onto 250 kg of cores in a perforated Driacoater type 900 (Driam) with 6 nozzles under the machine settings listed in Table 22.

Table 22: Machine settings (Driacoater type 900, batch size: 250 kg)

Parameter	**Setting**
Inlet air temperature	70 °C
Outlet air temperature	48 °C
Core temperature	50 °C
Air flow	4400 m^3/h
Spray pressure	6 bar
No. nozzles	6
Spray rate	700 g/min
Spraying time	55 min
Drying time at end of process	5 min/60 °C
Amount of solid applied	4.8 mg/cm^2 = 3.8 %

Subsequent to film coating, the properties of the coated tablets were compared to those of uncoated cores. Table 23 shows that the coating, apart from affecting the colour, only increased the hardness of the tablets a little; the other properties, e.g. disintegration time and release of active ingredient were not significantly affected.

Table 23: Properties of propranolol tablets before and after film coating

Parameter	**Uncoated cores**	**Coated tablets**
Appearance	White	Red, glossy
Hardness	93 N	109 N
Disintegration time	0 %	0 %
Friability	5.53 min	5:47 min
Active ingredient release	10 min 49 %	10 min 54 %
	20 min 98 %	20 min 99 %

Kollicoat IR coatings have an inherent gloss. If the coating is to have a brilliant gloss, the coated tablets can be subsequently sprayed, after drying, with a 5 % aqueous solution of macrogol 6000. An amount of 0.3 – 0.6 mg magrogol/cm^2 is all that is required.

2.3.2.4 Formulation of caffeine tablets with a white Kollicoat IR coating

In this case, tablet cores of the following composition were used:

Caffeine (50 mg), Ludipress (229 mg), Kollidon CL (10 mg), microcrystalline cellulose (40 mg), magnesium stearate (1 mg).

The white spray suspension containing 19 % Kollicoat IR was prepared with the composition shown in Table 24. It is designed for use in the film coating of approximately 5 kg of caffeine cores (330 mg, 9 mm) but can also be used for other types of core.

Table 24: Typical white spray suspension with Kollicoat IR

	Weight (g) for 5 kg cores	**%**
Polymer solution:		
Kollicoat IR	100	19.2
Water	264	50.8
Pigment solution:		
Talcum	37.4	7.2
Titanium dioxide	18.6	3.6
Water	100	19.2
Total	520	100

- Dissolve the Kollicoat IR in water while stirring.
- Suspend the talcum and pigments in water under vigorous stirring and homogenise in a corundum disk mill.
- Stir the pigment suspension into the polymer solution to make the spray suspension.
- Continue to stir the spray suspension during the entire process.

The spray suspension was sprayed onto 5 kg of cores in a perforated Accela Cota 24" with a single nozzle using the machine settings listed in Table 25. Characteristic of this formulation is the short spraying duration resulting from the high concentration of polymer in the spray suspension.

Table 25: Machine settings (Accela Cota 24", batch size: 5 kg)

Parameter	**Setting**
Inlet air temperature	60 °C
Outlet air temperature	39 °C
Core temperature	35 °C
Air flow	180 m^3/h
Spray pressure	3 bar
Spray rate	30 g/min
Spraying duration	18 min
Drying time at end of process	4 min/60 °C
Amount of Kollicoat IR applied	3 mg/cm^2

Subsequent to film coating, the properties of the coated tablets were compared to those of uncoated cores. Table 26 shows that the coating does not alter the properties of the caffeine tablets.

Table 26: Properties of caffeine tablets before and after film coating

Parameter	Uncoated cores	Coated tablets
Appearance	White	White, glossy
Hardness	116 N	119 N
Disintegration time	0 %	0 %
Friability	0:58 min	0:51 min
Active ingredient releas	10 min 93 %	10 min 92 %
	20 min 93 %	20 min 98 %

Kollicoat IR coatings have an inherent gloss. If the coating is to have a brilliant gloss, the coated tablets can be subsequently sprayed, after drying, with a 5 % aqueous solution of macrogol 6000. An amount of 0.3 – 0.6 mg magrogol/ cm^2 is all that is required.

2.3.2.5 Stability of tablets coated with Kollicoat IR

Tablets containing 40 mg propranolol-HCl were produced and coated with 3.8 % Kollicoat IR. In order to investigate the influence of the coating on the stability of its properties, the coated tablets were stored for 6 months under stress conditions (40 °C/75 % relative humidity). Subsequently, the changes in properties were measured and compared with those of the uncoated tablets prior to storage. No significant influence on appearance, hardness, disintegration time, friability and active ingredient release was established. Fig. 16 illustrates this using the example of tablet hardness and disintegration time.

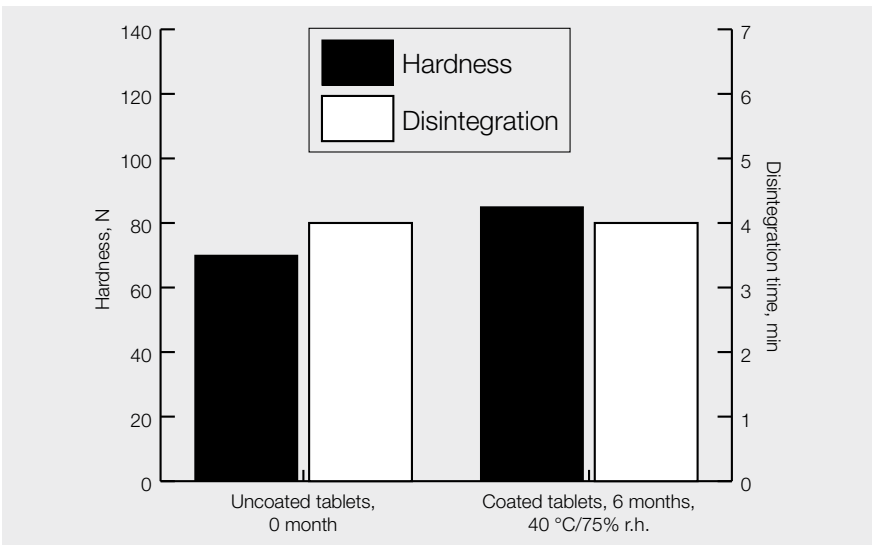


Fig. 16: Tablet hardness and disintegration time of coated propranolol tablets

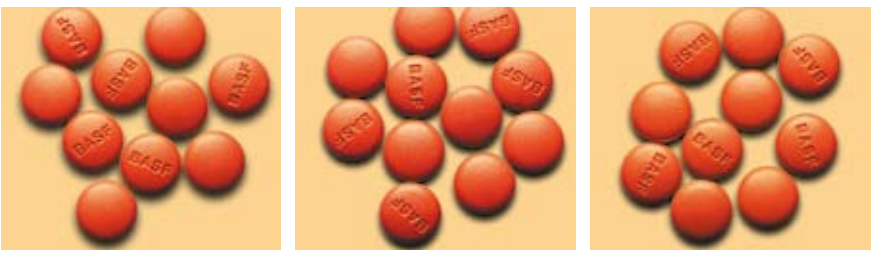
2.3.2.6 Scale-up of film coating with Kollicoat IR

The red coated propranolol tablet formulation described in section 2.3.2.3 was produced in various batch sizes and compared using different machines. Initially, batch sizes of 5 and 15 kg were coated in an Accela Cota 24". Subsequently, a 250 kg core batch was coated in a Driacoater 900. The coatings contained 3.8 % solid material. The machine settings used were as shown in Table 27.

Table 27: Machine settings for the film coating of propranolol tablets (scale-up)

Parameter	**5 kg batch, Accela Cota 24"**	**5 kg batch, Accela Cota 24"**	**250 kg batch, Driacoater 900**
Inlet air temperature:	71° C	73° C	70° C
Outlet air temperature:	47° C	50° C	47° C
Core temperature	45° C	45° C	--
Air flow, absolute	83 m^3/h	223 m^3/h	4400 m^3/h
Air flow per kg cores	16.6 m^3/h	14.9 m^3/h	17.6 m^3/h
No. nozzles	1	1	6
Spray rate, absolute	14 g/min	42 g/min	700 g/min
Rel. spray rate/kg cores	2.8 g/min	2.8 g/min	2.8 g/min
Drying time at end of process	5 min/60 °C	5 min/60 °C	5 min/60 °C
Amount of coating applied	4.8 mg/cm^2 = 3.8 %	4.8 mg/cm^2 = 3.8 %	4.8 mg/cm^2 = 3.8 %

The parameters used for the scale-up test were friability but especially appearance, tablet hardness, disintegration time and active ingredient release. One of the major parameters for the scale-up test proved to be the relative spray rate for 1 kg of cores. Using the same relative spray rate, there no significant differences were observed, as is shown in Figs 17 and 18 and Table 28. In a second scale-up experiment, the relative spray rate was more than doubled; in this case, a certain influence on the hardness and disintegration of the tablets was established. Thus, conversion from laboratory scale to production scale presented no problems using Kollicoat IR.



5 kg batch *15 kg batch* *250 kg batch*

Fig. 17: Appearance of coated propranolol tablets on scale-up

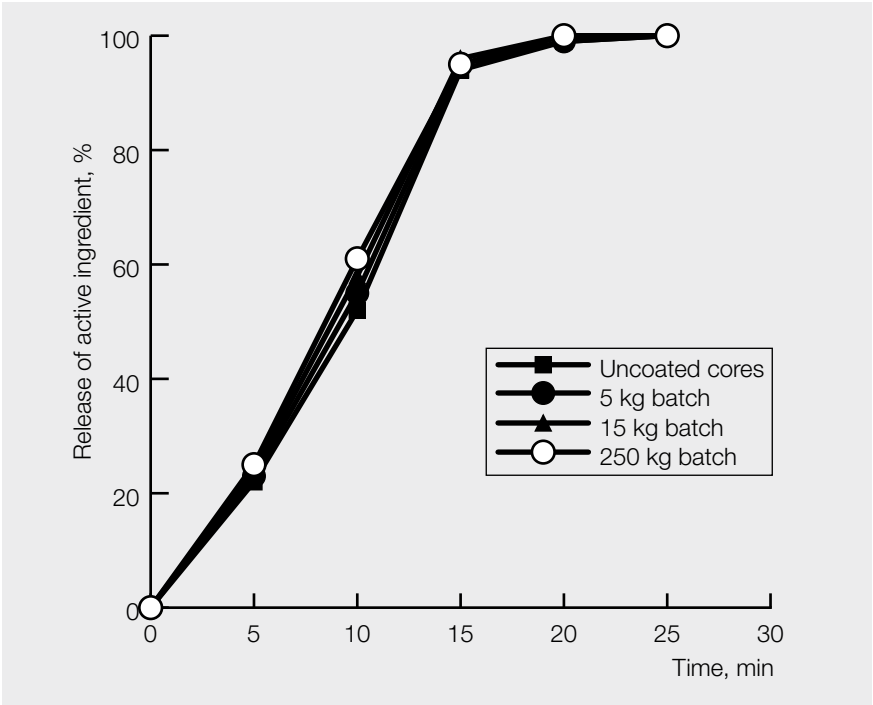


Fig. 18: Active ingredient release from propranolol tablets (scale-up)

Table 28: Hardness and disintegration of coated propranolol tablets (scale-up)

	Uncoated cores	**5 kg batch**	**15 kg batch**	**250 kg batch**
Tablet hardness	93 N	107 N	102 N	104 N
Disintegration time	5:53 min	5:56 min	5:47 min	5:59 min

2.3.2.7 Cost of film coating with Kollicoat IR grades

In the pharmaceutical industry today the question of production cost, including that of coatings, is constantly being raised – and not only for the manufacture of generics. This aspect has therefore also been taken into account with respect to the use of the Kollicoat IR grades. In the case of the pure material costs for polymers, plasticizers, talcum powder and pigments, the difference between coating with Kollicoat IR grades and hypromellose is so small that it can be practically neglected for comparative purposes. However, production costs are a different matter.
With Kollicoat IR, the production of the polymer solution is simpler, and hence a little cheaper, than is the case with hypromellose; however, the decisive cost factor is the film coating process and this is practically entirely dependent on the solid concentration of the spray suspension. In the case of Kollicoat IR and Kollicoat IR White, this concentration is 20 % and more and hence substantially higher than in the case of hypromellose (10 – 15 %). This means that the spray time, and hence the cost, can be considerably reduced. In addition, the temperatures that can be achieved with cores comprising the Kollicoat IR grades are substantially higher than with hypromellose. In order to demonstrate this, two different batch sizes of 8.5 and 165 kg were used and coated with approximately 3.5 % solid using the XL lab 01 and Premium 200 (both Manesty) equipment. The minimum times required for manufacture of the spray suspension and for the coating process were then calculated.
Table 29 shows the results using comparable formulations of Kollicoat IR White and a mixture of two hypromellose types (HPMC). It can be seen that in the case of hypromellose, more than double the time was required for producing the coatings. This is reflected directly in the manufacturing costs.

Table 29: Minimum times required for tablet film coating with formulations of Kollicoat IR and hypromellose with a coating of approx. 3.5 %

Parameter	**Kollicoat IR White**		**Hypromellose**	
Batch size	8.5 kg	165 kg	8.5 kg	165 kg
- Maximum core temperature	50 °C	50 °C	38 °C	46 °C
- Solid concentration of the spray suspension	20 %	20 %	12 %	12 %
- Amount of spray suspension applied	1.49 kg	28.9 kg	2.48 kg	48.1 kg
- Spray rate	37.2 g/min	410 g/min	27.5 g/min	290 g/min
Minimum time for the coating process	**40 min**	**70 min**	**90 min**	**165 min**

2.3.3 Kollicoat IR as a binder in tablets, granules and pellets

2.3.3.1 Introduction

Kollicoat IR, due to its excellent adhesion properties, is also a good tablet binder when used in wet granulation processes. Its excellent solubility and, especially, its rapid dissolution make it ideal for use in instant-release tablets, water-dispersible tablets, granules as well as for effervescent tablets and granules. It can also be used in the manufacture of pellets.

In addition, Kollicoat IR is the binder of choice when other such agents, due to the formation of peroxides, negatively affect the stability of the active ingredient during storage. Kollicoat IR does not form peroxides (see section 2.2.11).

Also, if the tablet does not have enough plasticity, a fact that often causes capping of the tablet, Kollicoat IR can be the solution of choice.
The formulation for acetaminophen tablets described in section 2.3.3.3 is a typical example.

2.3.3.2 Vitamin C tablets with Kollicoat IR as binder

In the laboratory, vitamin C tablets were produced with the following composition:

I. Ascorbic acid (50 mg), lactose monohydrate (130 mg), microcrystalline cellulose (130 mg)
II. Binder (10 mg) in water
III. Kollidon CL (10 mg), magnesium stearate (2 mg).

Mixture I was granulated with solution II, dried and sieved. Mixture III was added and the whole compressed using various compression forces.

Comparative investigations with this formulation using different granulation technologies (mixer, fluidized bed) showed that Kollicoat IR as a binder produced practically identical granulate properties (flow behaviour, particle size, bulk density) as with other conventional binders such as Kollidon VA 64 and HPMC 2910, type 3 mPa·s. Due to the better stability of vitamin C, fluid bed granulation is recommended [2] as this essentially prevents hydrolysis of the ascorbic acid.
Furthermore, the compression force-hardness profile of the tablets produced from the granulates also showed no significant differences in properties (Fig. 19). Only the disintegration times of the tablets were somewhat higher than those of Kollicoat IR or Kollidon VA 64 in the case of HPMC at various compression forces (Fig. 20).

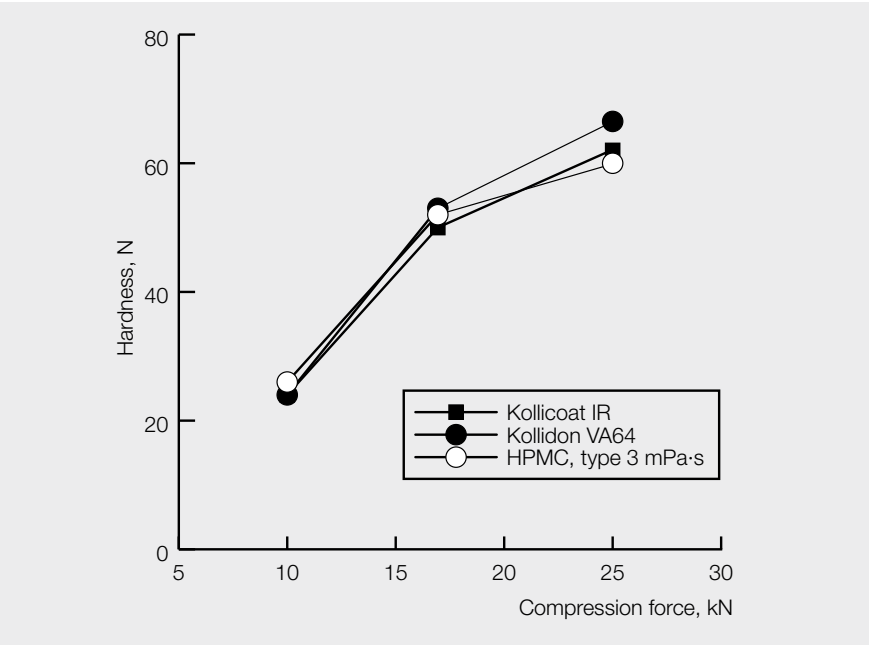


Fig. 19: Compression force-hardness profile of vitamin C tablets with various binders

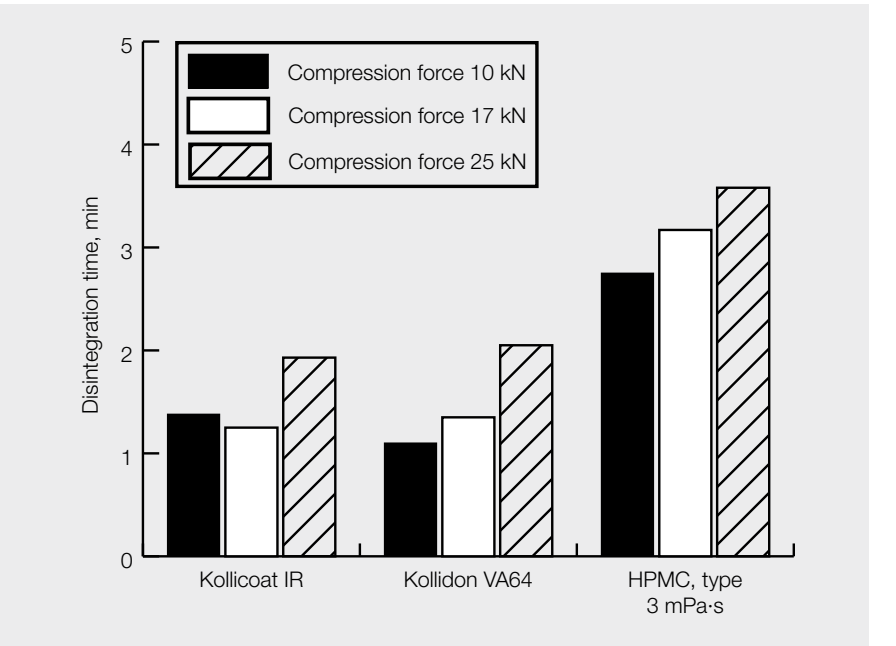


Fig. 20: Disintegration times of vitamin C tablets as a function of compression force and binder

2.3.3.3 Acetaminophen tablets with Kollicoat IR as binder

Tablets containing 500 mg acetaminophen (= paracetamol) were produced using the formulation shown in Table 30. Kollicoat IR was then compared with the strong binder povidone K90 [3] that is marketed as Kollidon 90F. Mixture I was granulated with solution II, dried and sieved. Component III was then added, briefly mixed in and the entire mixture compressed to tablets in a rotating press using high compression force (20 kN).

Table 30: Formulation of acetaminophen tablets

Components		Amount
I	Acetaminophen	500 mg
	Lactose monohydrate	50 mg
II	Kollicoat IR or Kollidon 90F	24 mg
	Water	q.s.
III	Kollidon CL	20 mg
	Magnesium stearate	6 mg

The results of the properties of the acetaminophen tablets are shown in Table 31. These clearly show that in the case of Kollicoat IR the hardness is greater and the friability less than in the case of Kollidon 90F. The most important difference, however, was that the inadequate plasticity brought about by the typical capping of the tablets was prevented due to the flexibility of Kollicoat IR. This was not the case with the relatively brittle binder povidone.

Table 31: Properties of acetaminophen tablets using two different binders

Parameter	Kollidon 90F	Kollicoat IR
Tablet weight	603 mg	617 mg
Diameter	12 mm	12 mm
Hardness	40 N	54 N
Disintegration time	1 min	3 min
Friability	2 %	0 %
Proportion of capped tablets	25 %	0 %

2.3.3.4 Acetaminophen instant granules with Kollicoat IR as binder

A readily soluble binder of high binding power is required if water-soluble instant granules are to be produced. This is therefore a further application area for Kollicoat IR. A typical example is acetaminophen instant granules of composition shown in Table 32.

Table 32: Formulation of acetaminophen instant granules

	Components	Amount
I	Acetaminophen	490 g
	Sorbitol	490 g
	Aspartame	2 g
	Aroma	0.06 g
II	Kollicoat IR	27 g
	Water	153 g

The components of I are mixed for 10 min, solution II is prepared and then sprayed onto agitated mixture I in a granulator. The moist granulate is first passed through a 3 mm sieve (3 mm), then a 1 mm sieve and finally, after drying, through a 1 mm sieve.

The granules thus obtained dissolve within 1 minute in water.

2.3.4 Kollicoat IR as a film-former in sprays

The good film-forming properties, excellent solubility in water (and hence good washability), high flexibility, adhesive power and low level of tackiness make Kollicoat IR ideal as a film-forming agent in sprays for topical application to skin and the mucous membranes.

A typical example is wound spray containing the disinfectant povidone-iodine that was developed according to the formulation given in Table 33. A brown solution of low viscosity is obtained that can be easily sprayed, that spreads readily and that is easy to wash off. Furthermore, the formulation showed relatively good stability when subjected to a stress test (14 days, 52 °C) that corresponds to storage over a period of more than a year at room temperature. Only 10 % was lost, a good value for this relatively unstable active ingredient in solution.

Table 33: Formulation of a povidone-iodine wound spray

Components	Content
PVP-iodine 30/06 (BASF)	10 g
Kollicoat IR	5 g
Ethanol, 96 %	42 g
Water	43 g

2.4 Applications for Kollicoat IR White in film coating

2.4.1 General aspects

Kollicoat IR White is a ready-made mixture based on film-forming agent Kollicoat IR and is for immediate use (for composition, see section 2.1.2.2). It is mainly intended for use in white tablets; however, other pigments can be added for colour if required. It has all the advantages of film former Kollicoat IR, e.g. rapid dissolution in water, a high degree of adhesion also on lipophilic surfaces, its enormous flexibility and its low viscosity in water.

With Kollicoat IR White, a white, readily soluble coating is obtained. It can be used to mask taste, to facilitate swallowing tablets or to improve the stability of the active ingredient by decreasing contact with oxygen and moisture.

Due to the very high flexibility of Kollicoat IR, Kollicoat IR White requires no additional plasticizer. In addition, the flexibility prevents the coating from cracking during storage, especially if the relative humidity varies. Even if the cores contain a swelling disintegrant such as crospovidone (Kollidon CL), the coating retains its strength during storage – also if the storage conditions may not be ideal.

The applications of Kollicoat IR White are described in the following section using a number of formulations as examples.

2.4.2 Manufacture and processing of a Kollicoat IR White spray suspension

The manufacture of a spray suspension of Kollicoat IR White for film-coating tablets and capsules is both easy and quick. The following method is recommended:
Stir the required amount of water well. The stirring speed must be such that little or, better, no foam is produced. Add Kollicoat IR White slowly but continuously. Continue stirring for a further 10 – 15 minutes; the white spraying suspension is then ready for use (see also Fig. 2 in chapter 2.2.3.2).

To obtain coloured coatings, water-soluble colorants or ready-made colour mixes, e.g. Sepispers Dry, can be added directly. However, colour lakes or iron oxide pigments can also be used. They must, however, be separately dispersed in water beforehand and then homogenized before being added to the Kollicoat IR White suspension.

Due to the low viscosity of aqueous Kollicoat IR White suspensions, a much higher concentration can be used than for other commercially available ready-made film-coating mixtures. This reduces the spraying time considerably and hence the overall processing costs (see chapter 2.3.2.7). Spray suspensions containing 20 – 27 % of solids can be prepared with ease at room temperature as their viscosity is always below the critical limit of 250 mPa·s (see chapter 2.2.4.2). Spray suspensions of Kollicoat IR White can be used in all coating machines used for tablets and capsules. The general operating conditions and settings for this type of processing are summarised in Table 34.

Table 34: Normal conditions and machine settings for the processing of Kollicoat IR White

Parameter	Setting range
Normal concentration of Kollicoat IR White	15 – 30 %
Inlet air temperature	50 – 80 °C
Outlet air temperature	30 – 45 °C
Spray pressure	2 – 4 bar
Temperature of the spray suspension	20 – 70 °C

Cleaning of the machines from spray suspension residues is also a simple procedure: cold or warm water is all that is required (see chapter 2.6).

2.4.3 Formulations with Kollicoat IR White

2.4.3.1 Formulation of acetylsalicylic acid tablets with a white Kollicoat IR White coating

Cores of the following composition were produced:
Acetylsalicylic acid (100 mg), Ludipress (150 mg), microcrystalline cellulose (50 mg), magnesium stearate (1.5 mg).

209 g of Kollicoat IR White were stirred into 836 g of water; this represented the amount necessary for a batch of 6 kg of a 20 % spray suspension. The suspension was stirred for a further 15 minutes.

The machine settings of the Accela Cota 24" are summarised in Table 35. Although the inlet air temperature was relatively low at 60 °C and the spraying pressure was only 2 bar, the entire spraying process took only 35 minutes.

Table 35: Machine settings for the film coating of white acetylsalicylic acid tablets (Accela Cota 24")

Parameter	Setting
Batch size	6 kg
Inlet air temperature	60 °C
Outlet air temperature	36 °C
Core temperature	35 °C
Inlet flow rate	210 m^3/h
Outlet air flow rate	410 m^3/h
Spray pressure	2 bar
No. nozzles	1
Spray rate	30 g/min
Spraying time, total	35 min
Subsequent drying	4 min/60 °C
Amount applied	5 mg solid/cm^2

The properties of coated acetylsalicylic acid tablets differ from those of the cores in that they were a little harder (Table 36). The release of the active ingredient (Fig. 21) corresponded approximately to that of uncoated cores.

Table 36: Properties of acetylsalicylic acid tablets before and after film coating with Kollicoat IR White

Parameter	**Uncoated cores**	**Coated tablets**
Appearance	White	White
Hardness	67 N	75 N
Disintegration time	3‘ 17“	3‘ 29“
Friability	0 %	0 %

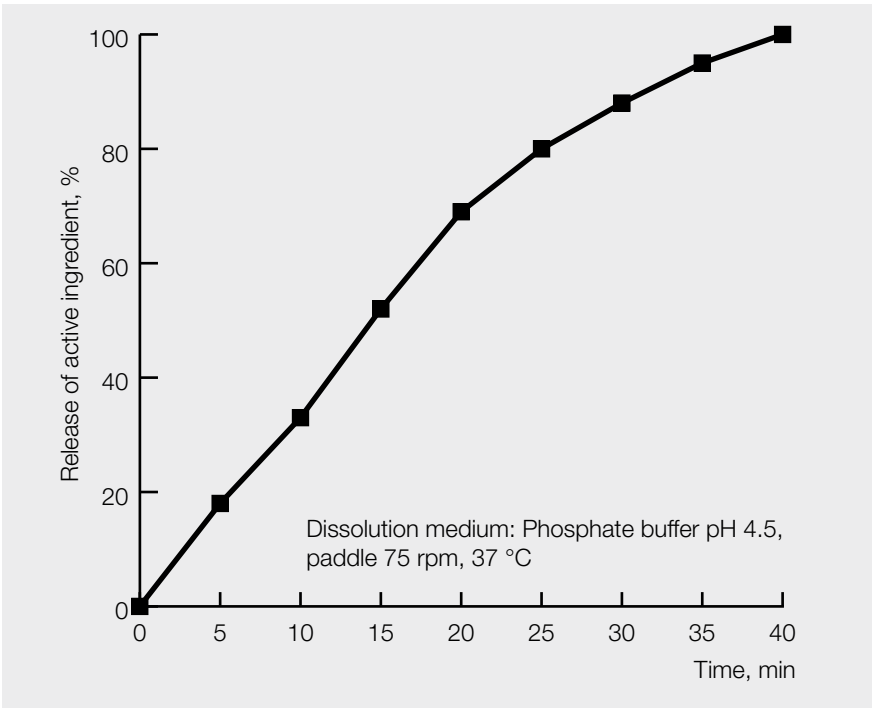


Fig. 21: Release of acetylsalicylic acid tablets coated with Kollicoat IR White

2.4.3.2 Formulation of propranolol tablets with a blue Kollicoat IR White coating

Cores of the following composition were produced:
Propranolol-HCl (40 mg), Ludipress (97.5 mg), microcrystalline cellulose (97.5 mg), Kollidon VA 64 (12.5 mg), magnesium stearate (2.5 mg).
The tablet weight was 250 mg and the diameter 9 mm.

The formulation of the spray suspension was designed for the coating of 250 kg of cores. This particular production run is somewhat more complex than for a simple white suspension as the insoluble indigotin-aluminium colour lake first has to be suspended and homogenised (e.g. using a high-speed mixer) before being added to the Kollicoat IR White suspension (Table 37).

Table 37: Formulation of a blue Kollicoat IR White spray suspension

	Weight (kg) for 250 kg cores	**Content (%)**
Polymer suspension		
Kollicoat IR White	7.755 kg	18.8
Water	25.0 kg	60.6
Colour lake suspension		
Indigotin colour lake E 132	0.495 kg	1.2
Water	8.0 kg	19.4
Total	41.25 kg	100

The machine settings for coating a batch of 250 kg tablet cores using a Driacoater type 900 are given in Table 38. In this case also, the entire spraying duration was only 60 minutes; in this time, a coating of 3 % solid was applied to the tablets.

Table 38: Machine settings for blue propranolol tablets (Driacoater 900)

Parameter	**Setting**
Batch size	250 kg
Inlet air temperature	70 °C
Outlet air temperature	45 °C
Core temperature	47 °C
Air flow	4600 m^3/h
Spray pressure	4 bar
No. nozzles	6
Spray rate	700 g/min
Spraying time, total	60 min
Subsequent drying	5 min/60 °C
Amount applied	3 % solids

The properties of blue-coated propranolol tablets differed from those of the cores in that they were, as usual, a little harder (Table 39). As the other parameters, e.g. disintegration time and active ingredient release were not affected, this is of no consequence; in fact it can be assessed positively.

Table 39: Properties of propranolol tablets before and after blue film coating with Kollicoat IR White

Parameter	Uncoated cores	Coated tablets
Appearance	White	Blue
Hardness	94 N	112 N
Disintegration time	5‘ 51“	6‘ 02“
Friability	0 %	0 %
Active ingredient release	10 min: 51 % 20 min: 99 %	10 min: 53 % 20 min: 99 %

2.4.3.3 Formulation of vitamin C tablets with a red Kollicoat IR White coating

Cores of the following composition were produced:

Ascorbic acid C97 (103.1 mg), Ludipress (180.0 mg), Kollidon VA 64 (14.4 mg), Kollidon CL (5.0 mg), magnesium stearate (2.5 mg).
The tablet weight was 300 mg and the diameter 8.5 mm.

The formulation of the spray suspension was designed for 1 kg of cores. The formulation is somewhat different to that given for the blue tablets in section 2.4.3.2 as here part of the Kollicoat IR White is homogenised together with the insoluble iron oxide pigment. In this way, the pigment suspension has somewhat more volume and is also stabilised; it thus mixes in a more uniform manner with the polymer suspension produced previously by stirring in Kollicoat IR for 15 minutes. Table 40 shows the precise composition of the red suspension.

Table 40: Formulation of a red Kollicoat IR White spray suspension

	Weight for 1 kg cores	Content (%)
Polymer suspension		
Kollicoat IR White	25.9 g	18.5
Water	105.0 g	75
Colour lake suspension		
Kollicoat IR White	1.8 g	1.3
Indigotin colour lake E 132	1.8 g	1.3
Water	5.6 g	4
Total	140.1 g	100

In a laboratory experiment, the cores were coated using a Hi-Coater machine. The machine settings for an experimental batch of 1 kg tablet cores are given in Table 41. In this case also, the entire spraying duration was very short, a coating of 3.1 % solid being obtained for the tablets.

Table 41: Machine settings for red vitamin C tablets (Hi-Coater)

Parameter	**Setting**
Batch size	1 kg
Inlet air temperature	54 – 57 °C
Outlet air temperature	34 – 35 °C
Spray pressure	1.5 bar
No. nozzles	1
Spray rate	5.2 – 5.4 g/min
Spraying time, total	28 min
Subsequent drying	8 min
Amount applied	3.1 % solids

The properties of the red-coated vitamin C tablets differed only from those of the cores in that they were somewhat harder (Table 42); as the disintegration time remained unchanged, this can be assessed positively.

Table 42: Properties of vitamin C tablets before and after red film coating with Kollicoat IR White

Parameter	**Uncoated cores**	**Coated tablets**
Appearance	White	Red
Hardness	150 N	180 N
Disintegration time	5‘ 18“	5‘ 6“
Friability	0 %	0 %

2.5 Applications for Kollicoat Protect as a tablet coating

2.5.1 General aspects

Kollicoat Protect is a mixture of the film-forming agents Kollicoat IR and polyvinyl alcohol (see chapter 2.1.2 for composition). It is designed for white and coloured tablet and capsule coatings. Due to its very low permeability with respect to oxygen and water, its primary application is as a protective film against oxidation and hydrolysis of the active ingredient. Examples of these applications are given in chapters 2.5.3.1 and 2.5.3.2. In addition, it can be used to mask taste (an example is given in chapter 2.5.3.3), to facilitate the swallowing of tablets, to improve their appearance or as sub-coating.

It possesses all the advantages of Kollicoat IR, e.g. rapid dissolution in water, a high degree of adhesion, also on lipophilic surfaces, enormous flexibility and low viscosity in water.

Kollicoat Protect allows smooth and rapidly dissolving coatings to be produced. Due to its high degree of flexibility, coating formulations using Kollicoat Protect do not require the addition of a plasticizer. In addition, the flexibility prevents the coating from cracking during storage, especially if the relative humidity varies. Even if the cores contain a swelling disintegrant such as crospovidone (Kollidon CL), the coating retains its strength during storage – also if the storage conditions may not be ideal.

The applications of Kollicoat Protect are described in the following sections using a number of formulations as examples.

2.5.2 Manufacture and processing of spray suspensions using Kollicoat Protect

The manufacture of a polymer solution of Kollicoat Protect for film-coating tablets and capsules is both straightforward and quick. However, at certain stirring speeds foam may form. The formation of foam can be best prevented or at least reduced by adding 0.1 % of a 30 % simethicon emulsion or 0.75 % Labrasol. Normally, one of the following two methods can be used:

a) Spray solution containing a water-soluble colorant:
Stir Kollicoat Protect and the soluble colorant into the required amount of water. Set the stirring speed so that as little foam as possible is generated. Continue stirring for a further 30 min. If necessary, add an anti-foaming agent beforehand (see chapter 2.2.3.3).

b) Spray suspension with white and/or coloured pigment or colour lake:
Stir Kollicoat Protect into the required amount of water to obtain the polymer solution. Set the stirring speed so that as little foam as possible is generated. Continue to stir for a further 30 min.
To prepare the pigment suspension, stir the insoluble components, e.g. talcum powder, titanium dioxide, iron oxide or colour lake into the required amount of water and homogenise in a high-speed stirrer or corundum disk mill. Stir the pigment suspension into the polymer solution to make the spray suspension. Stir continuously during the entire spraying process.

Specific application examples with various tablet cores and different spray suspensions are given in section 2.5.3. Spray suspensions containing Kollicoat Protect can be processed in all machines for the film coating of tablets and capsules, e.g. perforated-, fluidized bed-, immersion sword- and "Kugel" coaters etc. Using these machines with settings as given in Table 43, very good results have been achieved.

Table 43: Normal conditions and machine settings for the processing of spray suspensions of Kollicoat Protect

Parameter	**Setting range**
Concentration of solids in the spray suspension	15 – 25 %
Inlet air temperature	50 – 80 °C
Outlet air temperature	30 – 50 °C
Spray pressure	3 – 5 bar
Temperature of the spray suspension	20 – 70 °C

Cleaning of the machines from spray suspension residues is also a simple procedure: cold or warm water is all that is required (see chapter 2.6).

2.5.3 Formulations with Kollicoat Protect

2.5.3.1 Formulation of acetylsalicylic acid tablets (100 mg) with a white coating as a protection against humidity

Acetylsalicylic acid was selected for this particular application because of its high sensitivity to hydrolysis. In this way, the protective effect of Kollicoat Protect can best be shown.

Cores of the following composition were produced:
Acetylsalicylic acid (100 mg), Ludipress (150 mg), microcrystalline cellulose (50 mg), magnesium stearate (1.5 mg). The tablet weight was 301 mg and the diameter 9 mm.

The 20 % spray suspension was prepared as described in general method b) in chapter 2.5.2. The composition was as shown in Table 44 and was designed for the coating of 6 kg of cores.

Table 44: Composition of a spray suspension of Kollicoat Protect as a white protective coating

Components	**Weight (g) for 6 kg of cores**	**Content (%)**
Kollicoat Protect	125,40	12
Talcum	52,25	5
Titanium dioxide	31,35	3
Water	836,00	80
Total	1045,00	100

The machine settings of the Accela Cota 24“ are given in summary in Table 45. Although the inlet air temperature was relatively low at 60 °C and the spraying pressure was only 2 bar, the entire spraying process took only 35 minutes.

Table 45: Machine settings for the white Kollicoat Protect film for acetylsalicylic acid tablets (Accela Cota 24”)

Parameter	**Setting**
Batch size	6 kg
Inlet air temperature	60 °C
Outlet air temperature	36 °C
Core temperature	35 °C
Inlet flow rate	210 m^3/h
Outlet air flow rate	410 m^3/h
Spray pressure	2 bar
No. nozzles	1
Spray rate	30 g/min
Spraying time, total	35 min
Subsequent drying	4 min/60 °C
Amount applied	5 mg solid/cm^2

The coated tablets obtained had a white, glossy coating that covered the engravings on the tablet surface excellently. Fig. 22 shows a microscope photo of a tiny section of such an engraving. The irregular surface caused by the letters is completely covered and closed.

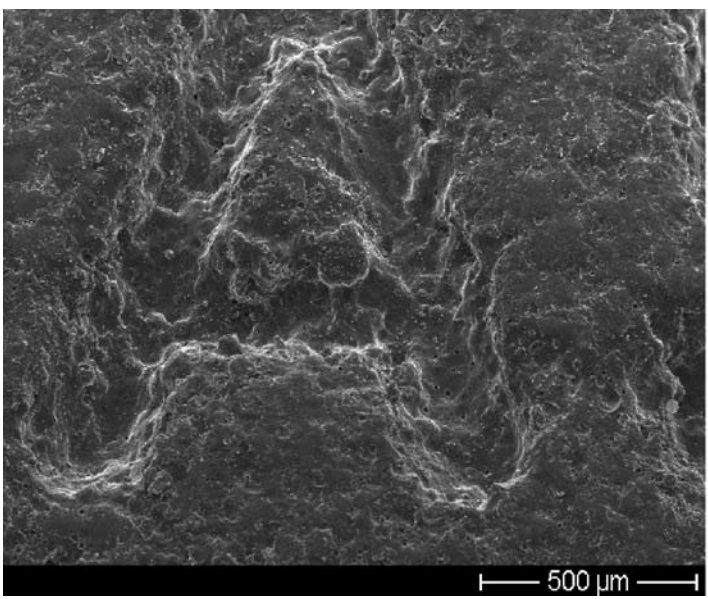


Fig. 22: Photo of an engraving on Kollicoat Protect-coated acetylsalicylic acid tablets

The properties of acetylsalicylic acid tablets were hardly affected by the protective coating; however, there was an small increase in hardness. The release curve is also practically identical to that of identical cores coated with Kollicoat IR White (see Fig. 21 in chapter 2.4.3.1).

Hydrolysis of acetylsalicylic acid in the tablets coated with Kollicoat Protect was investigated over a period of 6 months under various storage conditions (25 °C/60 % and 30 °C/70 % relative humidity). In the case of the Kollicoat Protect coating, a smaller amount of free salicylic acid was determined than with a coating of Kollicoat IR White (Fig. 23).

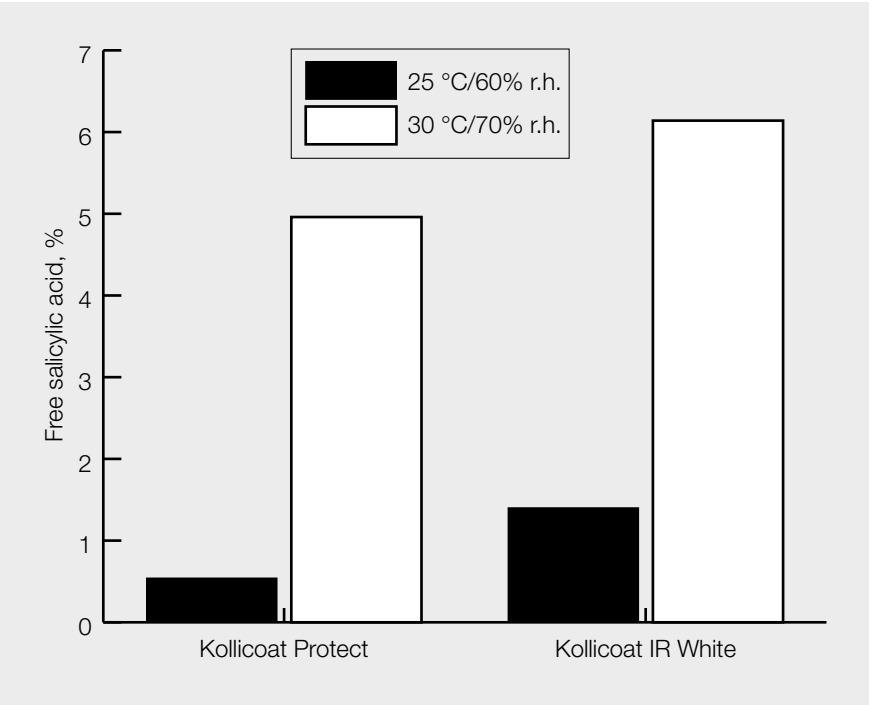


Fig. 23: Hydrolytic formation of free salicylic acid in coated acetylsalicylic acid tablets on being stored for 6 months

2.5.3.2 Formulation of vitamin C tablets (100 mg) with a red protective coating against humidity (Kollicoat Protect)

Cores of the following composition were produced:
Ascorbic acid C97 (103.1 mg), Ludipress (180.0 mg), Kollidon VA64 (14.4 mg), Kollidon CL (5.0 mg), magnesium stearate (2.5 mg).
The tablet weight was 300 mg and the diameter 8.5 mm.

Manufacture of the 21 % spray suspension was by general method b) as described in chapter 2.5.2. The formulation is shown in Table 46.
It was designed for coating 1 kg of cores.

Table 46: Formulation of a red Kollicoat Protect spray suspension

	Weight for 1 kg of cores	Content (%)
Polymer suspension		
Kollicoat Protect	16.8 g	12
Water	82.6 g	59
Colorant lake suspension		
Talcum	7.0 g	5
Titanium dioxide	14.2 g	3
Sicovit iron oxide, yellow 10	1.4 g	1
Water	28.0 g	20
Total	140.0 g	100

In a laboratory experiment, the cores were coated using a Hi-Coater coating machine. The machine settings for an experimental batch size of 1 kg of tablet cores are the same as shown in Table 41 (coating with Kollicoat IR White, section 2.4.3.3). In this case too, the total spraying time was very short, a coating being obtained containing 3.15 % solids.
The properties of the vitamin C tablets with Kollicoat Protect red protective coating differed only from the other cores in that they were somewhat harder (Table 47).

Table 47: Properties of vitamin C tablets before and after red film coating with Kollicoat Protect

Parameter	Uncoated cores	Coated tablets
Appearance	White	Red
Hardness	150 N	181 N
Disintegration time	5:18 min	5:45 min
Friability	0 %	0 %

2.5.3.3 Formulation of pseudo-ephedrine tablets (90 mg) with a white coating for taste masking using Kollicoat Protect

Pseudo-ephedrine hydrochloride is an active ingredient with a bitter taste; this is very much enhanced by its very good solubility. For this reason, it is suitable for use as a test substance in experiments designed to mask taste as it is immediately tasted if the tablets remain uncoated.
Using direct compression technology, the following tablet cores were produced:
Pseudo-ephedrine-HCl (BASF) (90 mg), Ludipress (204 mg), Aerosil 200 (3 mg), magnesium stearate (3 mg). The weight of the bi-convex tablets was 300 mg and the diameter 9 mm.

5 kg of the pseudo-ephedrine tablet cores were coated with a white spray suspension in an Accela Cota 24" coating machine. Coatings of 10, 15 and 20 mg/cm^2 were obtained. The formulation for the spray suspension, the spraying conditions and the machine settings are summarised in Table 48. The spraying time was able to be considerably shortened due to the higher spraying rate used.

Table 48: Formulation of a spray suspension with Kollicoat Protect for taste masking and the spraying conditions (Accela Cota 24")

Spraying suspension	**Content (%)**
Kollicoat Protect	12
Talcum	6
Titanium dioxide	2
Water	80
Spraying conditions	**Setting**
Inlet air temperature	58 – 62 °C
Outlet air temperature	37 °C
Product temperature	32 °C
Spray pressure	2 bar
Spray rate	24 – 26 g/min
Spraying nozzle (diameter)	1 mm
Air flow	389 m^3/h
Subsequent drying time	3 min/60 °C
Spraying duration	154 min
Amount applied (solid)	10, 15 und 20 mg/cm^2

The effect of taste masking was tested subjectively; the tablet was placed in the mouth and the time noted for the first bitter taste to occur. The following results show that a coating of 20 mg/cm^2 is adequate to mask the taste for more than one minute:

Coating	**Time to occurrence of bitter taste**
Without	< 1 sec.
10 mg/cm^2	14 – 24 sec.
15 mg/cm^2	46 – 47 sec.
20 mg/cm^2	78 sec.

2.6 Cleaning the machines after processing with Kollicoat IR grades

When processing with coating suspensions, polymer, pigment and excipient residues often collect on the inside walls of the machine and in the tubing and spraying systems.
As the three Kollicoat IR grades all consist of water-soluble polymers, cleaning solutions can be aqueous and require no organic solvents. Sometimes warm water only is all that is required for the cleaning procedure. If the residues prove to be difficult to remove, brushes or plastic scrapers can be used.

3. Kollicoat MAE grades

3.1 Product range, structure, packaging

3.1.1 Product range

The Kollicoat MAE grades comprise two types differing in composition and form of availability. Kollicoat MAE 30DP is an aqueous dispersion and Kollicoat MAE 100P a powder for preparing aqueous dispersions or solutions in organic solvents. The BASF article numbers are listed in Table 49.

Manufacture of both products is in Germany and in accordance with cGMP.

Table 49: Kollicoat MAE grades

Product	BASF article number	PBG number
Kollicoat MAE 30DP	50893396 (25 kg)	10209320
Kollicoat MAE 100P	51209751 (20 kg)	10234572

3.1.2 Chemical structure, composition

3.1.2.1 Kollicoat MAE 30DP

The chemical structure of both Kollicoat MAE grades consists of a methacrylic acid-ethyl acrylate co-polymer, the two monomers being bound in the molar ratio of 1:1. This is an anionic co-polymer that can be neutralised by bases such as sodium hydroxide. Fig. 24 illustrates the precise chemical structure. The mean molecular weight (Mw) is approximately 250,000.

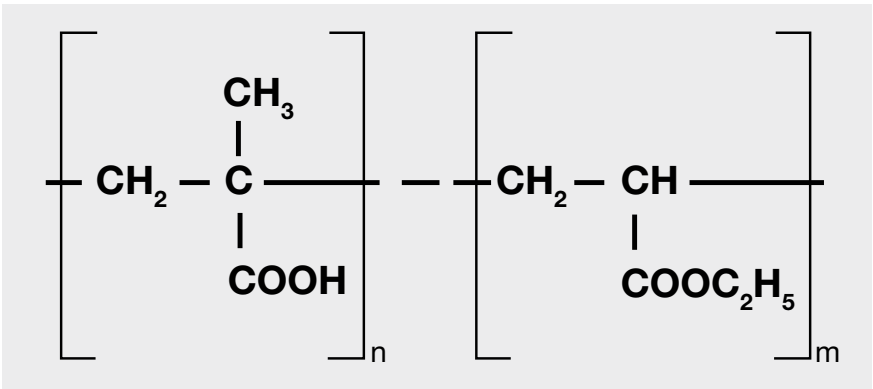


Fig. 24: Chemical structure of the polymer of the Kollicoat MAE grades

The aqueous dispersion Kollicoat MAE 30DP has a solid content of 30 %. Besides the methylacrylic acid-ethyl acrylate co-polymer, it contains two stabilisers; this constellation prevents sedimentation and separation of the co-polymer. The precise composition is shown in Table 50. The fatty components of both stabilisers are of plant origin.

Table 50: Composition of Kollicoat MAE 30DP

Components	Content
Methacrylic acid-ethyl acrylate co-polymer (1:1)	27.0 %
Polysorbate 80	2.3 %
Sodium lauryl sulphate	0.7 %
Water	70.0 %

3.1.2.2 Kollicoat MAE 100P

Kollicoat MAE 100P is a powder consisting mainly of the same methacrylic acid-ethyl acrylate co-polymer (1:1) as in Kollicoat MAE 30DP (see Fig. 24). It is manufactured from Kollicoat MAE 30DP; however, in this case, prior to drying, approx. 6 mole % of the co-polymer is neutralised with sodium hydroxide in order to enable it to be dispersed in water when used as a tablet coating. This partial neutralisation is reflected in the specifications by the higher value of sulphate ash. Without this, for this application, sodium hydroxide would have to be added as in the case of the competitive product to obtain a dispersion. In addition, Kollicoat MAE 100P, due to the manufacturing process used, contains the same two stabilisers as is the case in Kollicoat MAE 30DP. This is the reason why aqueous dispersions made from Kollicoat MAE 100P have the same application properties and the same physical stability. The precise composition of the powder is shown in Table 51.

Table 51: Composition of Kollicoat MAE 100P

Components	Content
Methacrylic acid-ethyl acrylate copolymer (1:1), partially neutralised with 6 mole % sodium hydroxide	97.0 %
Polysorbate 80	2.3 %
Sodium lauryl sulphate	0.7 %

3.1.3 Packaging

Due to the different forms available, the packaging of the two Kollicoat MAE grades is also different.
Kollicoat MAE 30DP is packaged in a 25 kg polyethylene drum (packaging article number 6700039). It can be obtained if required in 1000-L vessels.
Kollicoat MAE 100P in contrast is packaged in a 20 kg carton (packaging article number 67906095) with a polyethylene inliner.

3.2 Product properties

3.2.1 Description

As they are manufactured according to cGMP, both Kollicoat MAE grades possess high pharmaceutical quality. Kollicoat MAE 30DP is a low-viscosity, milk-like white dispersion with a solid content of 30 %; it has a typically slight inherent odour. Kollicoat MAE 100P is a white, powder that can be suspended in water and also has a slight characteristic odour.
If a drop of the aqueous dispersion (Kollicoat MAE 30DP directly produced or made from Kollicoat MAE 100P) is allowed to dry on a glass plate, a clear, brittle film is obtained.

3.2.2 Specifications, pharmacopoeias

Kollicoat MAE 30DP is included as a dispersion in monograph form in all important pharmacopoeias (European Pharmacopoeia, United States Pharmacopoeia, Japanese Pharmaceutical Excipients) and fulfils all the requirements of these pharmacopoeias.
Kollicoat MAE 100P corresponds to the specifications listed in the draft monograph [4] as published in the official Ph.Eur. newsletter “PHARMEUROPA”; this is scheduled to be published in the Ph.Eur. Supplement 5.7 in the course of 2006 and subsequently implemented.
A 30 % dispersion of Kollicoat MAE 100P in water corresponds to the same monographs as Kollicoat MAE 30 DP. Table 52 gives an overview of the various monographs and the corresponding pharmacopoeias.

Table 52: Pharmacopoeial monographs for the Kollicoat MAE grades

Product	Pharmacopoeia	Monograph title
Kollicoat MAE 30 DP	Ph.Eur.	Methacrylic acid – ethyl acrylate co-polymer (1:1), 30 % dispersion
	USP-NF	Methacrylic acid co-polymer dispersion
	JPE	Methacrylic acid co-polymer LD
Kollicoat MAE 100P	Ph.Eur.	Methacrylic acid-ethyl acrylate co-polymer (1:1), type B

Testing takes place according to the general methods listed in Ph.Eur. or with methods developed specially by BASF AG for the Kollicoat MAE grades. These can be obtained upon request. Table 53 lists the current valid parameters, limits and methods. The actual specifications are listed in the current technical data sheets for the relevant products.

Table 53: Specifications for the Kollicoat MAE grades

Parameter	Kollicoat MAE 30DP	Kollicoat MAE 100P	Method
Identity	Corresponds	Corresponds	Ph. Eur.
Appearance of the film	Corresponds	Corresponds	Ph. Eur.
Viscosity	Max. 15 mPa·s	Max. 100 mPa·s	Ph. Eur. (see below)
Agglomerates	Max. 1.0 %	--	(see below)
Acid value	300-330 mg KOH/g dry substance	280-310 mg KOH/g dry substance	DIN 53402
pH	2.0 – 3.0	--	Ph. Eur.
Density	1.062 – 1.072	--	DIN 53217
Solids content	28.5 – 31.5 %	Min. 95 %	Ph. Eur.
Methacrylic acid units	46.0 – 50.6 %	43.2 – 47.6 %	Ph. Eur.
Monomers (total)	Max. 100 ppm	Max. 100 ppm	Ph. Eur.
Arsenic	Max. 1 ppm	Max. 2 ppm	USP
Heavy metals	Max. 20 ppm	Max. 20 ppm	Ph. Eur.
Sulphate ash	Max. 0.1 %	Max. 3.0 %	Ph. Eur.
Organic volatile impurities	Corresponds	Corresponds	USP
Microbiology	Corresponds to categories 2 and 3A	Corresponds to categories 2 and 3A	Ph. Eur.

The viscosity of Kollicoat MAE 30DP is determined according to the Ph.Eur. monograph or EN ISO 3219 using a shear rate of 250 s^{-1} at 20 °C.
The viscosity of Kollicoat MAE 100P is determined in a 20 % aqueous dispersion at 20 °C using a Brookfield Viscometer (rotor 2, 100 rpm). The dispersion should be stirred for 3 – 4 h prior to being determined (see chapter 3.2.4).

The content of agglomerates in Kollicoat MAE 30DP is determined by filtration of 100 g of product using a 90-µm sieve. The residue on the sieve is dried at 105 °C prior to being weighed.

3.2.3 Solubility, miscibility, dispersibility

3.2.3.1 Kollicoat MAE 30DP

Kollicoat MAE 30DP is excellently miscible with water in any ratio without losing its milky, white appearance. Even in a slightly alkaline aqueous medium it forms a clear solution. As can be seen in Fig. 25, dissolution begins at a pH of approx. 5.5 and increases rapidly with increasing pH [13]. Kollicoat MAE 30DP also dissolves readily in a ratio of 1:5 in 2-propanol, ethanol and acetone, forming a clear-to-slightly opalescent solution. When the organic solvent is being initially added, a precipitate is formed; however, this is redissolved on adding further solvent.

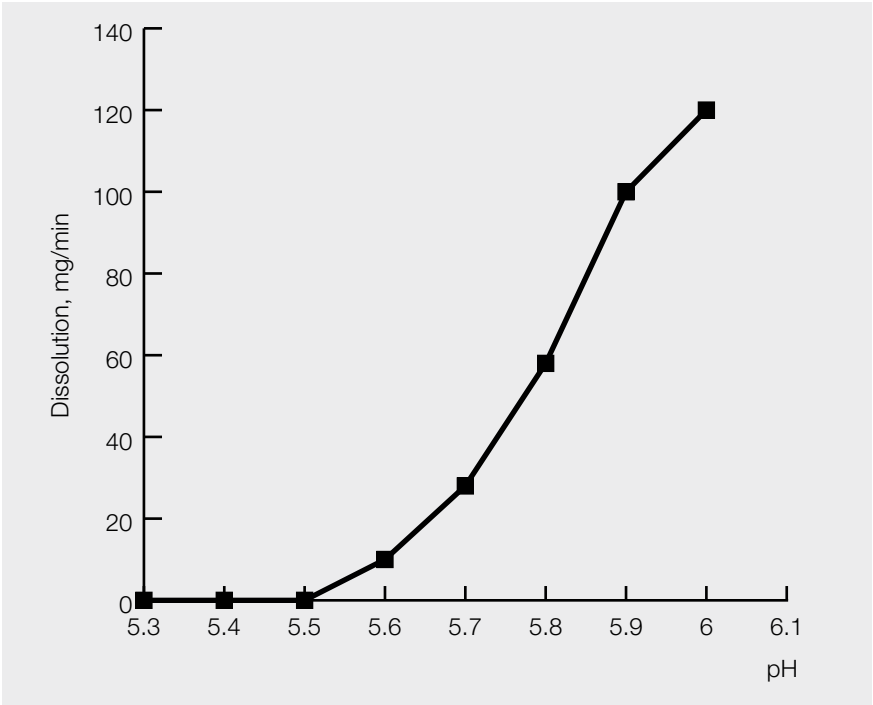


Fig. 25: Dissolution of Kollicoat MAE 30DP in aqueous medium as a function of pH

3.2.3.2 Kollicoat MAE 100P

Kollicoat MAE 100P, due to its partial neutralisation, can be directly dispersed in water without the need for alkaline additives such as sodium hydroxide. In this way, dispersions are obtained with practically the same properties as Kollicoat MAE 30DP and its aqueous dilutions. When dispersing in water, the following points have to be taken into account:

- The product must be added slowly to well-stirred water.
- Especially at the beginning when the viscosity increases, too much air should not be incorporated by the stirring action.
- The product should be added in such a way that the powder is wetted immediately and no lumps are formed.
- A stirrer should be used that can cope with the initial rapid increase in viscosity.
- Foaming should be kept to a minimum.

Stirrers with no horizontal blades are preferable, e.g. paddle stirrers. The initial high viscosity is reduced during the dispersion process (see chapter 3.2.4). Manufacture of a completely homogeneous dispersion takes 2 – 4 h when continuously stirred. For tablet, capsule and granule coatings, a dispersion consisting of 20 % solids has proven to be effective.

Kollicoat MAE 100P, just like Kollicoat MAE 30DP, dissolves in slightly alkaline, aqueous milieu (see Fig. 25). It is also readily soluble in ethanol and methanol.

3.2.4 Viscosity

The viscosity of Kollicoat MAE 30DP is so low that it is practically non-discernible with the naked eye. It is normally within the range 5 – 10 mPa.s. This makes it suitable for spraying tablets if the coatings are to contain relatively high concentrations of solid (e.g. 15 % polymer and 5 % pigments and talcum).

In preparing an aqueous dispersion of Kollicoat MAE 100P, the viscosity increases very rapidly to about 100 mPa·s within the first few minutes due to the initial swelling and surface viscosity of the particles. This then decreases slowly to 30 – 40 mPa·s after a longer period of stirring. It is thus recommended that the dispersion be stirred for at least three hours; in this way, it can be readily sprayed. Fig. 26 shows viscosity as a function of stirring time for a 20 % dispersion.

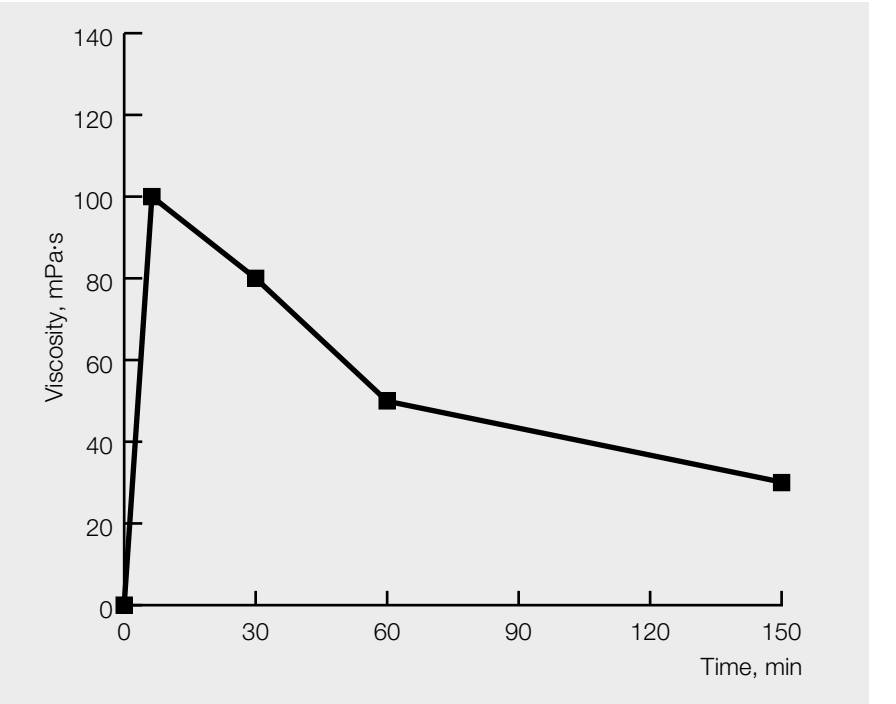


Fig. 26: Viscosity of 20 % Kollicoat MAE 100P on dispersing in water as a function of stirring time

3.2.5 Hygroscopicity

The hygroscopicity of the Kollicoat MAE grades is very low. This means that, even if stored in an open condition, adsorption of water is minimal. A tablet coated with Kollicoat MAE (8 mg/cm^2) when immersed in water for 2 hours adsorbs only less than 5 % of its coating weight (see chapter 3.2.7.2).

3.2.6 Particle size and bulk density

3.2.6.1 Kollicoat MAE 30DP

The suspended particles of a dispersion of Kollicoat MAE 30DP are so fine that they do not sediment during storage. They also coagulate well to form a film on the surface of tablets if the minimum film-forming temperature (MFT) is exceeded. The mean size of the latex particles is normally within the range of 120 nm and distribution is according to a Gauß curve. Fig. 27 shows a typical example.

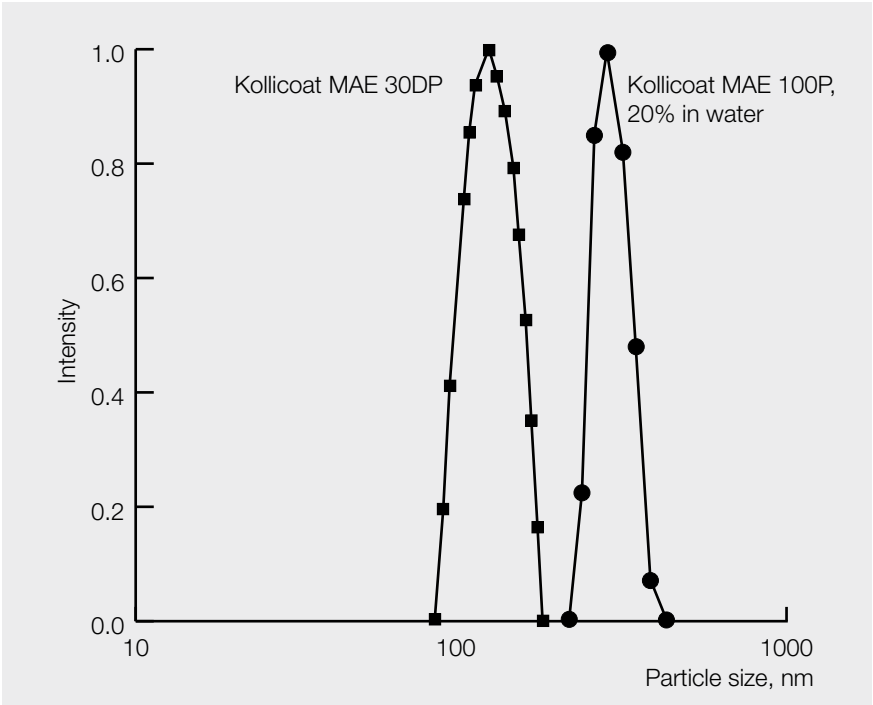


Fig. 27: Particle size distribution of a batch of Kollicoat MAE 30DP and a redispersed batch of Kollicoat MAE 100P (20 % in water)

3.2.6.2 Kollicoat MAE 100P

The mean particle size of commercially available Kollicoat MAE 100P is approximately 120 µm (typical value). In contrast to the latex particles in Kollicoat MAE 30DP, the size of the powder particles of Kollicoat MAE 100P is of minor importance for applications and for its stability.
If 20 % Kollicoat MAE 100P is dispersed in water as described in chapter 3.2.3.2, the suspended latex particles have a mean diameter of approximately 300 nm (typical value, see Fig. 27).

The bulk density of Kollicoat MAE 100P is normally within the range 0.3 – 0.5 g/ml.

3.2.7 Properties of Kollicoat MAE films

3.2.7.1 Plasticity, elongation at break, minimum film-forming temperature

The films that are obtained from dispersions of Kollicoat MAE 30DP and Kollicoat MAE 100P are practically identical. They are brittle and have an elongation at break of under 1 %. For this reason, a plasticizer must always be added for applications; this gives the product the necessary plasticity and enables the minimum film-forming temperature to be reduced. Fig. 28 shows the influence of various concentrations of triethyl citrate as a plasticizer on the plasticity of Kollicoat MAE films. The addition of 10 % (based on the polymer) has little influence on the plasticity; however, 20 % triethyl citrate increases the elongation at break to over 12 %.

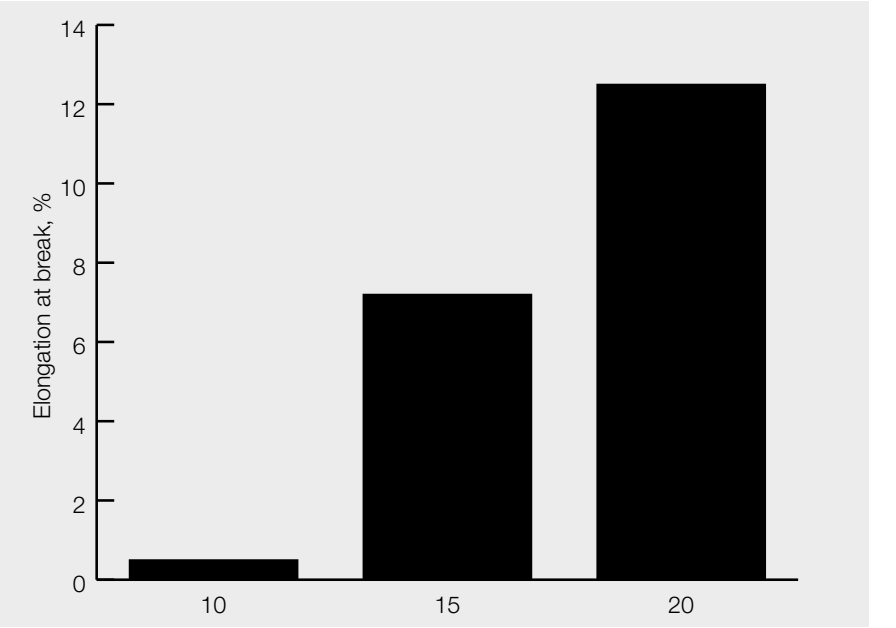


Fig. 28: Elongation at break of Kollicoat MAE films as a function of the concentration of plasticizer triethyl citrate

For the formation of a closed film of dispersed latex polymer particles on the tablet surface, the minimum film-forming temperature (MFT) must be significantly exceeded (see chapter 3.3.1). A schematic illustration of film formation is shown in chapter 4.2.7.2. It is recommended that the temperature of the cores during the spraying process is at least 20 °C over the MFT. This can be best achieved by adding a plasticizer that reduces this temperature. In the case of Kollicoat MAE films without any additives, the MFT is 22 – 27 °C; this is too high for acceptable film formation during the spraying process. Table 54 shows the influence of various plasticizers on the MFT [5].
The addition of triethyl citrate or triacetin e.g. lowers the MFT to below 0 °C. Some plasticizers even raise the MFT.

Table 54: Influence of various plasticizers on the MFT of Kollicoat MAE films [5].

Plasticizer	**10 % additive**	**20 % additive**
No plasticizer: 27 °C		
Triethyl citrate	< 0 °C	< 0 °C
Acetyltriethyl citrate	10 °C	6 °C
Tributyl citrate	39 °C	29 °C
Acetyltributyl citrate	40 °C	33 °C
Triacetin	< 0 °C	< 0 °C
Dibutyl phthalate	41 °C	35 °C
Macrogol 6000	15 °C	< 0 °C

Fig. 29 shows how the plasticizer 1,2-propylene glycol, not listed in table 54, lowers the MFT in concentrations of 10 and 20 % (based on the polymer) to 4 °C .

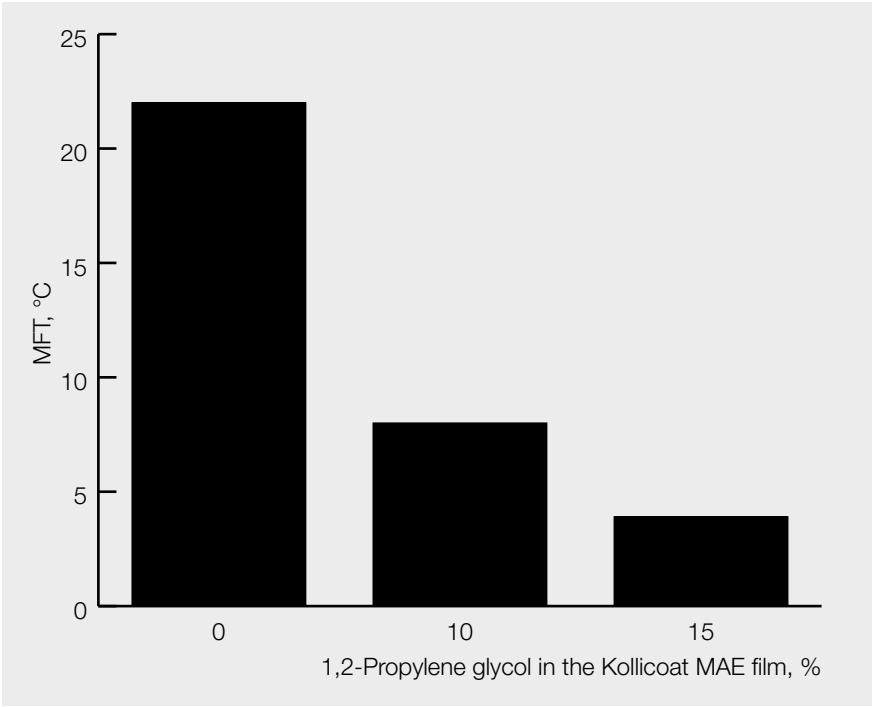


Fig. 29: Influence of plasticizer 1,2-propylene glycol on the minimum film-forming temperature (MFT) of Kollicoat MAE films

3.2.7.2 Dissolution behaviour and water uptake of Kollicoat MAE films

Kollicoat MAE films are completely insoluble in acid medium (e.g. 0.1 N hydrochloric acid or gastric juice). However, at pH 5.5 and above, they dissolve at increasing speed. Details are given in chapter 3.2.3, Fig 25. For this reason, the films are optimally suited for gastric juice-resistant (enteric) tablet coatings that dissolve only after passing through the stomach.

Due to the low hygroscopicity of the Kollicoat MAE polymer, the films, including plasticizers and pigments, adsorb very little water. To demonstrate this, caffeine tablet cores containing the strongly hygroscopic disintegrant crospovidone (Kollidon CL [3]) were coated with an 8 mg/cm^2 thick coating. To enable comparison to be made, Kollicoat MAE, the gastric juice-resistant polymers hydroxypropylmethyl cellulose-acetate succinate (HPMC-AS), cellulose acetate phthalate (CAP) and hydroxypropylmethyl cellulose phthalate (HPMCP) were sprayed onto the cores. These, as is the case with Kollicoat MAE, can be processed in the form of aqueous suspensions containing plasticizers and pigments.

The coated tablets were agitated for two hours at 37 °C in artificial gastric juice in a tablet dissolution apparatus. The increase in weight was then determined. Fig. 30 shows that the adsorption, at 3 – 4 %, was significantly lower in the case of tablets coated with Kollicoat MAE. As the tablets were gastric juice-resistant, and as no disintegration was observed after 2 hours in the gastric juice as a result of Kollidon CL (which swells in water), it can be assumed that the water was adsorbed only by the tablet coatings.

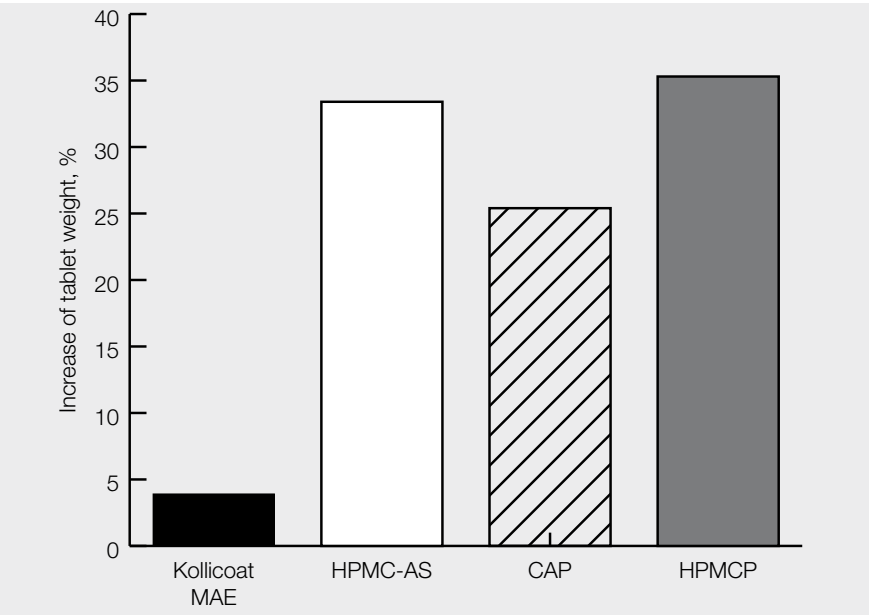


Fig. 30: Water uptake by gastric juice-resistant (enteric) caffeine tablets coated with various polymers subsequent to immersion in gastric juice during 2 hours (8 mg coating/cm^2)

3.2.7.3 Water vapour permeability of films

The water vapour permeability of the Kollicoat MAE films was tested at a relative humidity of 85 % and compared to two other film-forming agents (cellulose acetate phthalate and hydroxypropylmethyl cellulose-acetate succinate) that are also used as enteric coatings.15 % triethyl acetate was added as a plasticizer. Fig. 31 shows that the permeability to water vapour, calculated to represent one day, of the Kollicoat MAE films of coating thickness 100 µm was 75 g.100µm/m^2·d – less than one third of that of cellulose derivatives CAP and HPMC-AS.

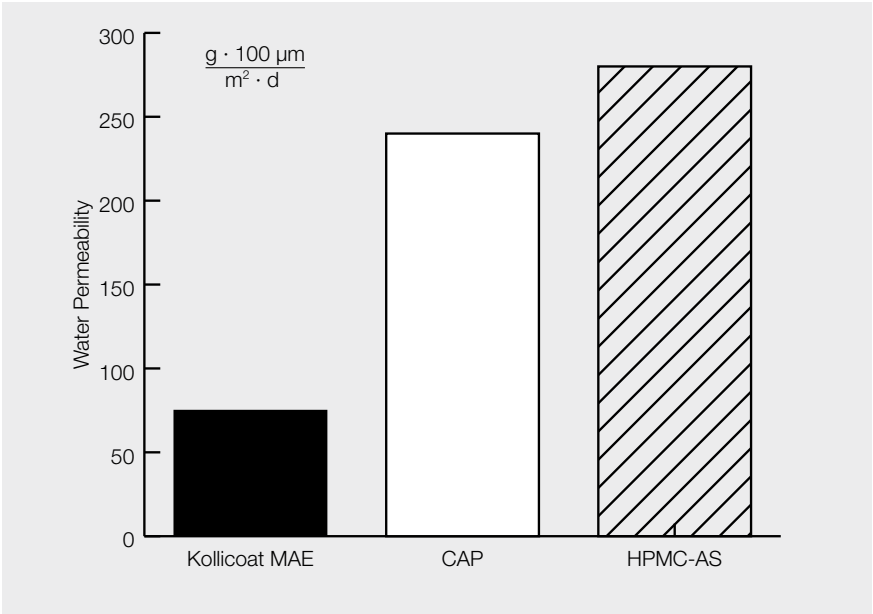


Fig. 31: Water permeability of polymer films at 85 % relative humidity

3.2.7.4 Proton permeability of films

The permeability of Kollicoat MAE films to protons is an important factor for the gastric juice resistance of coated tablets and capsules. This was measured in 0.1 N hydrochloric acid in a permeability cell using two isolated films to which pigments and talcum had been added. Measurement was made after 2 hours and calculated to represent a film thickness of 100 µm. The spray suspension of the films used as comparators were also aqueous in nature and contained the polymers hydroxypropylmethyl cellulose-acetate succinate (HPMC-AS), cellulose acetate phthalate (CAP) and hydroxypropylmethyl cellulose phthalate (HPMCP). The results shown in Fig. 32 show that the proton penetration of the Kollicoat MAE films is only a fraction of the cellulose derivative films used for comparison.

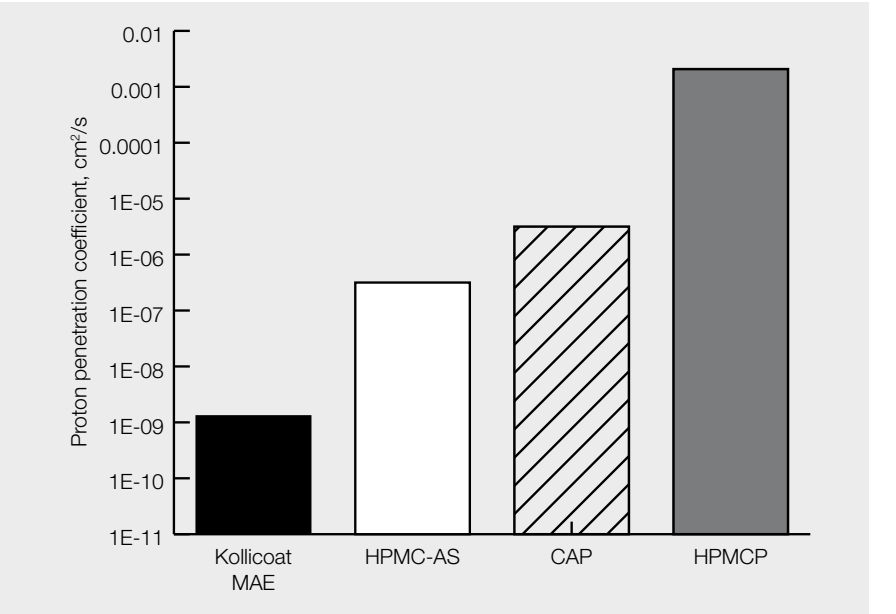


Fig. 32: Proton penetration of films made of gastric juice-resistant polymers containing pigments and talcum after 2 hours

3.2.8 Stability, storage

Both Kollicoat MAE grades fulfil the specifications as listed in chapter 3.2.2 regarding storage for at least 18 months in unopened packages at room temperature.

If the Kollicoat MAE 30DP dispersion is subjected to temperatures below 0 °C or if it is shaken too vigorously so that strong foaming occurs, the particles may coagulate. The product can then no longer be sprayed. Temperatures of over 30 °C should, however, also be avoided.
Kollicoat MAE 100P in powder form has a major advantage over the dispersion in that it is insensitive to such high and low temperatures. This can be a major advantage in countries with warm or cold climates.

If a container of Kollicoat MAE 30DP dispersion has been opened but not used up, care must be taken to ensure that no microbiological contamination occurs. For this reason, such a container, once opened, should be securely closed after use and used up as quickly as possible thereafter.

3.3 Applications of the Kollicoat MAE grades

3.3.1 General

The applications for both Kollicoat MAE grades are the same: the preparation of enteric tablets, capsules, granules and crystals. Tablets and capsules are normally coated with 3 – 6 mg solid/cm^2. This means that the tablet or capsule surface increases in weight by 4 – 8 % depending on the type of surface. In the case of pellets rendered spherical, granules or crystals, larger amounts (in %) are required to obtain the same coating thickness. Thus, in the case of crystals with large and irregular surfaces and depending on the diameter and structure of the particles, up to 30 % increase in weight can occur for gastric juice-resistant applications.
Apart from this application as an enteric coating, coatings with the Kollicoat MAE grades can be used to mask unpleasant tastes or to protect from the effects of high humidity.

All formulations of spray suspensions of Kollicoat MAE require the presence of a plasticizer as otherwise the plasticity of the polymer would be too low and the minimum film-forming temperature (MFT), approx. 27 °C, too high (see chapter 3.2.7.1). The amount of plasticizer required is generally within the range 15 – 20 % based on the polymer. Triethyl citrate and, especially, 1,2-propylene glycol have proven to be suitable for this purpose. The two scanning electron microscope (SEM) diagrams in Fig. 33 illustrate just how film formation proceeds and how it is dependent on the MFT. Fig. 33A shows an acrylate film with still separate latex particles of the suspension below the MFT. Fig. 33B shows a homogeneous film at the end of the process above the MFT [6].

In formulations containing Kollicoat MAE grades, it should be taken into account that these polymers can initiate numerous incompatibilities with and between other excipients; these can result in coagulation of the particles of the dispersion. Table 55 shows the interactions that can take place between plasticizers and surfactants in various concentrations and povidone K30 when used as a normal stabiliser of the pigment suspension in a spray suspension of Kollicoat MAE. The only excipients tested that showed no reaction were plasticizers 1,2-propylene glycol and macrogol 6000. With no povidone K30, such reactions occurred just as rarely as in spray suspensions with other film-forming agents and all the mentioned excipients, including povidone. The reactions caused were initiated by the ionic Kollicoat MAE polymer. Similar effects were observed with Kollicoat MAE 30DP in the presence of talcum and copovidone.

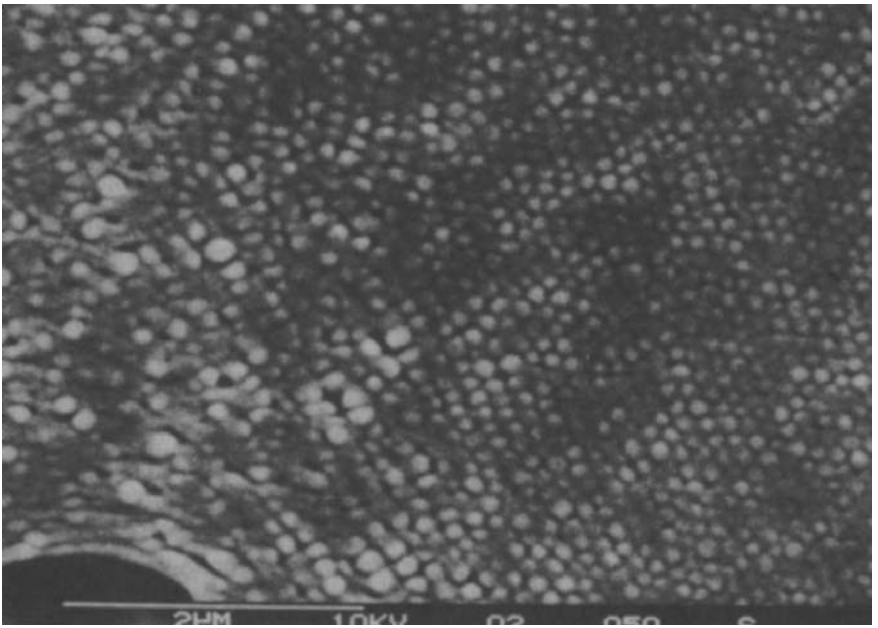


Fig. 33A: Film layer of separated acrylate latex particles of the dispersion prior to film formation below the MFT [6].

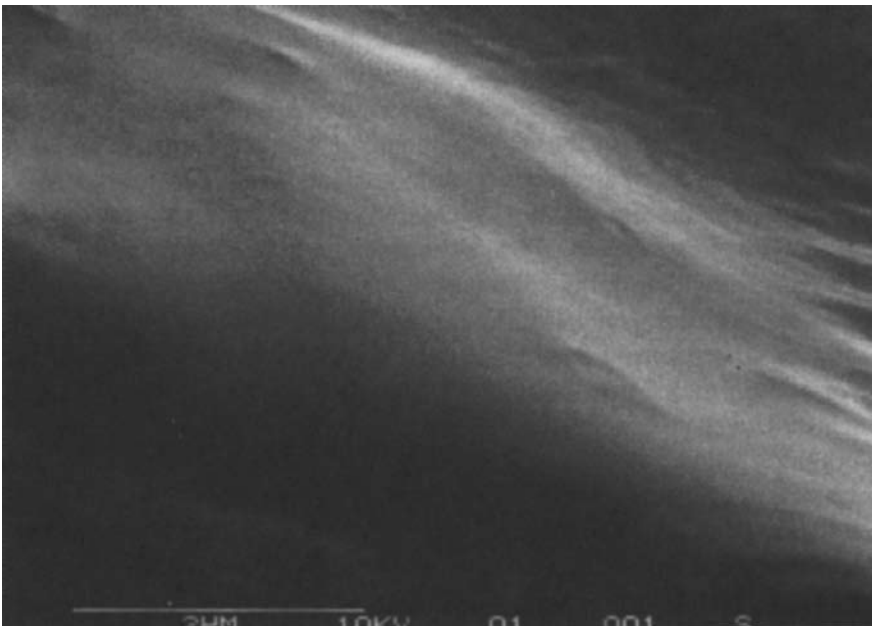


Fig. 33B: Homogeneous film subsequent to the formation of film by the particles from Fig. 33A above the MFT [6].

Table 55: Interaction brought about by Kollicoat MAE between povidone K30 and other excipients in spray suspensions

Excipient (besides povidone K30)	**Concentration of excipient based on Kollicoat MAE polymer**	**Observed interaction in the spray suspension**
1,2-Propylene glycol	10 % 20 % 30 %	None None None
Triethyl citrate	10 % 20 % 30 %	Initiation of coagulation Coagulation Coagulation
Macrogol 400 (Lutrol E400)	10 % 20 % 30 %	Coagulation Coagulation Coagulation
Macrogol 6000	10 % 20 % 30 %	None None None
Macrogol-glycerolhydroxy-stearate (Cremophor RH 40)	10 % 20 % 30 %	Initiation of coagulation Coagulation Coagulation

The favourable behaviour of 1,2-propylene glycol is a reason for recommending it as a plasticizer for Kollicoat MAE coatings and why it is used in all the formulations presented here. As tested in the case of enteric coated caffeine tablets, 1,2-propylene glycol in concentrations of 10 – 25 %, based on the polymer, had neither an influence on the resistance to gastric juice nor on the release of the active ingredient on adjusting the pH of the medium to pH 6.8 after 2 hours in artificial gastric juice.

The difference in the application of the two Kollicoat MAE grades is mainly in the preparation of the spray suspension. Preparation is easiest in the case of Kollicoat MAE 30DP. The prepared polymer dispersion is diluted with plasticizer solution and the homogenised pigment suspension stirred in.
In the case of Kollicoat MAE 100P, the powder must first be dispersed in water, as described in chapter 3.2.3.2. Only then can the plasticizer be added followed by mixing along with the homogenised pigment suspension. In addition, Kollicoat MAE 100P can be processed while in organic solution; however, today, for ecological reasons, this application is of secondary importance only. In this case, the spray suspension is prepared by dissolving the polymer in a mixture of 2-propanol and acetone and mixing this with the homogenised pigment suspension prior to spraying. Table 56 gives an overview of the differences and possibilities for preparing a spray suspension with the two Kollicoat MAE grades.

Table 56: General methods of manufacture of Kollicoat MAE spray suspensions

	Kollicoat MAE 30DP	**Kollicoat MAE 100P**
Manufacture of an aqueous polymer suspension	Dissolve the plasticizer in water and stir in Kollicoat MAE 30DP	Disperse the polymer in water, add the plasticizer and dissolve by stirring
Manufacture of organic polymer solution	--	Dissolve polymer and plasticizer in 2-propanol and acetone (1:1)
Manufacture of spray suspension	Stir the homogenised pigment suspension into the polymer suspension	Stir the homogenised pigment suspension into the polymer suspension/ solution

Release of the active ingredient after the prescribed 2 hours of gastric resistance is always identical in both Kollicoat MAE grades.

Some tablet cores contain water-sensitive active ingredients and their stability can be affected if water is able to enter and bring about hydrolysis. Also, if the tablet contains a highly effective disintegrant such as Kollidon CL, even small amounts of water can initiate swelling. In both cases either great care must be taken when spraying with the aqueous suspension, i.e. the procedure must be carried out slowly, or the cores have to be protected with a sub-coating. Sub-coating can be carried out as follows:

- Warm the cores in a coating apparatus to approx. 35 °C and spray on a 10 % solution of Kollidon VA64 in 2-propanol or ethanol until a coating thickness of e.g. 0.4 mg/cm^2 is attained. Then proceed to coating with Kollicoat MAE using the same apparatus.

Such a sub-coating is also recommended when the cores show a high degree of friability or if they are not hard enough.
The following formulations with enteric coated tablets or crystals of propranolol-HCl, acetylsalicylic acid and sodium diclofenac are typical examples of the application of Kollicoat MAE grades.

3.3.2 Formulations of enteric tablet coatings

3.3.2.1 Coloured enteric coating of propranolol tablets

In this example used for the comparison of the two Kollicoat MAE grades, tablet cores of the following composition were used:
Propranolol-HCl (40 mg), Ludipress (97.5 mg), Kollidon VA64 (12.5 mg), microcrystalline cellulose (97.5 mg), magnesium stearate (2.5 mg).

The red spray suspensions containing the Kollicoat MAE grades were prepared with the compositions shown in Table 57. They are intended for use in the film coating of approximately 5 kg of cores (250 mg, 9 mm) but can also be used for other cores of a similar size.

Table 57: Typical red spray suspensions with Kollicoat MAE 30DP or Kollicoat MAE 100P

	Weight (g) for 5 kg cores	%
Polymer suspension		
Alternative I		
Kollicoat MAE 30 DP	495.00	50.00
1,2-Propylene glycol	22.28	2.25
Water	319.27	32.25
Alternative II		
Kollicoat MAE 100P	148.50	15.00
1,2-Propylene glycol	22.28	2.25
Water	665.77	67.25
Pigment solution		
Talcum	39.60	4.0
Titanium dioxide	4.95	0.5
Sicovit red iron oxide	4.95	0.5
Water	103.95	10.5
Total	990.0	100.0

- Manufacture of the polymer suspension:
  Alternative I: Mix 1,2-propylene glycol with the water and stir in Kollicoat MAE 30DP.
  Alternative II: Disperse Kollicoat MAE 100P in water and stir for a further 3 hours. Add the 1,2-propylene glycol.
- Manufacture of the pigment suspension:
  Suspend both pigments and talcum under vigorous stirring and then homogenise in a corundum disk mill.
- Manufacture of the spray suspension:
  Stir the pigment suspension into the polymer suspension. Continue stirring the spray suspension during the entire coating procedure in order to prevent sedimentation.

The spray suspension was sprayed onto 5 kg of cores in a perforated Accela Cota 24" with a single nozzle under the machine settings listed in Table 58.

Table 58: Machine settings and spraying conditions (Accela Cota 24"); batch size: 5 kg)

Parameter	**Setting**
Inlet air temperature	50 °C
Outlet air temperature	37 °C
Core temperature	32 °C
Spray pressure	2 bar
Spray rate	40 g/min
Spraying time	30 min for 4 mg coating/cm^2
Drying time at end of process	5 min/50 °C
Amount applied	4 – 12 mg/cm^2

After coating with both alternatives (Kollicoat MAE 30DP or Kollicoat MAE 100P) and using various coating thicknesses, the release of active ingredient propranolol-HCl was checked according to Ph.Eur. No difference was established between the two Kollicoat MAE types (Fig. 34); however, a coating that was too thickly applied, e.g. 12 mg coating/cm^2, delayed release significantly once the pH was adjusted to 6.8 (Fig. 35). In this particular case, a coating of 6 mg /cm^2 proved best.

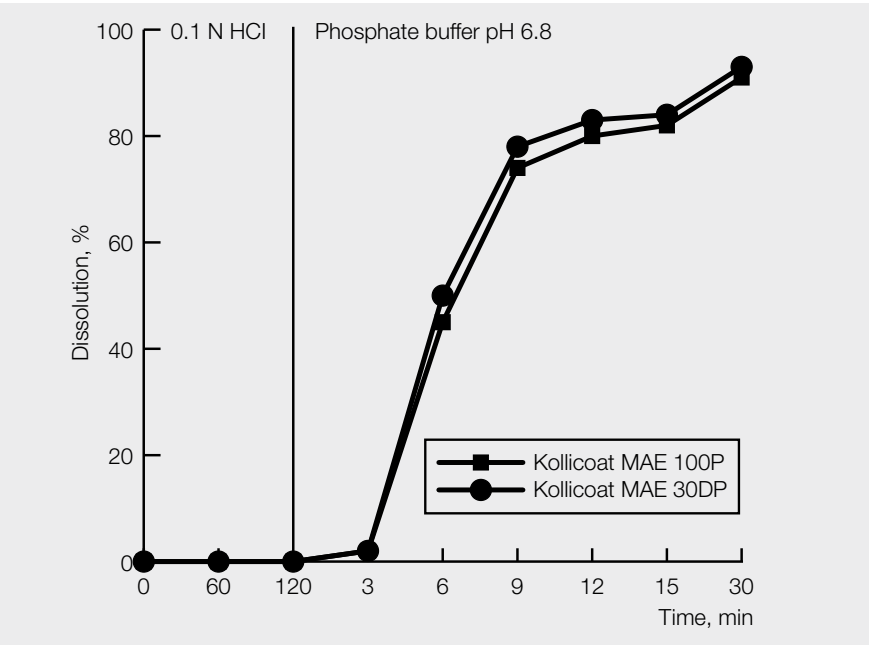


Fig. 34: Release of propranolol tablets coated with 6 mg/cm^2 Kollicoat MAE 30DP or Kollicoat MAE 100P

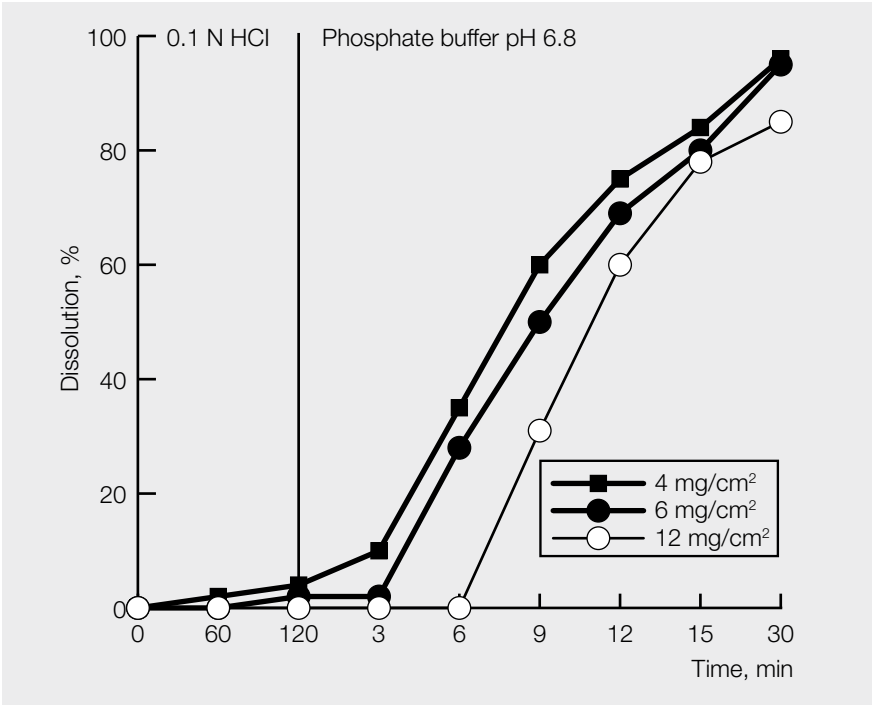


Fig. 35: Release of propranolol tablets as a function of the coating amount of Kollicoat MAE 100P (4, 6 and 12 mg/cm²)

3.3.2.2 Coloured enteric coating of acetylsalicylic acid tablets

This example was designed to compare the gastric juice resistance and the release of active ingredient subsequent to adjusting the pH to 6.8 with uncoated tablet cores. Cores of the following composition were produced: Acetylsalicylic acid (100.0 mg), Ludipress (148.5 mg), microcrystalline cellulose (50.0 mg), magnesium stearate (1.5 mg). The tablets had a weight of 300 mg, were formed as a bolus and had a diameter of 9 mm.

The spray formulation as described in chapter 3.3.2.1 (alternative I) was sprayed onto 5 kg of cores under the same conditions using an Accela Cota 24" machine (3 and 4 mg coating/cm²). Subsequently, the release of active ingredient from the coated tablets was determined after 2 hours of immersion in synthetic gastric juice and then in synthetic intestinal fluid and compared with that of uncoated cores in synthetic intestinal fluid only. Fig. 36 shows that the tablets were fully gastric juice-resistant with only 3 mg/cm² of coating and that active ingredient release from the tablets after changing the medium was almost as fast as from the uncoated cores.

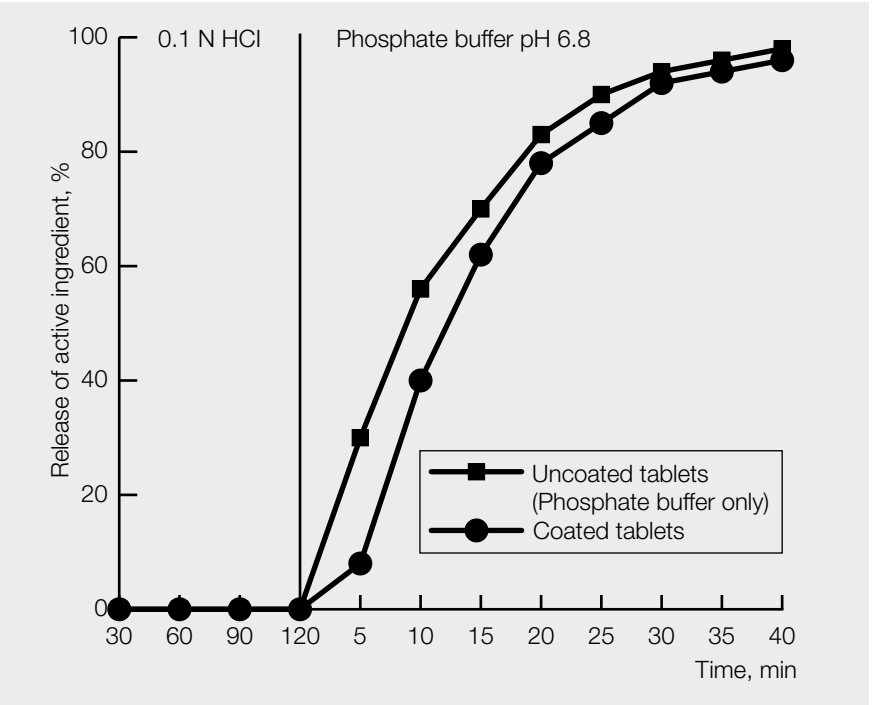


Fig. 36: Release of acetylsalicylic acid from tablets coated with Kollicoat MAE 30D compared with uncoated cores

3.3.2.3 Coloured enteric coating of diclofenac tablets

Diclofenac tends to irritate the stomach mucosa and is hence often coated with an enteric film.
In this case, tablet cores of the following composition were used:
Sodium diclofenac (49.7 mg), Ludipress 201.4 mg, Kollidon VA64 (14.9 mg), Kollidon CL (5.0 mg), Aerosil 200 (1.2 mg), magnesium stearate (2.8 mg).
The tablets had a weight of 275 mg and a diameter of 9 mm.

The spray formulation as described in chapter 3.3.2.1 (alternative I) was sprayed onto 5 kg of cores under the same conditions using an Accela Cota 24" machine (4 mg coating/cm^2). Subsequently, the release of the active ingredient from the coated tablets was measured after 2 hours immersion in 0.1 N hydrochloric acid and subsequently in a phosphate buffer of pH 6.8. Fig. 37 shows that the tablets were gastric juice-resistant during the 2 hours and that subsequently there was rapid release of active ingredient.

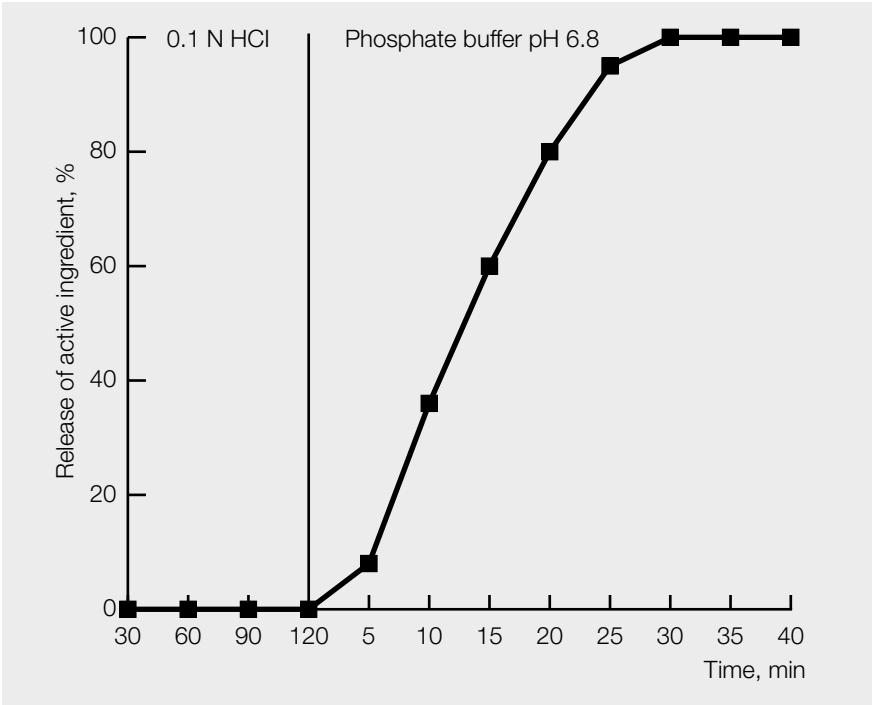


Fig. 37: Release of sodium diclofenac from tablets coated with Kollicoat MAE 30DP (4 mg /cm2)

3.3.3 Formulation of enteric coated pellets, granules and crystals

3.3.3.1 White enteric coating of diclofenac pellets

Gastric juice-resistant (enteric) pellets are also produced for marketing as hard gelatine capsules; these are filled into the capsules.
For this example application, uncoated pellets were produced with the following composition:
Sodium diclofenac 10 %, Kollidon VA64 2.5 %, microcrystalline cellulose 43.7 %, lactose monohydrate 43.7 %. The pellets, rendered spherical, had a diameter of 0.8 – 1.2 mm.

The spray suspensions containing both Kollicoat MAE grades were produced in the composition shown in Table 59 with a solid content of 22 % and a polymer content of 15 %. The indicated amounts were designed for coating 5 kg of pellets.

Table 59: Typical white spray suspensions with Kollicoat MAE 30DP or Kollicoat MAE 100P for pellets

	Weight (g) for 5 kg pellets	%
Polymer suspension:		
Alternative I		
Kollicoat MAE 30 DP	2250.0	50.0
1,2-Propylene glycol	67.5	1.5
Water	1435.0	31.9
Alternative II		
Kollicoat MAE 100P	675.0	15.0
1,2-Propylene glycol	67.5	1.5
Water	3010.5	66.9
Pigment solution		
Talcum	180.0	4.0
Titanium dioxide	45.0	1.0
Kollidon 30	22.5	0.5
Water	500.0	11.1
Total	4500.0	100.0

- Manufacture of polymer suspension
  Alternative I: Mix 1,2-propylene glycol with the water and stir in Kollicoat MAE 30DP.
  Alternative II: Suspend Kollicoat MAE 100P in water, stir for a further 3 hours and add the 1,2-propylene glycol.
- Manufacture of the pigment suspension:
  Dissolve Kollidon 30 in water, suspend the white pigment and the talcum under vigorous stirring and homogenise in a corundum disk mill.
- Manufacture of the spray suspension:
  Stir the homogenised pigment suspension into the polymer suspension. Continue stirring the spray suspension during the entire coating procedure in order to prevent sedimentation.

The spray suspension was sprayed onto 5 kg of pellets in a Hüttlin Kugelcoater HKC 5 TJ (Hüttlin) under the conditions listed in Table 60.

Table 60: Machine settings and spraying conditions (Hüttlin Kugelcoater – batch size: 5 kg)

Parameter	Setting
Inlet air temperature	60 °C
Outlet air temperature	32 – 35 °C
Spray rate	45 g/min
Spraying time	100 min
Total amount applied	3 mg/cm^2

The release of sodium diclofenac was tested using the coated pellets by placing them in artificial gastric juice and subsequently in artificial intestinal fluid for a period of 2 hours. Fig. 38 shows that the pellets released practically no active ingredient over the first two hours.

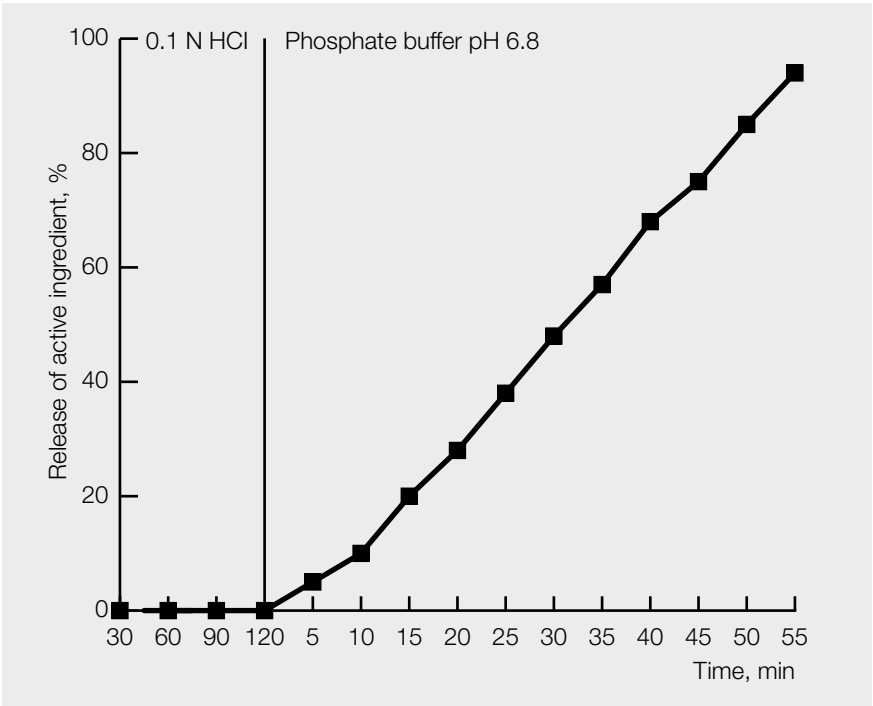


Fig. 38: Active ingredient release in enteric coated diclofenac pellets (3 mg coating/cm²)

3.3.3.2 Coloured enteric coating of acetylsalicylic acid crystals

The enteric coating of crystals is much more difficult than for tablets and pellets due to the greater and irregular surface area of the crystals. For this reason, the coating amounts required are significantly higher.

In this experiment, acetylsalicylic acid crystals of diameter 0.5 – 0.8 mm were used.

The spray suspension containing Kollicoat MAE 30DP was prepared with the composition shown in Table 61. It corresponded to alternative I as shown in Table 57 and had a solid content of 22.25 % and a polymer content of 15 %.

Table 61: Typical red spray suspension with Kollicoat MAE 30DP

	Weight (g) for 0.5 kg crystals	%
Polymer suspension		
Kollicoat MAE 30 DP	495.00	50.00
1,2-Propylene glycol	22.28	2.25
Water	319.27	32.25
Pigment solution:		
Talcum	39.60	4.0
Titanium dioxide	4.95	0.5
Sicovit red iron oxide	4.95	0.5
Water	103.95	10.5
Total	990.0	100.0

- Manufacture of polymer suspension:
  Mix 1,2-propylene glycol with the water and stir in Kollicoat MAE 30DP.
- Manufacture of the pigment suspension:
  Suspend both pigments and talcum under vigorous stirring and then homogenise in a corundum disk mill.
- Manufacture of the spray suspension:
  Stir the homogenised pigment suspension into the polymer suspension Continue stirring the spray suspension during the entire coating procedure in order to prevent sedimentation.

The spray suspension was sprayed onto 0.5 kg of crystals in an Aeromatic Strea® -1 fluidized bed granulator (Niro) using the “top spray” procedure under the conditions listed in Table 62.

Table 62: Machine settings and spraying conditions (Aeromatic Strea -1, batch size: 0.5 kg)

Parameter	Setting
Inlet air temperature	60 °C
Outlet air temperature	35 °C
Spray rate	30 – 35 g/min
Spraying nozzle	1 mm
Spray pressure	1 bar
Spraying time	100 min
Amount of solid applied	5.9 mg/cm^2 (weight increase 31 %)

Different amounts of spray suspension were sprayed onto the acetylsalicylic acid crystals within the range 3 to almost 6 mg/cm^2. Due to the fact that, at 4 mg/cm^2 after 2 hours in gastric juice, a too high proportion of the active ingredient was released due to the irregularity of the crystal surface, a coating of at least 6 mg/cm^2 is recommended. This corresponds to a polymer coating of approx. 30 %. Fig. 39 shows the release from crystals with a coating of 5.9 mg/cm^2 compared with uncoated crystals.

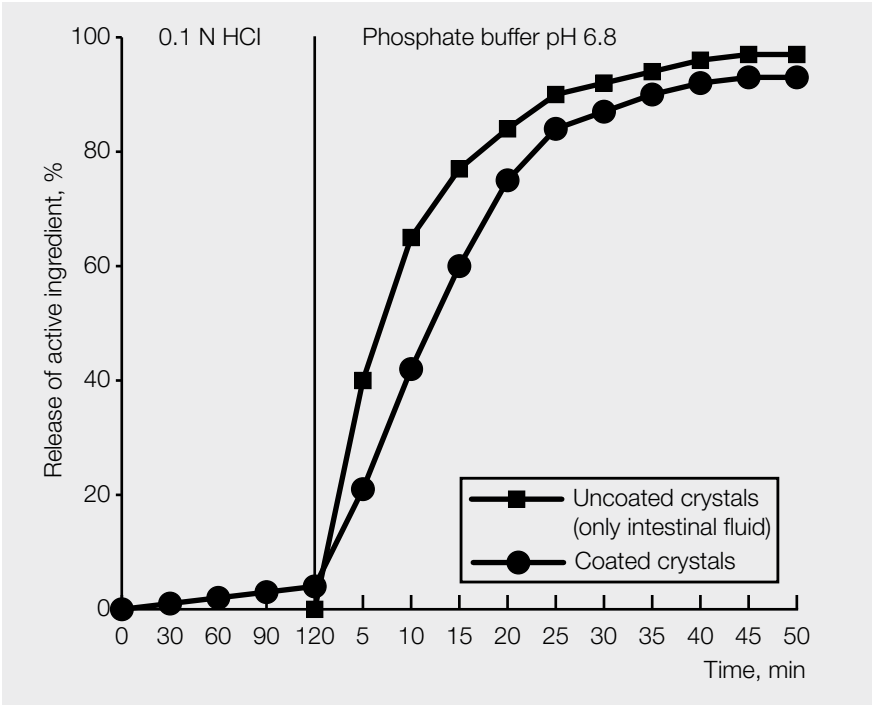


Fig 39: Release of active ingredient from crystals of acetylsalicylic acid coated with Kollicoat MAE 30D pre- and post-coating (5.9 mg coating/cm^2).

The influence of the Kollicoat MAE coating on stability in the form of the content of free salicylic acid generated due to hydrolysis was determined on storing coated acetylsalicylic acid crystals under various conditions. Table 63 shows that, even under stress conditions of 40 °C and a relative humidity of 75 %, only 1 % free salicylic acid was detected.

Table 63: Stability of acetylsalicylic acid crystals coated with Kollicoat MAE by measurement of the free salicylic acid produced by hydrolysis

Storage conditions	**Content of free salicylic acid**	
	3 months	**6 months**
Crystals prior to coating: 0.18 %		
25 °C/45 % relative humidity	0.22 %	0.50 %
30 °C/70 % relative humidity	0.71 %	0.84 %
40 °C/75 % relative humidity	1.02 %	-

3.3.4 Formulation of a transparent enteric coating for soft gelatine capsules

Kollicoat MAE grades can also be used for enteric coatings for soft gelatine capsules.

The formulation in Table 64 is designed for the coating of 5 kg of soft gelatine capsules. As this particular coating has to be extremely flexible, 20 % of the plasticizer 1,2-propylene glycol (based on the polymer) was added. Triethyl citrate (25 %) can also be used as an alternative. The spraying suspension comprises only highly concentrated polymer suspension without any addition of pigments and contains 25.2 % solid or 21 % polymer.

Table 64: Typical colourless spray suspensions with Kollicoat MAE 30DP or Kollicoat MAE 100P for soft gelatine capsules

	Weight (g) for 5 kg capsules	**%**
Alternative I		
Kollicoat MAE 30 DP	1680.0	70.0
1,2-Propylene glycol	100.8	4.2
Water	619.2	25.8
Alternative II		
Kollicoat MAE 100P	504.0	21.0
1,2-Propylene glycol	100.8	4.2
Water	1795.2	74.8
Total	2400.0	100.0

- Manufacture of polymer suspension
  Alternative I: Mix 1,2-propylene glycol with the water and stir in Kollicoat MAE 30DP.
  Alternative II: Suspend Kollicoat MAE 100P in water, stir for 3 hours and add the 1,2-propylene glycol.

The polymer suspension was sprayed onto 5 kg of soft gelatine capsules in a perforated Accela Cota 24” using the conditions and machine settings listed in Table 65.

Table 65: Machine settings and spraying conditions (Accela Cota 24", batch size: 5 kg), for coating soft gelatine capsules

Parameter	Setting
Inlet air temperature	50 °C
Core temperature	30 – 35 °C
Spray pressure	2 bar
Spray rate	30 – 50 g/min
Spraying time	70 min
Amount applied	12 mg solid/cm^2

3.3.5 Production times and costs of coating with Kollicoat MAE grades compared with other enteric film-forming agents

As today in the pharmaceutical industry – and not only for the production of generics – the question is always raised as to the costs of production, including that for coatings, this aspect has also been taken into account with respect to the use of Kollicoat MAE grades. The times required for the spraying of enteric coated tablets and for the subsequent drying and curing were established. The times required for the processing of Kollicoat MAE grades compared to those for other commercially available polymers for enteric coatings are listed in Fig. 40. Those used were the cellulose derivatives hydroxypropylmethyl cellulose phthalate in organic solution (HPMCP-SOLV), hydroxypropylmethyl cellulose phthalate in aqueous solution (HPMCP), hydroxypropylmethyl cellulose-acetate succinate (HPMC-AS) and cellulose acetate phthalate (CAP). It was taken into account that, for the Kollicoat MAE grades and for HPMCP-SOLV, a coating thickness of only 5.5 mg/cm^2 was necessary while double the thickness was required for the other polymers in preparing a good gastric juice-resistant (enteric) coating. The comparison shows that Kollicoat MAE is the most economical of the coatings as the processing time is the determining cost factor. In the case of HPMC-AS and, especially, CAP, the long subsequent curing period is relevant; this is necessary for homogeneous coating due to the high minimum film-forming temperature (MFT) of these polymers.

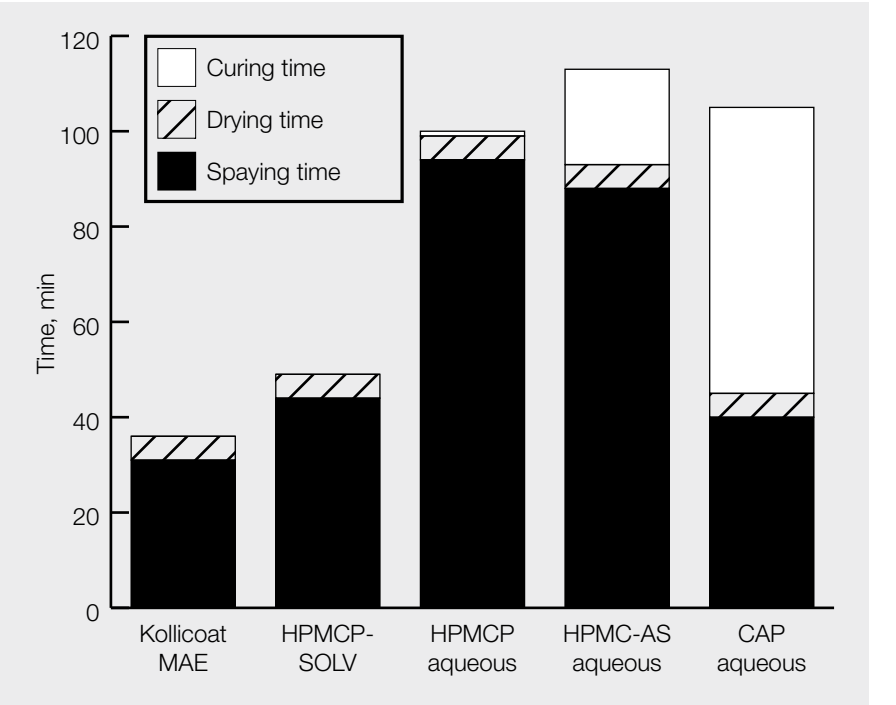
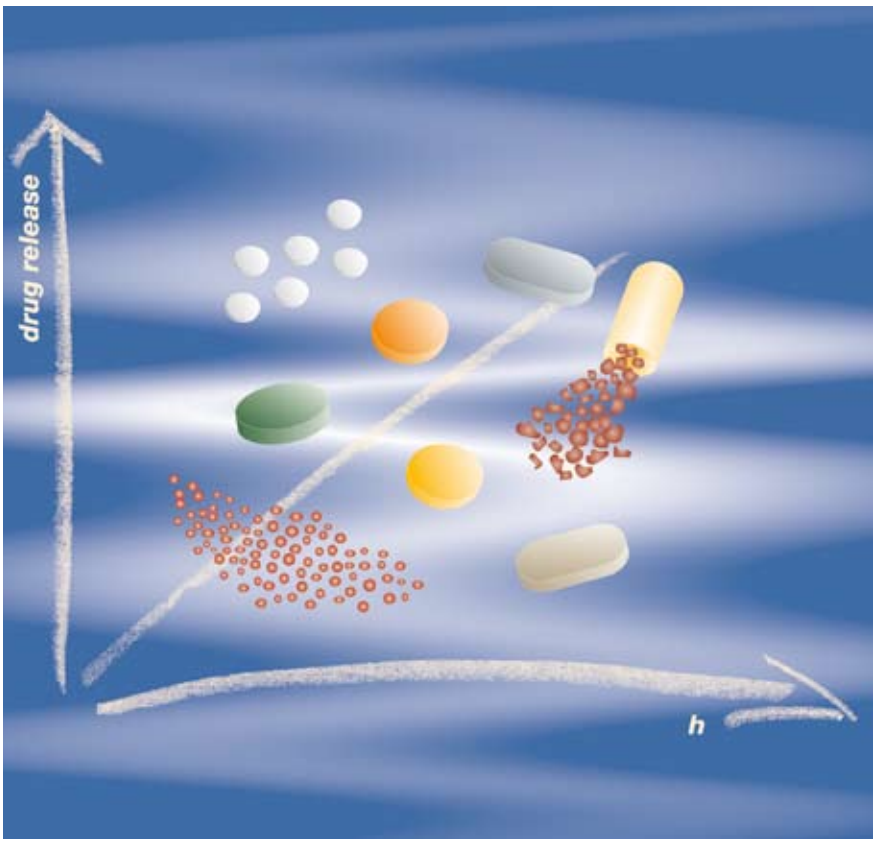


Fig. 40: Production times for the manufacture of enteric coatings with Kollicoat MAE and cellulose derivatives

3.3.6 Cleaning the machines after processing with Kollicoat MAE grades

When processing with coating spray suspensions, pigment and excipient residues often collect on the inside walls of the machine and in the tubing and spraying systems. As long as the films are in a fresh condition and capable of swelling, they can be mechanically removed with relative ease. Subsequent to longer drying periods, however, the films tend to harden. This renders cleaning somewhat more difficult.

As the Kollicoat MAE grades contain a polymer that is soluble in slightly alkaline medium, film residues can be easily removed with alkaline solution. A 5 – 10 % solution of sodium carbonate or sodium hydrogen carbonate in water has proven to be effective. Alkaline cleansing solutions such as those used for laboratory instruments are also suitable. If the residues prove to be difficult to remove, brushes or plastic scrapers can be used.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4. Kollicoat SR 30D

4.1 Chemical structure, composition, packaging

4.1.1 Chemical structure, composition

Kollicoat SR 30D is an aqueous dispersion of the homo-monomer polyvinyl acetate that is prepared from the monomer vinyl acetate; it has a solid content of 30 %. The dispersion contains the excipients povidone and sodium lauryl sulphate. The chemical structure of the polymer is illustrated in Fig. 41.

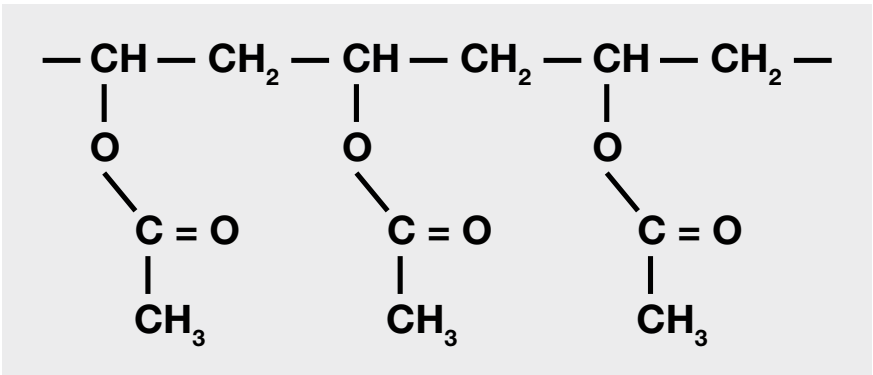


Fig. 41: Chemical structure of polyvinyl acetate

The excipients povidone (Kollidon 30) and sodium lauryl sulphate prevent sedimentation of the dispersed polyvinyl acetate latex particles during storage; their precise concentrations are given in Table 66. In addition, povidone increases the wettability and penetration of water of Kollicoat SR 30D films in gastric juice and intestinal fluid.

Table 66: Precise composition of the Kollicoat SR 30D dispersion

Components	Content
Polyvinyl acetate	27.0 %
Povidone K30 (Kollidon 30)	2.7 %
Sodium lauryl sulphate	0.3 %
Water	70.0 %

Kollicoat SR 30D has the BASF article number 50893290 (25 kg) and the PBG number 10201076.

4.1.2 Packaging

The standard packaging of the aqueous dispersion Kollicoat SR 30D consists of 25-L polyethylene drums. The packaging material number is on the exterior (67000739). Larger packages are available upon request.

Kollicoat SR 30D is practically insensitive to microbiological contamination. Thus, normally, once opened, the package can be reused providing it has been securely closed in the meantime.

4.2 Product properties

4.2.1 Description

As Kollicoat SR 30D is produced according to cGMP in Ludwigshafen, Germany, it is of high pharmaceutical quality. The suspension has a milky white-to-yellow appearance and has a slight characteristic odour.
The weight average molecular weight (Mw) of the polymer polyvinyl acetate in Kollicoat SR 30D is approximately 450,000. The viscosity average molecular weight (Mv) can also be characterised by the K-value [3]; this is normally within the range 65 – 85.

4.2.2 Specifications, pharmacopoeias

By 2005, the polyvinyl acetate dispersion had not been included as a monograph in any of the pharmacopoeias; however, inclusion of the monograph is planned for the European Pharmacopoeia (Ph.Eur.). Initial draft monographs have already been published in the official Ph.Eur. newsletter "PHARMEUROPA" under the title "Poly(vinyl acetate) dispersion 30 per cent" [7, 8]. Kollicoat SR 30D corresponds to the final draft of 2005 that replaced the initial version and is scheduled to be included in Ph.Eur. Supplement 5.8 published at the end of 2006.

The two stabilisers also used, Kollidon 30 and sodium lauryl sulphate, are also of pharmacopoeial quality.

The current specifications of Kollicoat SR 30D are shown in Table 67.
The general methods used are those of Ph.Eur; however, some have been specially developed for this product by BASF. These methods can be made available on request. The actual specifications are listed in the current technical data sheet.

Table 67: Specifications of Kollicoat SR 30D

Parameter	Limit	Method
Identity	Corresponds	See below
Film formation	Corresponds	See below
pH	3.5 – 5.5	Ph.Eur.
Relative density	1.045 – 1.065	Ph.Eur.
Viscosity	Max. 100 mPa.s	Ph.Eur. or see below
Agglomerates	Max. 0.5 %	See below
Solid content	28.5 – 31.5 %	[8]
Sulphate ash	Max. 0.5 %	Ph.Eur.
Heavy metals	Max. 20 ppm	Ph.Eur.
Vinyl acetate monomer	Max. 100 ppm	HPLC [3, 8]
Microbiological status	Corresponds to category 3	Ph.Eur.

Identification is carried out using the following test procedure:
A film is compared to a reference spectrum using infrared spectroscopy.

Film formation is carried out using the following test procedure:
Mix 10 g Kollicoat SR 30D with 0.3 g of 1,2-propylene glycol, spread on a glass slide and allowed to dry. A colourless or slightly yellow film is formed.

The viscosity is measured with a Brookfield rotation viscosimeter according to DIN EN ISO 3219 at 20 °C and a shear of 100 rpm. An increase in the rotatory speed to 100 per second e.g. (see Ph.Eur. draft monograph) would, in the case of a thixotropic dispersion such as Kollicoat SR 30D, give rise to a decrease in viscosity although it would remain within specification.

The percentage of agglomerates can be measured using the following method:
100 g of Kollicoat SR 30D are passed through a 90-µm sieve. The residue is dried to constant weight at 105 °C and weighed.

4.2.3 Solubility, miscibility

Kollicoat SR 30D is miscible with water in any ratio and does not lose its milky appearance. If mixed with ethanol or 2-propanol in the ratio of 1:5, a slightly turbid solution of somewhat increased viscosity results. Solubility in acetone is slightly lower than in ethanol. On adding less hydrophilic organic solvents, the polymer first precipitates but dissolves again on adding further solvent.
Kollicoat SR 30D is insoluble in dilute acids or bases and retains its typical appearance in their presence.

4.2.4 Viscosity

The viscosity of Kollicoat SR 30D is always below 100 mPa·s. For this reason, it is practically always possible to use a higher concentration of the dispersion for spraying purposes. The viscosity can in fact be lowered a little by warming. Addition of ethanol or 2-propanol increases the viscosity slightly.

4.2.5 Hygroscopicity

The solid content of Kollicoat SR 30D has a very low degree of hygroscopicity. This is reflected in the low water uptake and practical non-existence of tackiness of the films.

4.2.6 Particle size

Dispersed particles of polyvinyl acetate latex in Kollicoat SR 30D normally have a mean diameter of approximately 170 nm (typical value). They are thus so fine that, under normal conditions, no sedimentation occurs. However, high temperatures, frost and too high a shear force brought about by vigorous stirring should be avoided otherwise agglomerates can form that make spraying impossible.

4.2.7 Properties of Kollicoat SR films

4.2.7.1 Dissolution behaviour

Kollicoat SR 30D films are insoluble in dilute acid and dilute alkali, e.g. artificial gastric juice and intestinal fluid. For this reason, they are excellently suited for use as sustained release polymers; this is because they enable active ingredient to be released, controlled principally by diffusion, over a longer period of time, depending on their coating thicknesses, solubility and any pore-forming additives contained.

4.2.7.2 Plasticity, minimum film-forming temperature (MFT)

The plasticity of Kollicoat SR 30D is high enough that, for some applications, no plasticizer is required. Mostly, however, a 10 % content of plasticizer, e.g. 1,2-propylene glycol, triethyl acetate or triacetin, is meaningful or even necessary if the plasticity or the elongation at break is to be increased. The fact that 10 % is adequate can be seen in Fig. 42, where the elongation at break of isolated films of thickness 150 µm and the addition of 5 and 10 % plasticizer at 23 °C and 54 % relative humidity is shown. Elongation at break values of 300 % and over have been achieved with only 10 % content. Interestingly enough, this also applies to 2-pyrrolidone (Soluphor P); this, to date, has rarely been used as a plasticizer but rather as a retarding co-solvent in parenteral products for veterinary applications.

The addition of a plasticizer is especially important if the granules or pellets coated with Kollicoat SR 30D are to be subsequently compressed to tablets. This is because there is a substantial mechanical stress on the coatings. Plasticity also plays a very important role in the case of sustained release film coatings of tablets as it helps to avoid cracks and other damage and even renders these reversible. A comparison with other film-forming agents such as ethyl cellulose regarding plasticity is given in chapters 4.3.3.1 and 4.3.5.1.

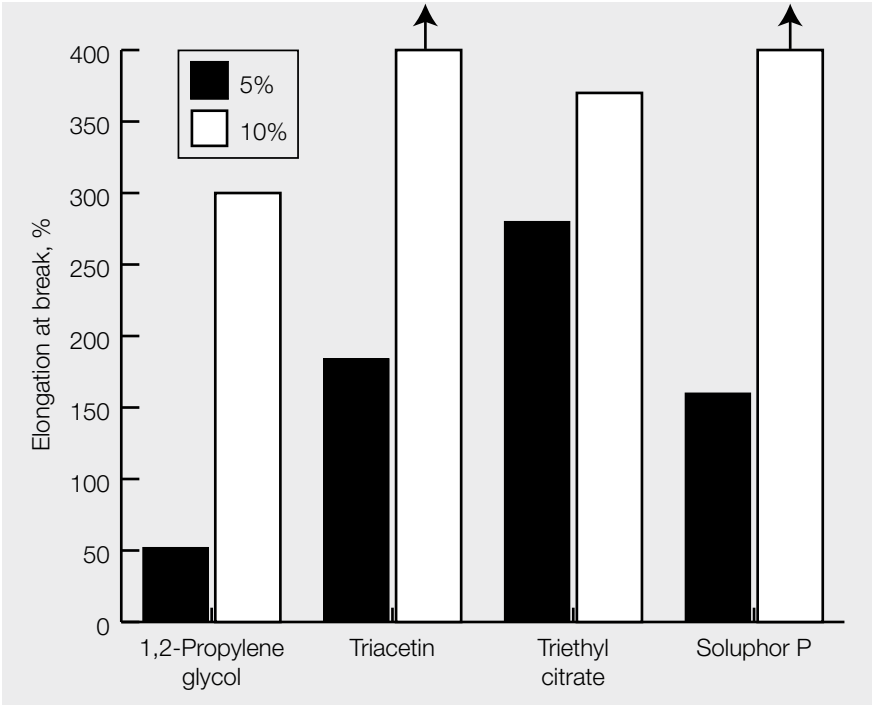


Fig. 42: Elongation at break of Kollicoat SR 30D films (thickness: 150 µm) with various plasticizers in concentrations of 5 and 10 % based on the polymer (23 °C, 54 % relative humidity)

It is a well-known fact that water acts as a plasticizer in polymer films. Fig. 43 illustrates that this is also the case with Kollicoat SR 30D where the elongation at break of 150 µm films with the addition of 5 and 10 % triacetin or 10 % 1,2-propylene glycol at various relative humidities is shown. With increasing humidity, the elongation at break increases due to the adsorption of water. Using triacetin as an example, it is clear that, at a plasticizer content of 10 %, the effect of the water is no longer a factor.

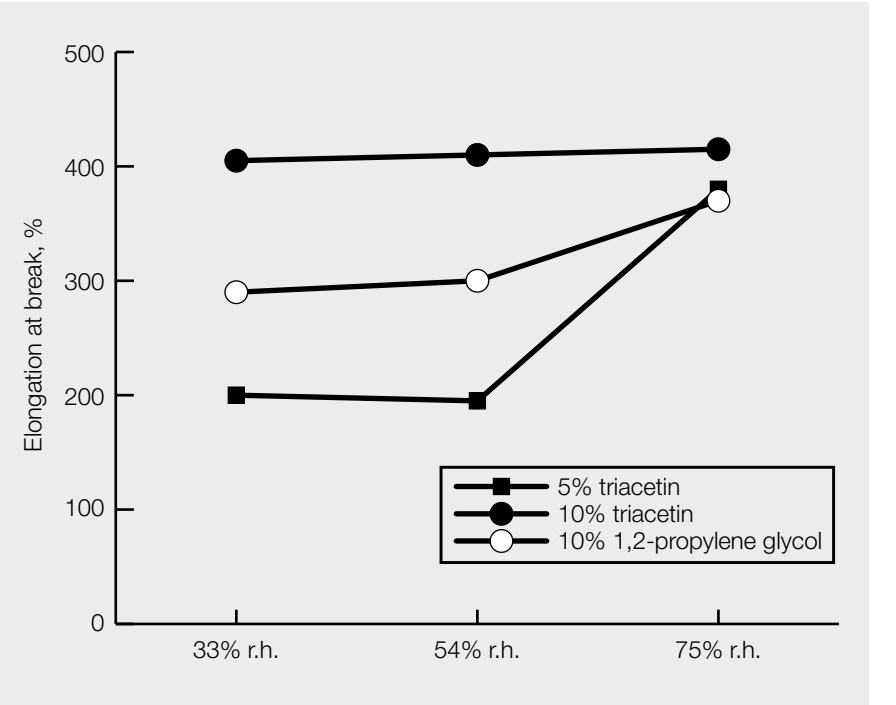


Fig. 43: Elongation at break of Kollicoat SR 30D films with plasticizers as a function of relative humidity

However, not only plasticity and elongation at break are influenced by the addition of plasticizers; film-formation is also affected in that the minimum film-forming temperature (MFT) is decreased. This is an important parameter as only a completely closed film guarantees reproducible sustained release of the active ingredient. To clarify this, the film formation is graphically illustrated in Fig. 44. After being sprayed onto the surface of the tablet or pellet, the individual latex particles of the dispersion are still enclosed within a layer of water. In the second stage, the water evaporates but the latex particles remain unchanged next to each other. Only when the MFT is exceeded is the final stage of film formation initiated; the individual particles coacervate.

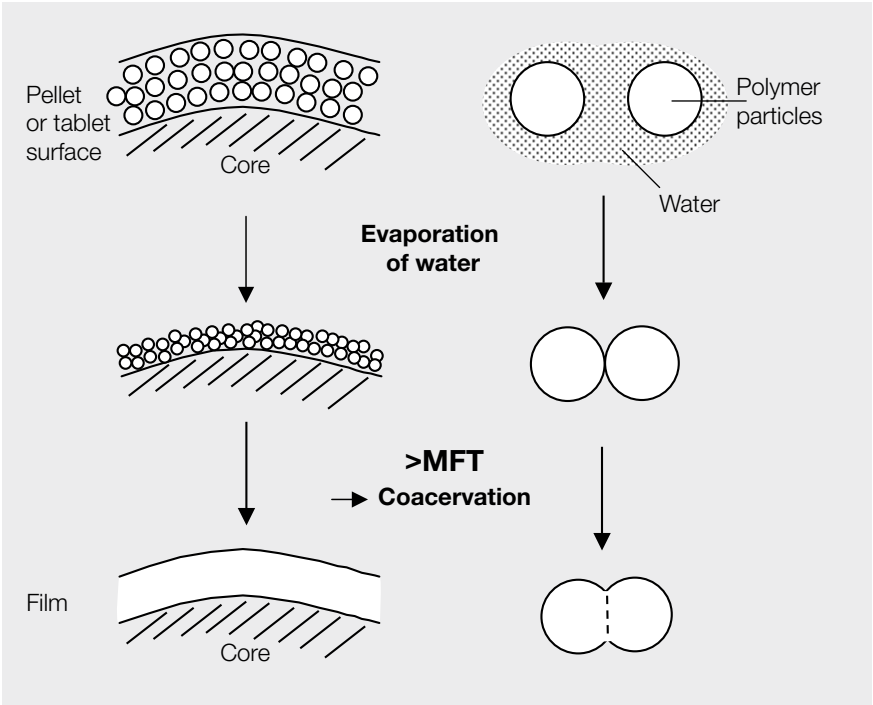


Fig. 44: Schematic illustration of film formation on a tablet or pellet surface

In Table 68, the influence on MFT by various concentrations of two plasticizers is shown [11]. 1,2-Propylene glycol decreases the MFT only slightly in comparison with triethyl citrate. However, as the MFT in the case of pure Kollicoat SR 30D films is already 18 °C, this is not a problem when coating granules, tablets or pellets, where this temperature is always exceeded. Curing after spraying, as is performed in the case of cellulose derivatives, is thus never necessary with Kollicoat SR 30D.

Table 68: Minimum film-forming temperature (MFT) of Kollicoat SR30D films with and without plasticizers [11]

Plasticizer	**Additive** (based on the polymer)	**MFT**
1,2-Propylene glycol	0 %	18 °C
	5 %	16 °C
	10 %	14 °C
	15 %	12 °C
Triethyl citrate	0 %	18 °C
	5 %	8 °C
	10 %	1 °C
	15 %	< 0 °C

4.2.7.3 Tackiness of films

The tackiness of films is an important property in the practical application of polymer coating. In the case of Kollicoat SR 30D films, this was investigated using the Hoessel method [1]. Simultaneously, the influence of various concentrations of the plasticizers 1,2-propylene glycol, triethyl citrate and triacetin was determined. The results of this investigation are shown in Fig. 45, where it can be seen that 1,2-propylene glycol has no influence on the tackiness. However, in the case of the other two plasticizers at a concentration of 10 %, based on the polymer, the tackiness, also perceptible by the finger test, exceeded the limit of 1.3.
This explains why in most formulations of pellets coated with Kollicoat SR 30D, as described in chapter 4.3.4, the recommended plasticizer is 1,2-propylene glycol. In the case of granules or pellets compressed to sustained release tablets after coating, the adhesive effect is not quite so important. Thus, in these cases, 10 % triethyl acetate or triacetin can be used. The addition of 0.1 % silica gel can prevent the particles from agglomerating.

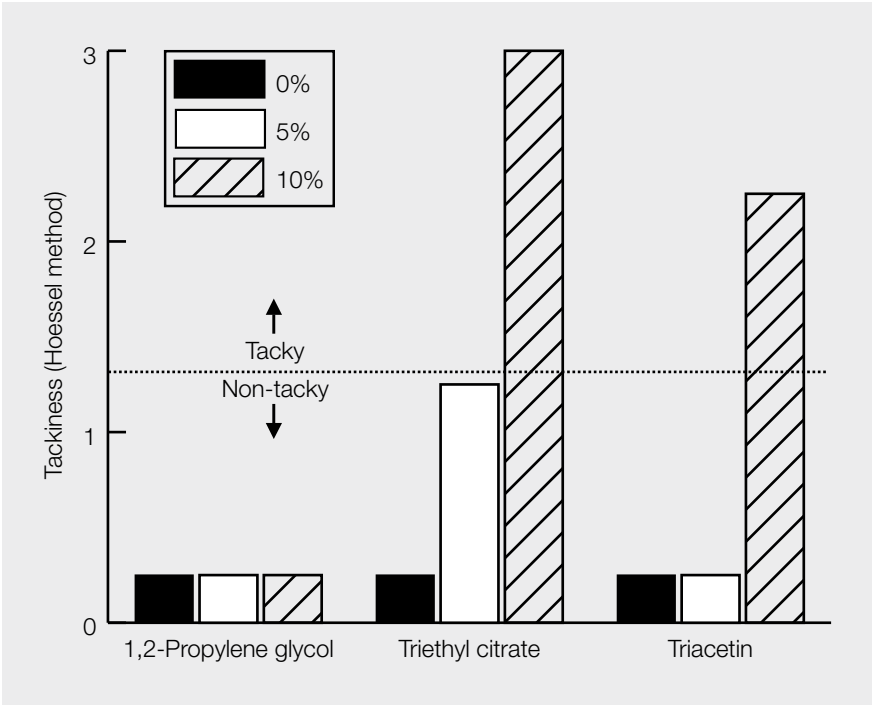


Fig. 45: The tackiness of Kollicoat SR 30D films with and without plasticizers

4.2.8 Stability, storage

Kollicoat SR30D should be stored at room temperature in unopened original packs. As in the case of all aqueous polymer dispersions, temperatures over 35 °C and under 0 °C should be avoided as under these conditions agglomeration can take place. Too strong shaking accompanied by the formation of foam has a similar effect. Agglomerates can block the spray nozzle, hence making the product unusable for this application. As the product is rather insensitive to microbiological contamination, opened but well resealed packages can normally be reused.

An unopened dispersion of Kollicoat SR 30D can be kept for more than 18 months at room temperature providing the valid specifications are maintained.

4.3 Applications of Kollicoat SR 30D

4.3.1 Overview and general information

The polymer polyvinyl acetate has been used as an excipient in drugs and foodstuffs throughout the world for a very long time. However, the fact that the pure polymer available on the market can only be processed in organic solvents limits its use considerably. It was only when aqueous dispersions such as Kollicoat SR 30D became available that this particular problem was solved.

Kollicoat SR 30D has a wide range of applications; it can be used for the production of sustained release tablets by compressing granules or pellets or for the film-coating of tablet cores. However, sustained release granules or pellets can also be products in their own right; they can also be used to fill hard gelatine capsules. Kollicoat SR 30D can be used to mask odour in instant-release granules and tablets. All of these applications are summarised in Table 69.

Table 69: Applications of Kollicoat SR 30D

Dosage form	**Manufacturing technology**
Sustained release matrix tablets	Granulation of the active ingredient with Kollicoat SR 30 and subsequent compression
	Film coating of pellets of active ingredient with Kollicoat SR 30 and subsequent compression
Sustained release film coated tablets	Film coating of tablet cores with Kollicoat SR 30
Sustained release pellets and granules	Film coating of pellets of active ingredient (drug pellets or drug layered nonpareilles) or granulation of the active ingredient with Kollicoat SR 30
Sustained release hard gelatine capsules	Film coating of pellets of active ingredient (drug pellets or drug layered nonpareilles) or granulation of the active ingredient with Kollicoat SR 30 and filling into hard gelatine capsules
Masking of odour and taste of normal granules and tablets	Granulation of the active ingredient with Kollicoat SR 30 and pore formers (and subsequent compression)

Most formulations should contain a plasticizer; normally, 10 %, based on the polymer, is adequate. 1,2-Propylene glycol (10 %) has proven most suitable for this purpose as it does not generate tackiness. However, 5 – 8 % triacetin can also be used (see chapter 4.2.7.3). If pellets containing 10 % plasticizer are allowed to stand at room temperature over a period of one week, a certain degree of pellet agglomeration can be observed with triethyl citrate in contrast to 1,2-propylene glycol. Table 70 lists these observations. However, this particular problem is easy to solve; addition of only 0.1 % silica gel is normally able to prevent such agglomeration.

Table 70: Effect on agglomeration of storing pellets coated with Kollicoat SR 30D for one week at room temperature

	Visual agglomeration	
Plasticizer	**Without silica gel**	**With 0.1 % silica gel**
Without	-	-
5 % 1,2-propylene glycol	-	-
10 % 1,2-propylene glycol	-	-
5 % triethyl acetate	+	-
10 % triethyl acetate	+	-

The amounts necessary for spray suspensions and solid coatings vary considerably for the different applications; however, release of active ingredient is also always determined by the thickness of the coating. In addition, the release of sparingly soluble active ingredients can be accelerated by adding hydrophilic pore formers such as Kollidon 30, lactose monohydrate, microcrystalline cellulose or Kollidon CL-M. In particular, in the case of granules with or without compression, the particle size exerts a major influence on release. This should always be borne in mind and carefully checked.

A fluidized bed granulator is recommended for the production of pellets and granules as this technology guarantees the most homogeneous coating possible. However, comparative studies have shown that granulation can also be carried out in a conventional mixer granulator. In this case, however, a somewhat higher amount of the sustained release polymer will be necessary in order to achieve the same release effect (see chapters 4.3.2.2 and 5.3.3.1).

Subsequent curing of the coated granules, pellets or tablets is not necessary when using Kollicoat SR 30D as the minimum film-forming temperature (MFT) is already 18 °C without the use of a plasticizer. Comparison of release from several formulations before curing and after treatment at 60 °C over a period of 2 h showed no significant differences. Even heating to 60 °C over 24 h did not affect release. Fig. 46 illustrates this using the example of propranolol sustained release pellets [11].

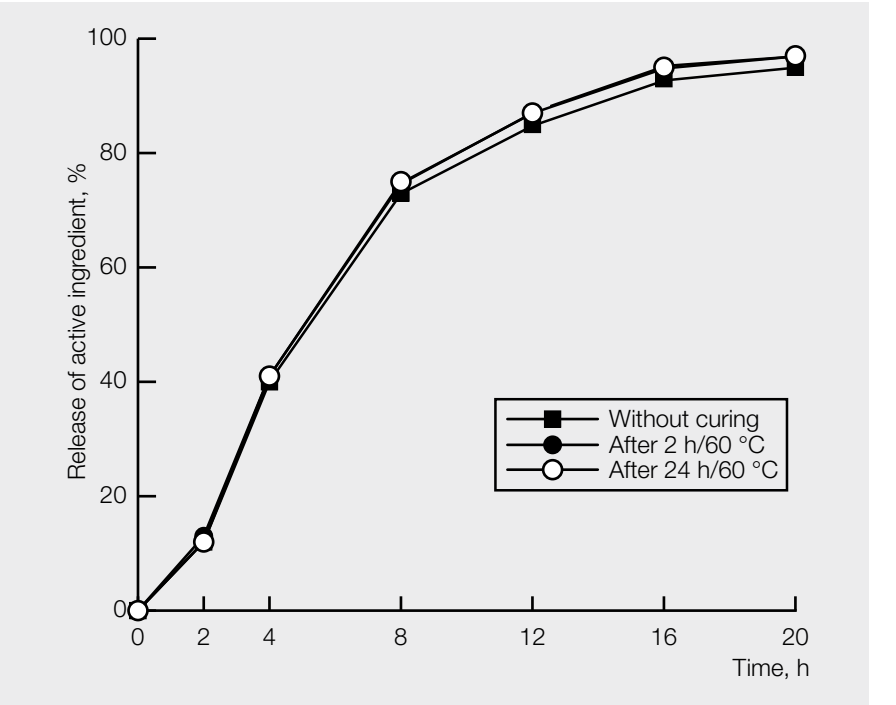


Fig. 46: Influence of curing at 60 °C on the release behaviour of propanolol sustained release pellets [11]

Films of Kollicoat SR 30D result in release behaviour that is independent of pH and ionic status. This was also investigated using a number of other formulations. Fig. 47 shows the influence of pH (0.08 N hydrochloric acid or phosphate buffer pH 6.8) on the release of theophylline from sustained release pellets. The curves are practically identical.

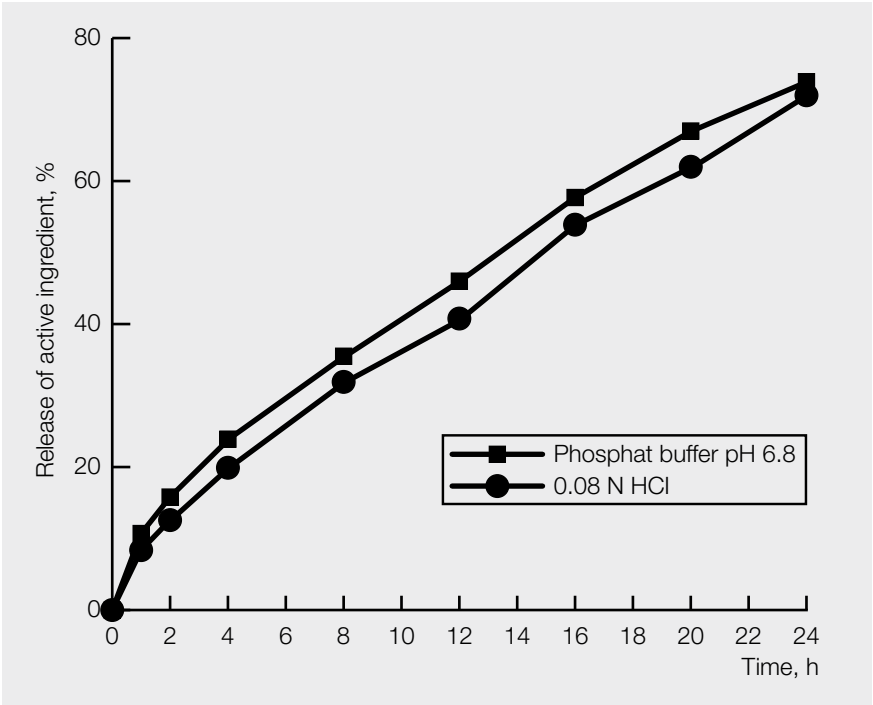


Fig. 47: Influence of pH of the medium on the release of theophylline sustained release pellets

During the formulation procedure, the polymer suspension is always formed by dissolving the plasticizer in water and then adding the Kollicoat SR 30D dispersion. The separately prepared and homogenised pigment suspension, including talcum and a stabiliser such as Kollidon 30, is then stirred into the polymer suspension to obtain the final spray suspension. The addition of talcum is always recommended to prevent adhesion of product to the walls of the apparatus used as well as agglomeration within the spray suspension. If the content of talcum is too high, however, the sustained release effect may be negatively affected (see chapter 4.3.4.4).

Incompatibilities between individual excipients and the polymer, as is known from several acrylate film formers, have not been observed when using Kollicoat SR 30D.

When carrying out stress tests on the storage of sustained release matrix tablets, it must be taken into account that, at temperatures over 40 °C and, especially, high relative humidity, the polyvinyl acetate matrix can be affected to such an extent by the glass transition temperature that release of the active ingredient may be slowed down.

4.3.2 Sustained release matrix tablets prepared by granulation with Kollicoat SR 30D and subsequent compression

4.3.2.1 Introduction

In this technology, the active ingredient, with or without filler, is granulated with Kollicoat SR 30D and, subsequent to the addition of further excipients, compressed to matrix tablets with controlled release properties. When using standard amounts of sustained release polymer of 10 – 30 %, a matrix structure is formed on compression that encloses the particles of active ingredient. Subsequent to penetration of gastric juice or intestinal fluid into the matrix, the active ingredient is slowly dissolved; it then diffuses through the matrix at a controlled speed.
Figs 48A and 48B show scanning electron microscope images of the surface of an ascorbic acid sustained release matrix tablet before and after partial dissolution of the active ingredient. Here it can be seen how the smooth surface of the tablet (Fig. 48A) changes into the sponge like matrix structure (Fig. 48B) formed by the addition of 12 % Kollicoat SR polymer after release of the active ingredient [9].

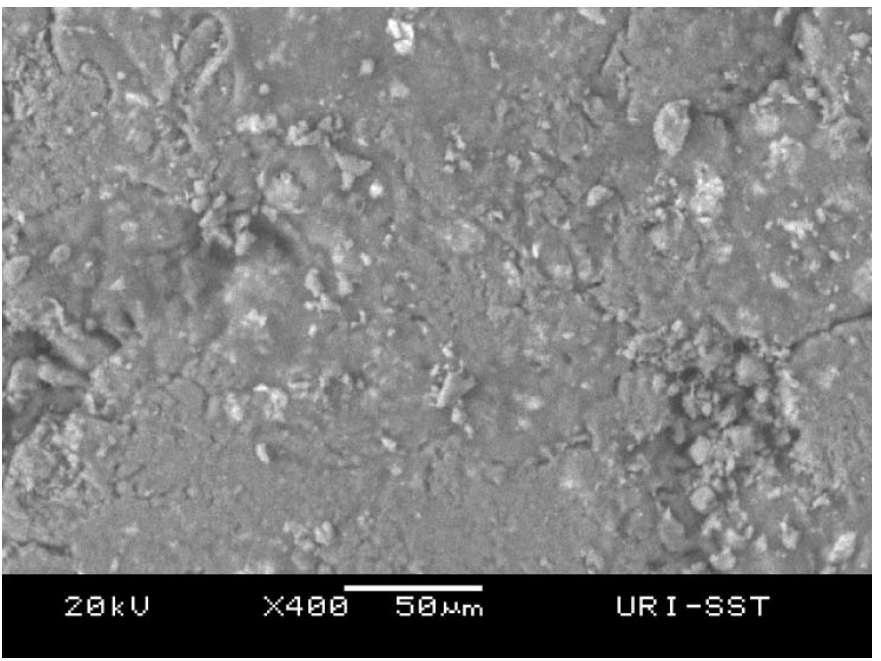


Fig. 48A: SEM photo of the surface of an ascorbic acid sustained release tablet containing Kollicoat SR 30D [9]

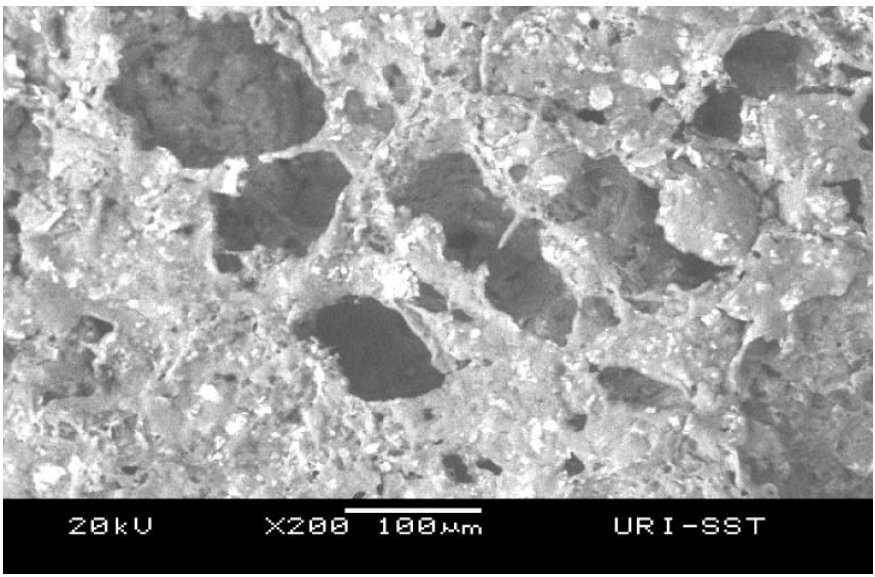


Fig. 48B: SEM photo of the tablet matrix structure of photo in Fig. 48A 8 h after release of the active ingredient [9]

Three important factors determine the amount of Kollicoat SR 30D necessary for sustained release matrix tablets:
- The solubility of the active ingredient
- The size and surface area of the active ingredient particles
- The required release profile.

To control the release, the amount of Kollicoat SR 30D can be varied, a hydrophilic pore former such as Kollidon 30, lactose monohydrate or microcrystalline cellulose added or the particle size of the active ingredient altered. Normally, the following amounts of Kollicoat SR polymer are required for release over a period of 24 h (solid, based on the weight of granules), depending on the solubility of the active ingredient in question:
- Soluble active ingredients (e.g. potassium chloride, propranolol-HCl): 20 – 30 %
- Sparingly soluble active ingredients (e.g. theophylline, carbamazepin): 5 – 15 %.

The formulation examples involving various active ingredients described in chapters 4.3.2.2 to 4.3.2.5 demonstrate this. However, if only the sustained release effect is to be achieved over a short period of time, the amounts of Kollicoat SR polymer can be correspondingly decreased. One example is ascorbic acid matrix tablets with release over a period of 8 h where approximately 12 % of Kollicoat SR polymer is required [9].

In most cases, the addition of a plasticizer such as triethyl citrate or 1,2-propylene glycol is recommended; this is because, in contrast to uncompressed granules, release of the active ingredient can be accelerated due to the mechanical stress caused by compression.

The following formulations with the soluble and insoluble active ingredients propranolol-HCl, theophylline, carbamazepin and potassium chloride are typical examples that demonstrate the use of Kollicoat SR 30D in sustained release matrix tablets. In the case of propranolol-HCl and theophylline tablets, comparison with hypromellose (Methocel K100M) was carried out. It was shown that for theophylline there was no difference in release whereas in the case of propranolol hypromellose prolonged release.

4.3.2.2 Propranolol sustained release matrix tablets 160 mg (granulation with Kollicoat SR 30D)

In this formulation example, the influence of compression force, amount of coating and granulation technology was investigated.

The soluble active ingredient propranolol-HCl was mixed with a filler and 20 – 30 % solid Kollicoat SR, based on the weight of granules, was sprayed onto the mixture in a "top-spray" fluidized bed granulator Aeromatic Strea-1. As a comparison, the mixture was sprayed using a mixer granulator (Diosna). The dry granules were lubricated with magnesium stearate and the flowability agent Aerosil 200 and mixed for 10 minutes. The mixture was then sieved and compressed to tablets of 10 mm diameter, convex surface and a weight of 325 mg using various compression forces (Table 71).

Measurement of release of the active ingredient always took place under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Table 71: Formulations and granulation conditions for propranolol sustained release tablets

Formulation	**1 (20 %)**	**2 (30 %)**
I Propranolol-HCl (BASF)	160.0 g	160.0 g
Filler (lactose monohydrate, microcrystalline cellulose or dicalcium phosphate)	97.3 g	65.1 g
II Kollicoat SR 30D	216.6 g (= 64.3 g solids)	325.0 g (= 96.5 g solids)
III Magnesium stearate	1.7 g	1.7 g
Aerosil 200	1.7 g	1.7 g
Granulation settings (fluidized bed granulator, „top-spray" method)		
Inlet temperature	55 °C	
Outlet air temperature	22 – 27 °C	
Nozzle diameter	0.8 mm	
Spray rate	Approx. 10 g/min	
Spray pressure	2 bar	

The factors influencing the formulations of Table 71 were investigated. Firstly, the difference in release of active ingredient between formulations 1 and 2 were established where lactose monohydrate was used as intragranular filler. Formulation 1 containing 20 % solid Kollicoat SR released the active ingredient propranolol-HCl over a period of 20 h; formulation 2 containing 30 % Kollicoat SR polymer released the active ingredient over a period of more than 24 h (Fig. 49). In this case and this particle size of active ingredient, 25 % solid Kollicoat SR would probably have been the right amount for release over 24 h.

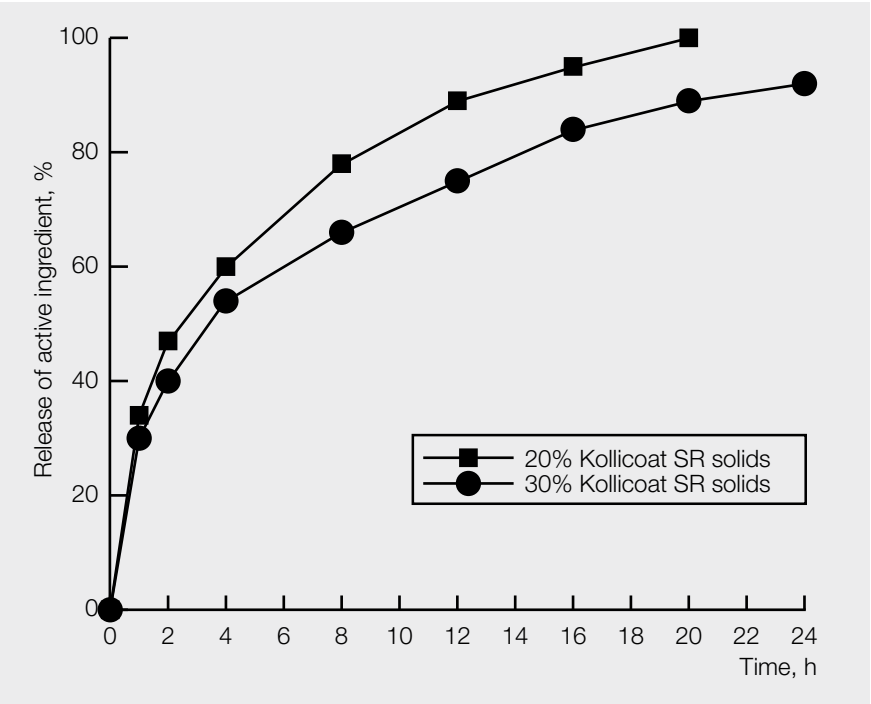


Fig. 49: Influence of the amount of Kollicoat SR polymer on the release of propranolol-HCl from sustained release matrix tablets (intragranular filler: lactose monohydrate)

Following this step, the influence of compression force on the release of propranolol-HCl and on the porosity of the tablets originating from formulation 1 was investigated. Although compression force has a direct effect on the porosity (in the case of all fillers, the porosity decreases with increasing compression force, see Table 72), it has no influence on release. In the case of all three compression forces used (between 10 and 25 kN), an identical release curve was obtained when lactose monohydrate was used as filler (Fig. 50). This is a very important property of Kollicoat SR 30D and it reflects the adequate flexibility necessary for the mechanical stress involved during compression and matrix formation. Should it be established that compression itself or different compression forces in fact influence the release of active ingredient, a plasticizer becomes indispensable. This is shown for the tabletting of sustained release pellets in chapter 4.3.5.

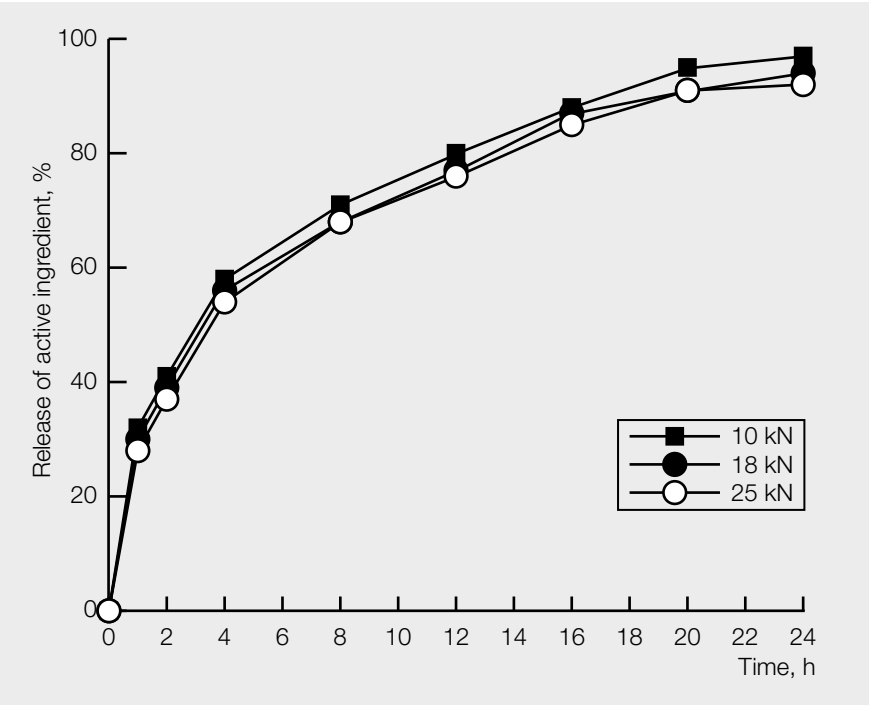


Fig. 50: Influence of compression force on the release of propranolol-HCl from sustained release matrix tablets (formulation 1, with lactose monohydrate)

Next, the influence of three different fillers on the hardness and porosity of the tablets produced by fluidized bed granulation was investigated. Table 72 shows that enormous degrees of hardness can be obtained with formulations 1 and 2 and all the fillers used. The hardness remains practically unaffected on increasing or decreasing compression force, as was shown in a further experiment. The porosity is significantly influenced by the compression force used and the filler can also play a part.

Table 72: Influence of intra-granular fillers on the hardness and porosity of propranolol sustained release matrix tablets

		Lactose monohydrate	Microcrystalline cellulose	Dicalcium phosphate
Hardness	Compression force			
Formulation 1	18 kN	255 N	300 N	280 N
Formulation 2	18 kN	257 N	325 N	280 N
Porosity	Compression force			
Formulation 1	10 kN	7.0 %	7.0 %	20.0 %
Formulation 1	18 kN	2.0 %	2.2 %	17.0 %
Formulation 1	25 kN	0.8 %	1.8 %	14.8 %

Finally, the influence of the granulation technology was investigated, the parameters selected being tablet hardness and release of the active ingredient propranolol-HCl. Fig. 51 shows that traditional mixer granulation in formulation 2 with lactose monohydrate as filler produces tablets of considerably less hardness than with fluidized bed granulation. Fig. 52 shows that in formulation 1 with lactose monohydrate as filler the sustained release effect with fluidized bed granulation is somewhat greater, i.e. with traditional mixer granulation the active ingredient propranolol is released a little quicker. In order to compensate for this, a little more sustained release polymer is required in order to achieve the same effect as with fluidized bed granulation. Thus, fluidized bed granulation is the recommended technology for sustained release matrix tablets.

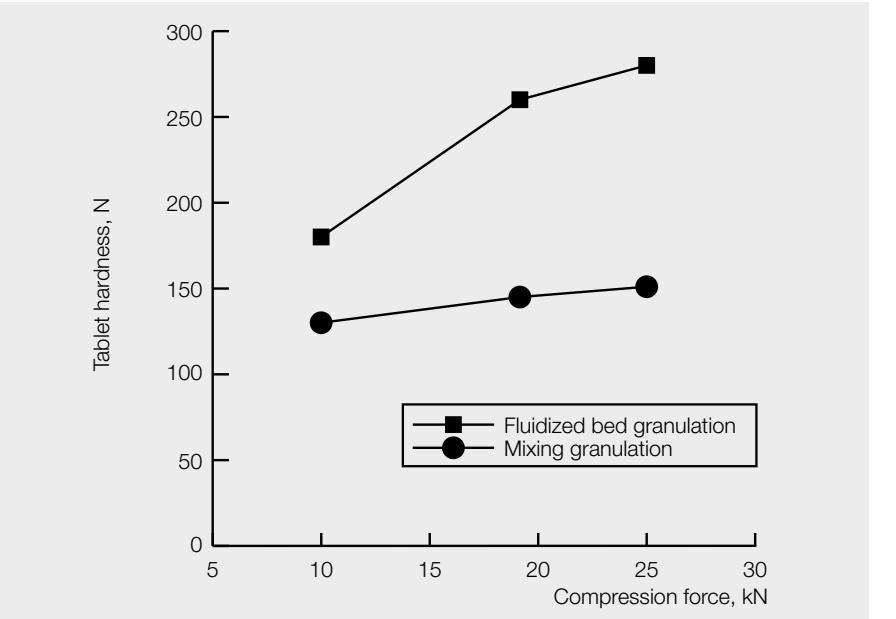


Fig. 51: Influence of granulation technology on the hardness of propranolol sustained release matrix tablets (formulation 2 with lactose monohydrate)

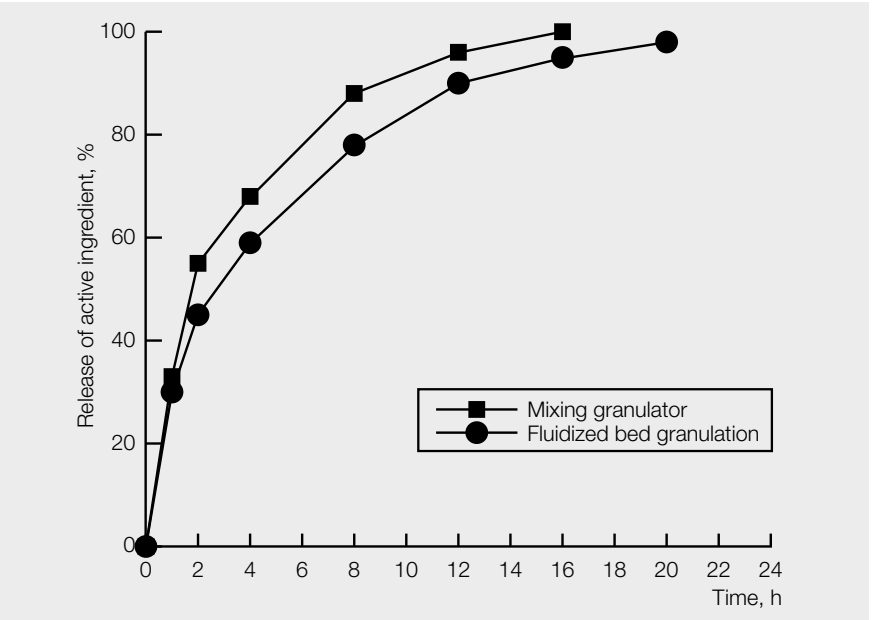


Fig. 52: Influence of granulation technology on the release of propranolol sustained release matrix tablets (formulation 1 with lactose monohydrate)

If tablets produced using formulation 2 with lactose monohydrate as filler were stored under stress conditions for 1 month at various temperatures, no difference in release could be observed at 40 °C. At 60 °C, the values of the release curve were on average 10 % lower than the initial values, i.e. release was delayed somewhat, presumably due to the sintering effect brought about by the glass transition temperature of the polymer being clearly exceeded. This temperature effect must be taken into account when carrying out stress tests on sustained release matrix tablets containing Kollicoat SR 30D.

4.3.2.3 Theophylline sustained release matrix tablets 400 mg (granulation with Kollicoat SR 30D)

This formulation example was used to determine the influence of coating amounts, the moistness of the granules as well as the particle size of the active ingredient and the intra-granular filler.

The active ingredient theophylline was mixed with a filler and this mixture sprayed with 7.5 and 10 % solid Kollicoat SR, based on the weight of granules, directly in an Aeromatic Strea-1 fluidized bed granulator.
The dry granules were mixed with magnesium stearate lubricant and flowability agent Aerosil 200 for 10 minutes and sieved. They were then compressed to 19 x 8.5 mm oblong tablets of approx. 800 mg weight with an active ingredient content of approx. 400 mg using a compression force of 18 kN. The granulation conditions for both formulations are summarised in Table 73.

Measurement of release of the active ingredient always took place under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Table 73: Formulations and granulation conditions for theophylline sustained release tablets of 400 mg weight

Formulation	**1 (7.5 %)**	**2 (10 %)**
I Granular theophylline 0.2/0.7 (BASF)	400 g	400 g
Lactose monohydrate	339 g	320 g
II Kollicoat SR 30D	202 g (= 61 g solids)	267 g (= 80 g solids)
III Magnesium stearate	4 g	4 g
Aerosil 200	4 g	4 g
Granulation settings (fluidized bed granulator, "top-spray" method)		
Inlet air temperature	55 °C	
Outlet air temperature	22 – 27 °C	
Nozzle diameter	0.8 mm	
Spray rate	Approx. 10 g/ml	
Spray pressure	2 bar	

Due to the insolubility of theophylline, the required amount of Kollicoat SR 30D is approximately only one third of the amount required for the soluble active ingredient propranolol-HCl (see chapter 4.3.2.1). As can be seen in Fig 53., the required amount of solid Kollicoat SR of 7.5 %, based on the weight of granules, is just right for release of active ingredient over a period of 24 h with the particle size of theophylline used (0.2 – 0.7 mm).

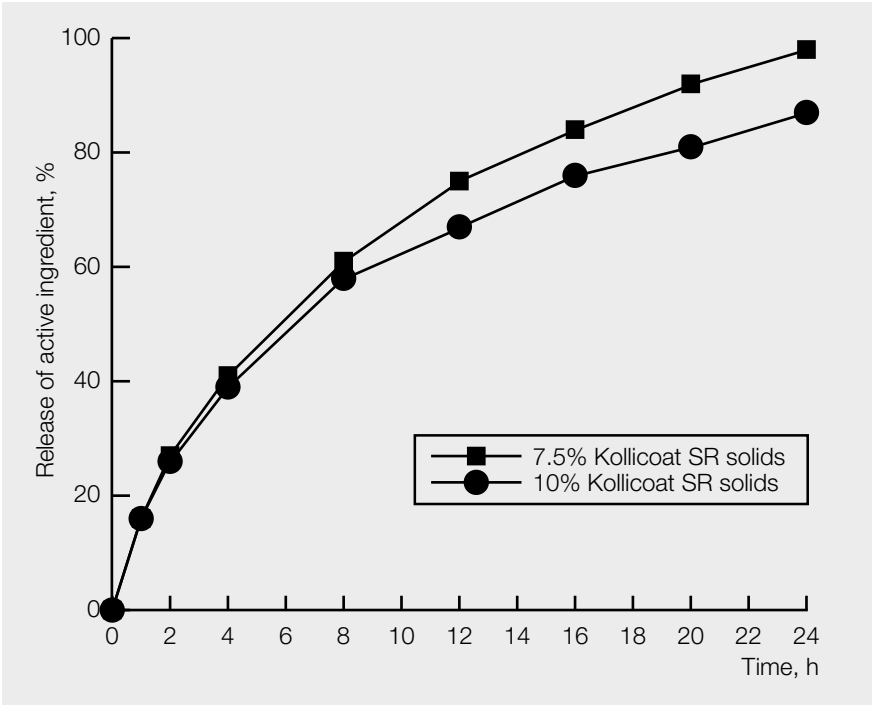


Fig. 53: Influence of the amount of Kollicoat SR on the release of theophylline sustained release matrix tablets

In order to determine the influence of the particle size of the active ingredient, formulations 1 and 2 were compressed to tablets with two further types of theophylline of different particle sizes. The mean particle sizes D [4.3] of the three theophylline types were 13 µm, 113 µm and 667 µm. Table 74 shows that the particle size is of some considerable significance. Normally, the mean particle size is directly proportional to release; the smaller the particles the more quickly the active ingredient is released due to the greater surface area. This was also observed on comparing the mean release times t50 of theophylline powder 200 and the other two types. However, it was surprising to note that the release from the powder was slower than from granules. The reason for this could be that the particles of the granules used have such an irregular structure that their surface area is significantly enlarged. As the particles are already 600 µm on average, they could well be too large; as a result, due to the low matrix content (max. 10 %), very wide pores and channels are formed when the tablets are dissolved. This in turn causes the active ingredient to diffuse more strongly.
It can be concluded from these results that it is very important to characterize the structure and size of the particles of the active ingredient before use in order to exclude undesired surprises.

Table 72: Influence of the particle size of theophylline on the mean release time t50 of sustained release matrix tablets

Theophylline (BASF)	**Mean particle size D [4.3]**	**Mean release time t_{50}**	
		7.5 % (formulation 1)	**10 % (formulation 2)**
Granules 0.2/0.7	667 µm	5.8 h	6.5 h
Powder	113 µm	8.2 h	10.9 h
Powder 200	13 µm	-	3.7 h

The influence of residual water in the granules on release was also investigated in formulation 1 of the theophylline sustained release matrix tablets. This is an important factor for the sensitivity of the formulation with respect to fluctuating production conditions. As can be seen in Fig. 54, water content within the range 2 – 7 % has no effect on the release of theophylline.

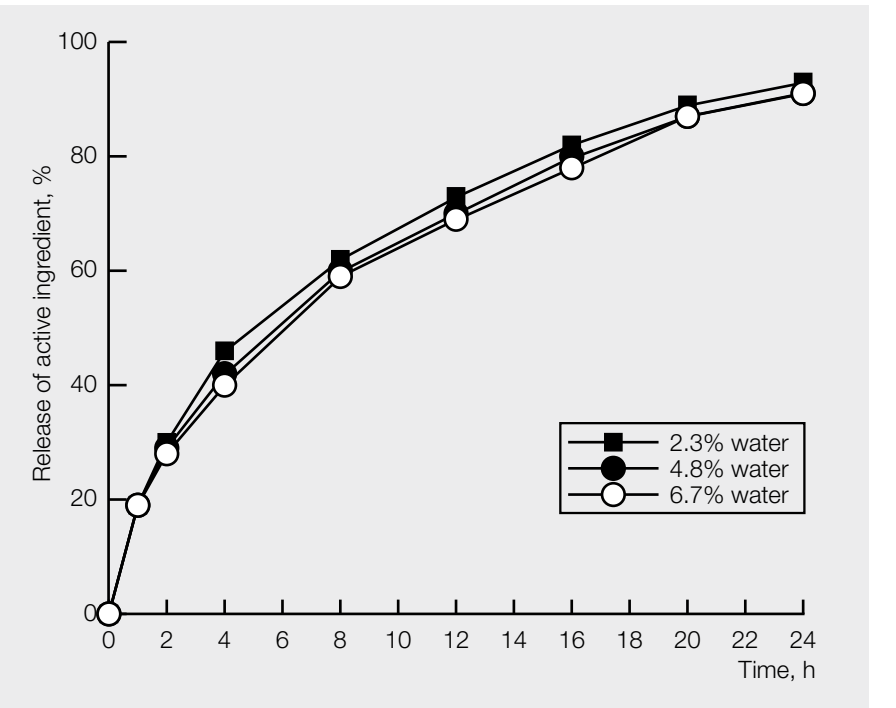


Fig. 54: Influence of residual water of the granules on release from theophylline sustained release matrix tablets (formulation 1)

In formulation 2 with 10 % Kollicoat SR polymer, instead of lactose monohydrate, two further intra-granular fillers were also tested without altering the other conditions. It was shown that in this case there was no significant difference in the release of theophylline between lactose monohydrate, microcrystalline cellulose and dicalcium phosphate (Fig. 55).

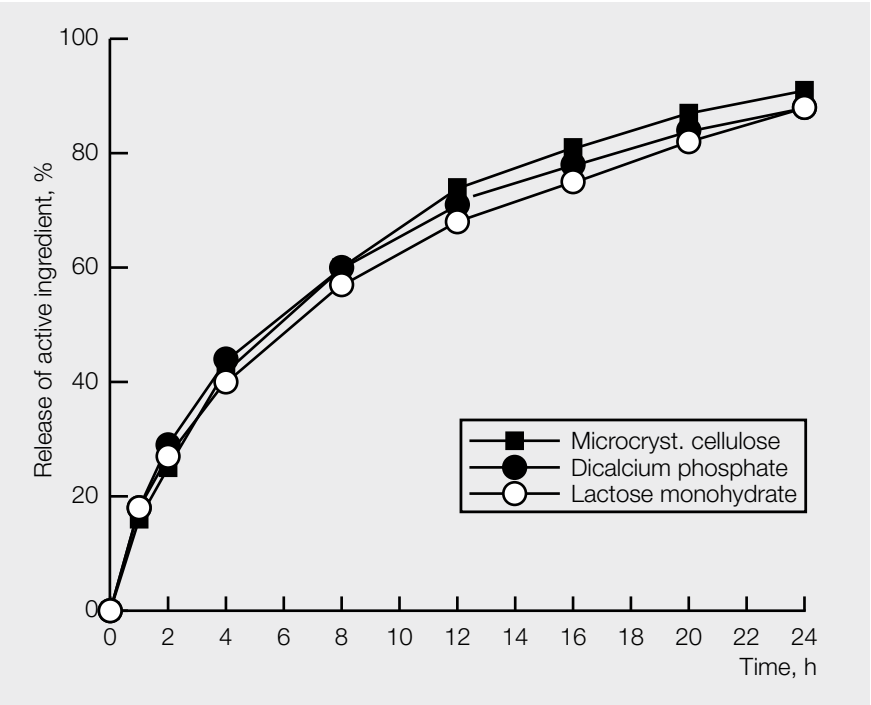


Fig. 55: Influence of the intra-granular filler on release from theophylline sustained release matrix tablets (formulation 2).

In order to investigate the influence of tablet surface and tablet form on release, the granules from formulation 1 were compressed into tablets with different diameters, forms and surfaces instead of simply oblong: flat, with a diameter of 12 mm (302 mm^2), flat, with a diameter of 10 mm (250 mm^2) and strongly convex with a diameter of 9 mm (216 mm^2). It was observed that the surface of the tablet played a certain role in the release of the theophylline. The difference was very slight between tablets of diameter 9 and 10 mm; however, release was significantly quicker from the 12 mm tablets.

4.3.2.4 Carbamazepin sustained release matrix tablets 200 mg (granulation with Kollicoat SR 30D)

In this formulation example, the influence of the pore former on release of the insoluble active ingredient carbamazepin was investigated.

Carbamazepin was mixed with the filler lactose monohydrate and strong pore former micronised crospovidone (Kollidon CL-M). 7.5 % solid Kollicoat SR, based on the weight of granules, was then sprayed onto the mixture in an Aeromatic Strea-1 "top spray" fluidized bed granulator. The dried granulate was mixed with magnesium stearate and Aerosil 200 for 10 minutes, sieved and compressed to tablets of 11 mm diameter, approx. 400 mg weight and with an active ingredient content of 200 mg using medium compression force. The formulation and tablet properties are summarised in Table 75.

Measurement of release of the active ingredient took place under the following conditions:
0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Table 75: Formulation and properties for carbamazepin sustained release matrix tablets 200 mg

Formulation	**Amount**
I Carbamazepin (Sintetica)	200 g
Lactose monohydrate	148 g
Kollidon CL-M	20 g
II Kollicoat SR 30D	99 g (= 29.7 g solids)
III Magnesium stearate	2 g
Aerosil 200	2 g
Tablet properties	
Weight	407 mg
Diameter	11 mm
Form	Biconvex
Hardness	136 N
Friability	< 0.1 %

To achieve the required release over a period of approx. 16 h, 5 % of micronised crospovidone (Kollidon CL-M) capable of swelling [3] was added as a strong pore former. Without this additive, release would have been too slow, as can be seen in Fig. 56.

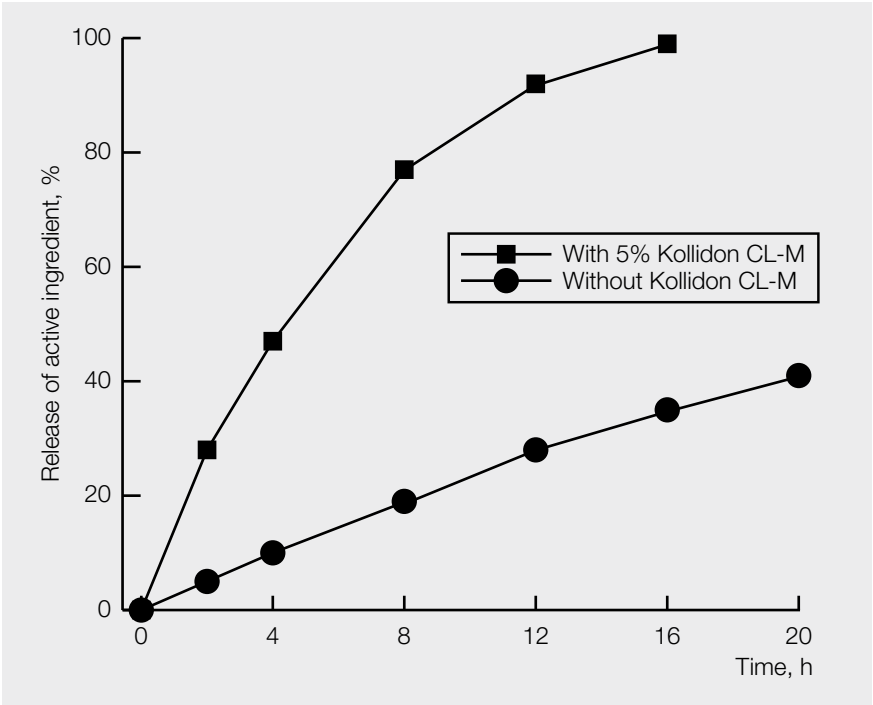


Fig. 56: Release of carbamazepin from sustained release matrix tablets with and without 5 % Kollidon CL-M as pore former

4.3.2.5 Potassium chloride sustained release matrix tablets 750 mg (granulation with Kollicoat SR 30D)

As a final example, sustained release matrix tablets produced by granulation of active ingredient with Kollicoat SR 30D was selected to demonstrate the effect of a very soluble and highly concentrated active ingredient. Simultaneously, the influence of compression force on release was investigated.

The active ingredient potassium chloride was granulated with Kollicoat SR 30D that had previously been mixed with a suspension of talcum in an Aeromatic Strea-1 fluidized bed granulator. The dry granules were mixed for 10 minutes with Ludipress LCE and magnesium stearate, sieved and compressed using medium compression force to oblong tablets with a weight of approx. 1350 mg and an active ingredient content of 750 mg. The formulation and tablet properties are summarised in Table 76.

In this case, the content of solid Kollicoat SR was 24 %, based on the weight of the granules. This was sufficient to achieve release over a period of 16 – 20 h (Fig. 57). As was observed in other formulation examples of this application of Kollicoat SR 30D, no influence of compression force on release of the active ingredient was observed.

Measurement of release of the active ingredient took place under the following conditions:
0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Table 76: Formulation, spraying conditions and properties of potassium chloride sustained release matrix tablets 750 mg

Formulation	**Amount**
I Potassium chloride	750 g
II Kollicoat SR 30D	900 g (= 270 g solids)
Talcum	108 g
Water	300 g
III Ludipress LCE	215 g
Magnesium stearate	7 g
Spraying conditions	
Process	Top spray
Inlet air temperature	70 °C
Outlet air temperature	40 °C
Spray rate	6 g/min
Tablet properties	
Weight	1350 mg
Form	Oblong, 19 x 8.5 mm
Hardness (compression force 7 kN/12 kN)	102 N/219 N
Friability (compression force 7 kN/12 kN)	1.4 %/0.1 %

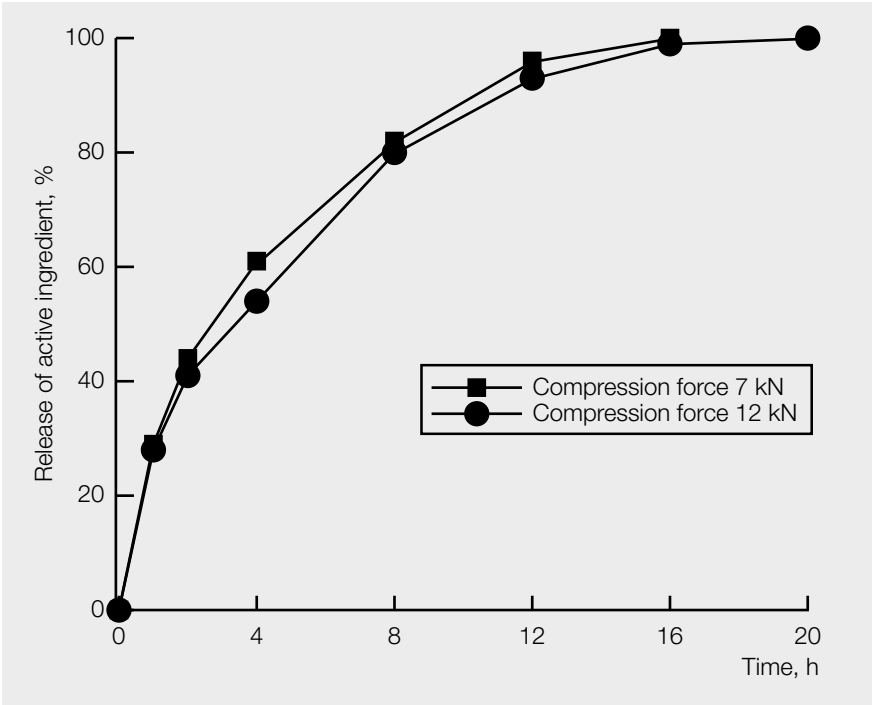


Fig. 57: Release of potassium chloride from sustained release matrix tablets with 24 % solid Kollicoat SR, based on the weight of granules

4.3.3 Sustained released film coated tablets prepared by coating cores with Kollicoat SR 30D

4.3.3.1 Introduction

Normally, the manufacture of sustained release tablets by coating instant release tablet cores with a sustained release coating is avoided; this is because the risk is too high of the active ingredient being released too quickly due to incomplete coating or, especially, damage to the coating. Using the example of sustained release tablets containing metoprolol tartrate, propranolol hydrochloride or pseudo-ephedrine hydrochloride, it was, however, proven that this particular risk can be excluded in the case of Kollicoat SR 30D as a film former. In this way, a very simple system for achieving sustained release is possible. This is mainly due to the plasticity and elasticity of Kollicoat SR films, which enable the films to self-repair damage so that release remains unaffected. In addition, the film will not rupture should the core begin to swell during storage or during release of the active ingredient. To demonstrate this effect, Table 77 shows the elongation at break of isolated films containing 5 % triacetin and 10 % 1,2-propylene glycol as plasticizers in comparison with other sustained release film formers ethyl cellulose and ammonium methacrylate co-polymer. The differences are so great that the surprising results obtained with Kollicoat SR 30D become understandable.

Table 77: Elongation at break of coating film formers with plasticizers (23 °C, 54 % relative humidity)

Sustained release film former	**Elongation at break (23 °C, 54 % relative humidity)**	
	5 % triacetin	**10 % 1,2-propylene glycol**
Kollicoat SR 30D	188 %	300 %
Ethyl cellulose dispersion	5.4 %	5.7 %
Ammonium methylacrylate co-polymer	< 2.0 %	< 2.0 %

In the formulation of metoprolol sustained release tablets given in chapter 4.3.3.2, the two co-polymers Kollicoat SR 30D and Kollicoat IR were combined in a ratio of 4:1 in order to increase the elasticity of the film. Experiments carried out with similar formulations containing propranolol-HCl and pseudo-ephedrine-HCl showed that the release profile could be altered by varying the ratio. The higher the proportion of soluble pore former Kollicoat IR, the more quickly the active ingredient was released.

4.3.3.2 Metoprolol tartrate sustained release film tablets 200 mg (film coating of the cores)

To produce the tablet cores, the active ingredient was granulated with Kollidon 30 as binder, dried, sieved and mixed for 10 minutes with the other excipients. The mixture was then compressed to biconvex cores with a weight of approx. 390 mg (Table 78).

Table 78: Formulation of tablet cores of metoprolol tartrate

Components	**Amount**
I Metoprolol tartrate (Moehs S.A.)	200 g
II Kollidon 30	5 g
Water	As required
III Dicalcium phosphate	160 g
Talcum	4 g
Aerosil 200	3 g
Magnesium stearate	4 g

5 kg of the metoprolol tartrate cores were coated with a red spray suspension of Kollicoat SR 30D in an Accela Cota 24". Table 79 lists the formulation of the spray suspension and the conditions of the film coating process.

To prepare the spray suspension, the pigments iron oxide and titanium dioxide were suspended with talcum in an aqueous solution of Kollidon 30 and Kollicoat IR and homogenised. The pigment suspension was stirred into the separately prepared aqueous mixture of triacetin and Kollicoat SR 30D. Kollidon 30 in this case served as a suspension stabiliser to prevent sedimentation and agglomeration of the pigments. Kollicoat IR is a very flexible film former that can also function as a pore former.

Table 79: Red spray suspension and spraying conditions for film coating metoprolol cores

Spray suspension	**Amount**
Kollicoat SR 30D	43.5 %
Triacetin	0.7 %
Kollicoat IR	3.3 %
Kollidon 30	0.5 %
Titanium dioxide	0.5 %
Sicovit red iron oxide	0.5 %
Talcum	3.5 %
Water	47.5 %
Coating parameters (Accela Cota 24")	**Settings**
Batch size	5 kg
Inlet air temperature	50 °C
Tablet core temperature	35 °C
Spray pressure	2.0 bar
Spray rate	22 g/min
Amount applied (solid)	4,6 to 10 mg/cm^2

The release of metoprolol tartrate was determined at three different applied amounts of coating. Measurement took place under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Fig. 58 shows that, for release over a period of 24 h, a coating of 10 mg solid per cm^2 of tablet surface is appropriate. The S-curve is brought about by the fact that it takes some time for the water to penetrate the film and for the active ingredient to begin to dissolve before diffusing through the film to the exterior. The thicker the film, the stronger the affect achieved.

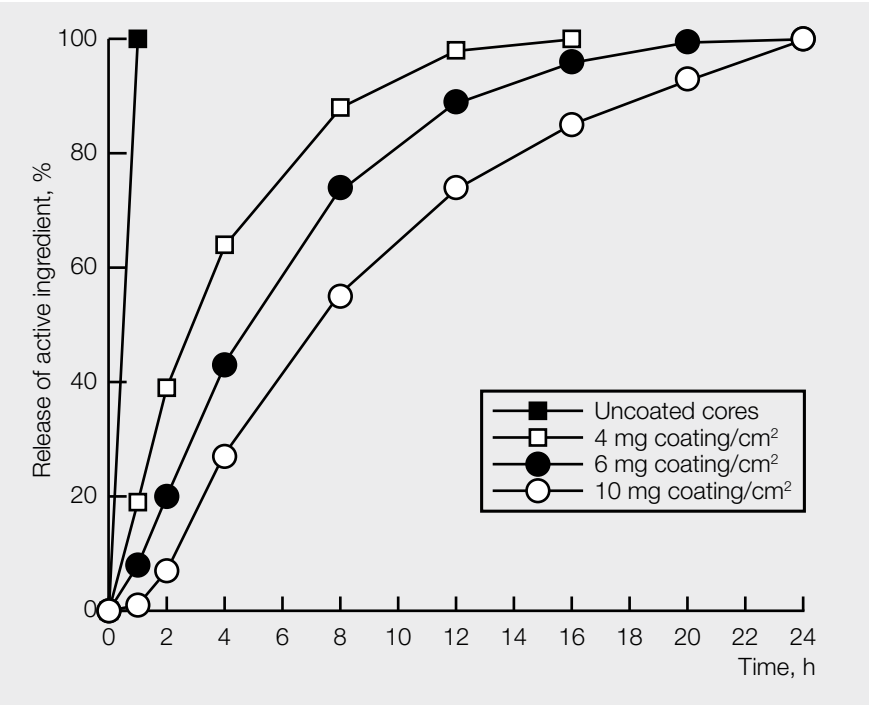


Fig. 58: Release of metoprolol tartrate from sustained release film tablets as a function of coating thickness

In order to investigate the sensitivity of the coating to mechanical stress and damage, two methods were selected that could well be described as being drastic in nature. In the first method – a friability test – the coated tablets were subjected to 500 revolutions in a friability apparatus with a falling height of 15.5 cm; thereafter, they were allowed to fall 20 times from a height of 1.5 m onto a stone floor. In the second method, the tablets were punctured with a needle in such a way that the coating was completely penetrated. Subsequent to both methods, the influence of release of active ingredient was determined. The results obtained were surprising, to say the least. In comparison with untreated tablets, not the slightest difference in release was observed (Fig. 59).
In the case of the punctured tablets, there must be some sort of mechanism whereby the damage is repaired. In this case, it is the high degree of plasticity that exists in the aqueous test medium that then, due to the swelling of the coating, closes off the holes.

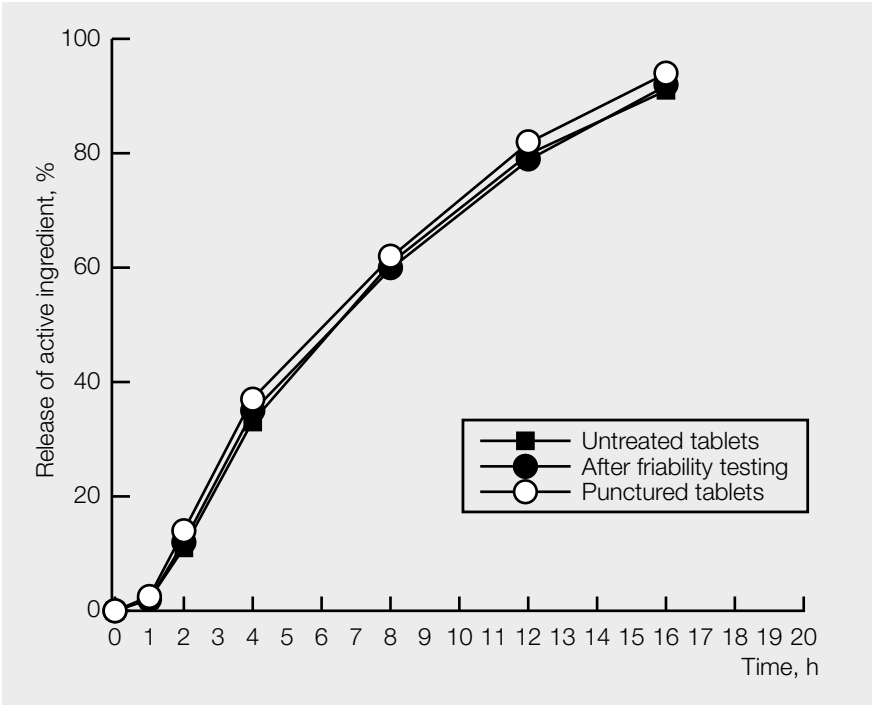
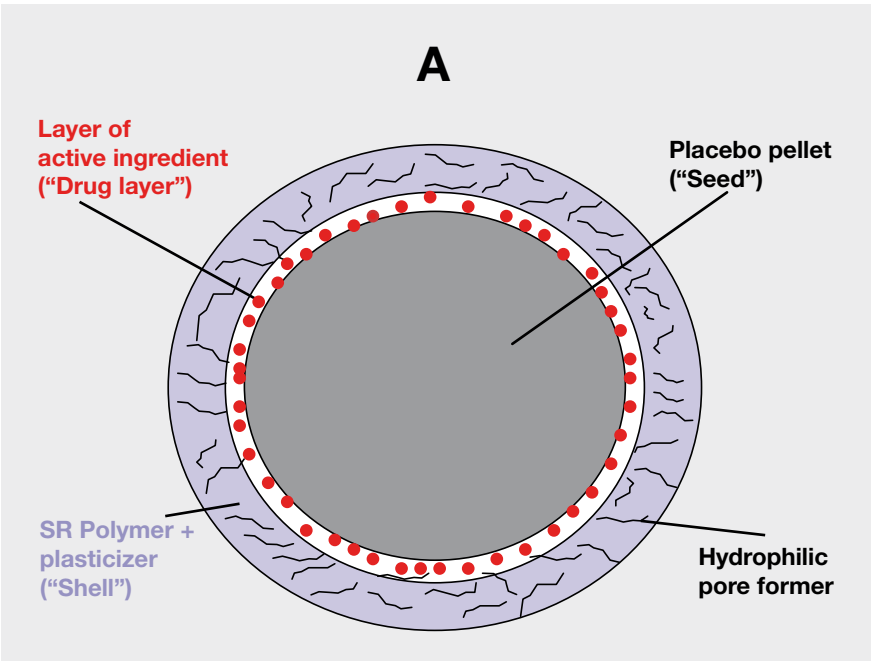


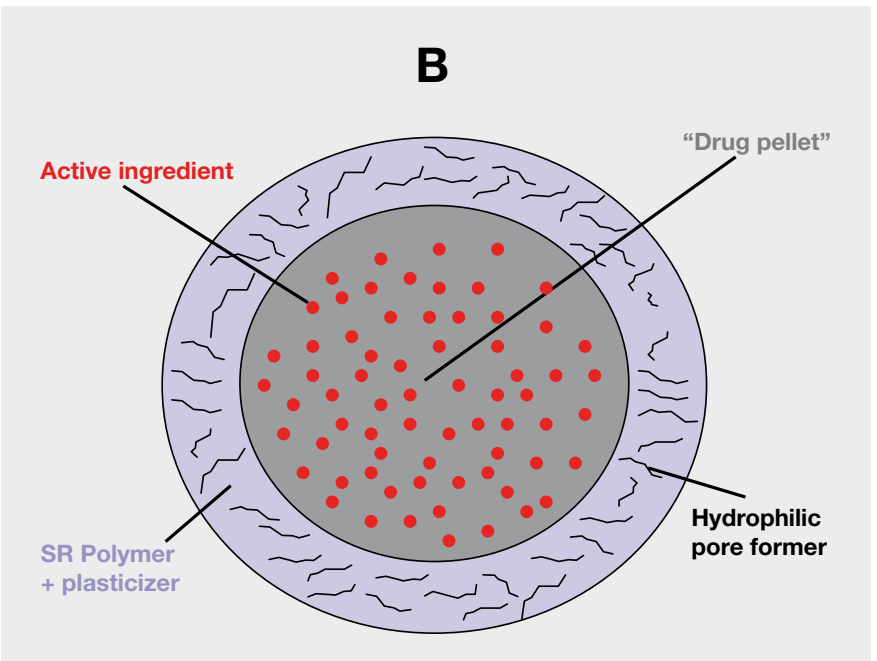
Fig. 59: Influence of mechanical stress and damage to the coating of metoprolol sustained release film tablets on the release of active ingredient

4.3.4 Sustained release pellets prepared by coating with Kollicoat SR 30 D

4.3.4.1 Introduction

Sustained release pellets can be marketed as such or filled into hard gelatine capsules. There are several possibilities for manufacturing coated pellets with sustained release properties. Two of these are schematically illustrated in Figs 60A and 60B. Of these two alternatives – "SR-coating of drug layered nonpareilles" and "SR-coating of drug pellets" – formulation examples will be given in the following chapters. In the first method, a placebo pellet is coated with one coating of the active ingredient and a soluble film former and then with the sustained release coating. In the second method, a pellet of active ingredient rounded in a spheronizer is provided with a sustained release coating.
A further alternative, whereby a placebo pellet coated with active ingredient analogue to alternative A is coated with an enteric sub-coating of Kollicoat MAE 30DP prior to being coated with the sustained release coating of Kollicoat SR 30D or where both Kollicoat grades are combined in the one coating, is described in the literature using the example of verapamil sustained release pellets [14].





Figs 60A and 60B: Schematic illustration of two possibilities for coating sustained release pellets:
A = "Drug layering of nonpareilles and SR-coating"
B = "SR-coating of drug pellets"

In order to control the release of active ingredient, the thickness of the sustained release coating can be varied. Pellets containing soluble active ingredients require a thicker sustained release coating than insoluble active ingredients. In the latter case, the addition of a pore former is recommended to accelerate release. However, talcum, the most-used anti-adhesive agent, can also alter the release properties in some formulations if larger quantities are added. Curing of the coated pellets is no longer necessary as the minimum film-forming temperature of Kollicoat SR films is low enough.

Should the pellets have to be subsequently compressed (see chapter 4.3.5), a plasticizer should always be added to Kollicoat SR 30D. 10 % triethyl citrate, triacetin or 1,2-propylene glycol is normally adequate for this purpose.

4.3.4.2 Propranolol sustained release pellets ("SR-coating of drug pellets")

Propranolol pellets containing 20 % of the soluble active ingredient were prepared by granulation with water in a mixer granulator. These were then passed through a 1.5 mm sieve, rounded for 10 minutes in a spheronizer and subsequently dried in a fluidized bed granulator. The formulation of these instant release pellets is given in Table 80.

Table 80: Formulation of propranolol-HCl pellets (20 %)

Components	Amount
I Propranolol-HCl (BASF)	200 g
Microcrystalline cellulose	517 g
Lactose monohydrate	258 g
Kollidon VA64	25 g
II Water	approx. 500 g

500 g of the rounded pellets with 20 % active ingredient were coated with the amounts listed in Table 81 without the addition of pigments in an Aeromatic Strea-1 "top-spray" fluidized bed granulator. To prepare the spray suspension, plasticizer 1,2-propylene glycol or triethyl acetate was mixed with water and Kollicoat SR 30D stirred in. Separately, talcum was suspended in water and homogenised in a colloid mill. The talcum suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 81: Spray suspension and spraying conditions for propranolol sustained release pellets (Aeromatic Strea-1)

Spray suspension	**Amount**
I Kollicoat SR 30D	249.4 g
1,2-Propylene glycol (or triethyl acetate)	7.5 g
Water	174.6 g
II Talcum	29.9 g
Water	44.9 g
Spraying conditions	**Settings**
Batch size (active ingredient pellets)	500 g
Inlet air temperature	60 °C
Outlet air temperature	35 °C
Pellet temperature	36 °C
Spray pressure	1.2 bar
Spray rate	3 g/min
Amount of inlet air	80 m^3/h
Spray nozzle	0.8 mm
Spraying time	39 min
Subsequent drying	5 min / 45 °C
Amount applied (506 g spray suspension)	3 mg/cm^2

Measurement of the release of active ingredient propranolol-HCl from the sustained release pellets was carried out under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm. As can be seen in Fig. 61, active ingredient release was practically linear over a period of 24 h.

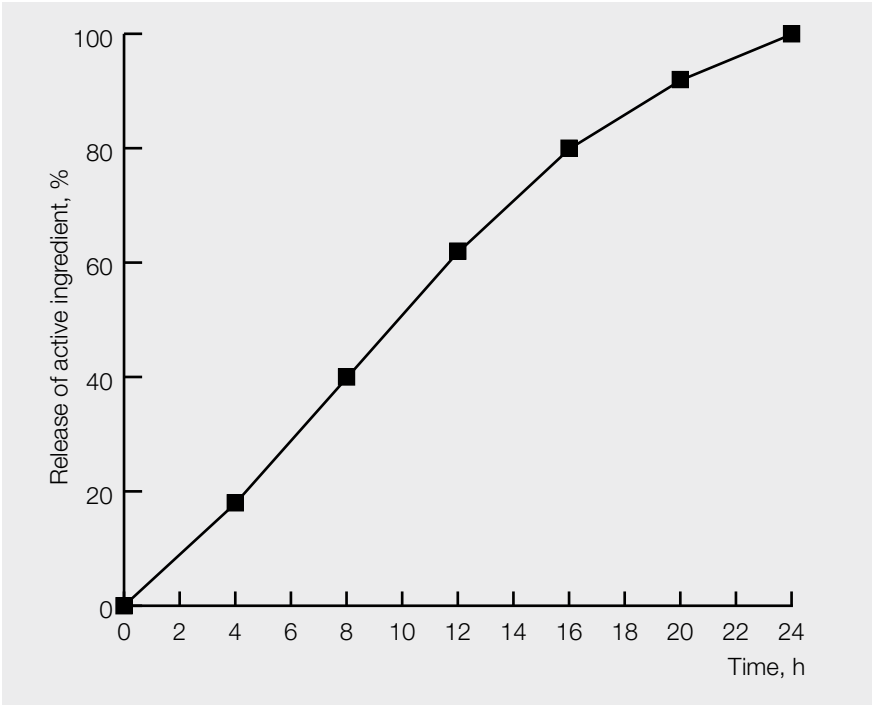


Fig. 61: Release of propranolol-HCl from sustained release pellets

A further formulation of propranolol sustained release pellets using the "SR-coating of drug layered nonpareilles" is described in chapter 4.3.5.2.

4.3.4.3. Ambroxol sustained release pellets ("SR-coating of drug layered nonpareilles")

Instant release pellets were produced by coating commercially available placebo pellets with a coating of the active ingredient ambroxol hydrochloride and HPMC 2910.

800 g of these pellets coated with the active ingredient were film coated with 5, 10, 15 and 20 % of a colourless film coating in a fluidized bed granulator GPCG1 (Glatt) using a process according to Wurster and the amounts and spraying conditions listed in Table 82.
To prepare the spray suspension, plasticizer triethyl acetate was mixed with water and Kollicoat SR 30D stirred in. Separately, talcum was suspended in water and homogenised with a high-speed stirrer. The talcum suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 82: Spray suspension and spraying conditions for ambroxol sustained release pellets (Glatt CPCG1)

Spray suspension	**Amount**
I Kollicoat SR 30D	533 g
Triethyl citrate	16 g
Water	433 g
II Talcum	56 g
Water	100 g
Spraying conditions	**Settings**
Batch size ("Drug layered nonpareilles")	800 g
Inlet air temperature	50 – 55 °C
Outlet air temperature	29 – 32 °C
Pellet temperature	35 – 40 °C
Spray pressure	1.2 bar
Spray rate	Approx. 4.5 g/ml
Amount of inlet air	90 m^3/h
Spray nozzle	1.2 mm
Spraying time	220 min
Subsequent drying	15 min/40 °C
Amount applied	5 – 20 % solids

Measurement of the release of active ingredient ambroxol-HCl from the pellets was carried out under the following conditions: 0 – 24 h in phosphate buffer pH 7.4 at 37 °C and 100 rpm. Active ingredient release was measured using coating amounts between 5 and 20 %. Fig. 62 shows that between 15 and 20 % coating there is practically no difference and that in this case a coating of 10 – 15 % would be appropriate for active ingredient release over a period of 24 h.

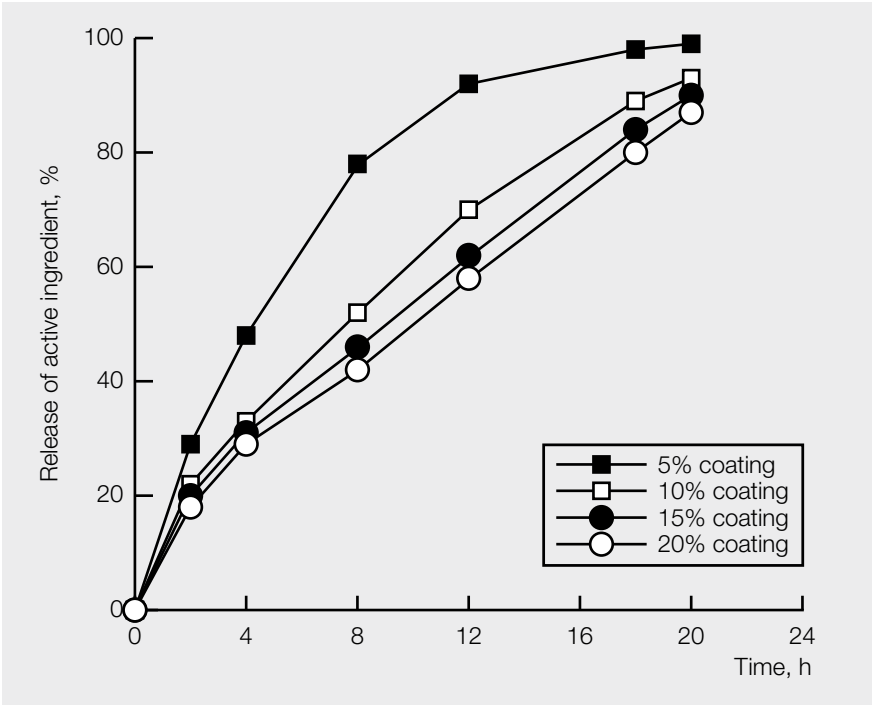


Fig. 62: Release of ambroxol-HCl from sustained release pellets

4.3.4.4. Caffeine sustained release pellets ("SR-coating of drug pellets")

In this formulation example with a red coating, the sustained release effect and the stability of release were investigated.

Caffeine pellets containing 10 % active ingredient were produced using extrusion granulation with water. After sieving, they were passed through a 1.5 mm sieve, rounded in a spheronizer, dried in a fluidized bed granulator and fractionated. The formulation of the active ingredient pellets is given in Table 83.

Table 83: Formulation of caffeine active ingredient pellets (10 %)

Components	Amount
I Caffeine (BASF)	100.0 g
Microcrystalline cellulose	437.5 g
Lactose monohydrate	437.5 g
Kollidon VA64	25.0 g
II Water	As required

500 g of the rounded pellets with 10 % active ingredient were coated with the amounts listed in Table 84 in an Aeromatic Strea-1 fluidized bed granulator.
To prepare the spray suspension, plasticizer 1,2-propylene glycol was mixed with water and Kollicoat SR 30D stirred in. Separately, talcum and the pigments iron oxide and titanium oxide were suspended in the solution of Kollidon 30 and homogenised in a colloid mill. The homogenised pigment suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 84: Spray suspension and spraying conditions for caffeine sustained release pellets (Aeromatic Strea-1)

Spray suspension	**Amount**
I Kollicoat SR 30D	190.0 g (57.0 g solid)
1,2-Propylene glycol	5.7 g
Water	148.0 g
II Talcum	14.2 g
Titanium dioxide	2.0 g
Sicovit red iron oxide	2.0 g
Kollidon 30	2.0 g
Water	42.4 g
Spraying conditions	**Settings**
Batch size (active ingredient pellets)	500 g
Inlet air temperature	60 °C
Outlet air temperature	33 – 35 °C
Pellet temperature	36 °C
Spray pressure	1.4 bar
Spray nozzle	0.8 mm
Subsequent drying	5 min/45 °C
Amount applied (406 g spray suspension)	3 mg/cm^2

Measurement of the release of active ingredient caffeine from the pellets was carried out under the following conditions:
0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm. As can be seen from Fig. 63, active ingredient release was over a period of 24 h.

In order to investigate storage stability and the influence of storage on the release of the active ingredient, the pellets were stored, closed, over a period of 2 years at room temperature. The release of active ingredient was subsequently measured. The results are shown in Fig. 63 compared with the initial values prior to storage. Within the range 4 – 12 h, a minor reduction in release was observed compared to the initial values. This, however, was so small that it could be practically neglected. At higher temperatures, e.g. 60 °C and, especially, in combination with higher relative humidities, release after storage can be significantly lower. This must be taken fully into account when carrying out stress tests with Kollicoat SR 30D.

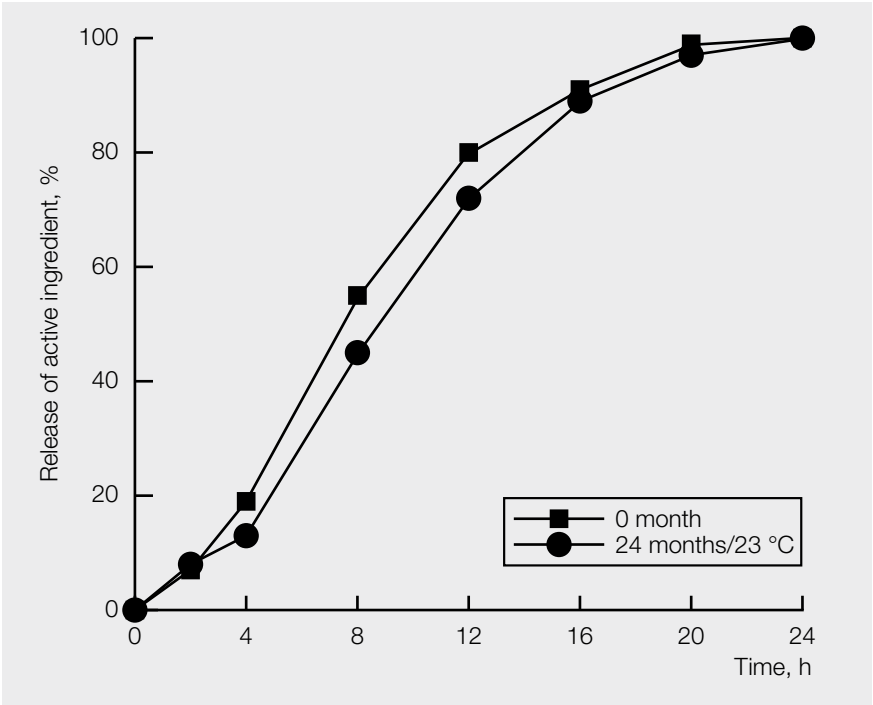


Fig. 63: Release of caffeine sustained release pellets after manufacture and storage over a period of 2 years at room temperature

If in this formulation 1,2-propylene glycol (10 %, based on the Kollicoat SR polymer) is replaced by other plasticizers, e.g. 5 or 10 % triethyl acetate or 5 % triacetin, the release of caffeine remained practically unchanged.

By increasing the amount of talcum from 25 %, based on the Kollicoat SR polymer, to twice the concentration, the speed of release increased from an approximate t_{50} value of 13 hours to one of approximately 11 hours, i.e. the level of the release curve was about 10 % higher. By increasing the amount of talcum threefold, the release speed accelerated significantly and the t_{50} value was approximately 6 hours.

4.3.4.5 Carbamazepin sustained release pellets ("SR-coating of drug pellets")

Carbamazepin pellets containing 50 % active ingredient were produced using extrusion granulation with water. After sieving, they were rounded in a spheronizer, passed through a 1.5 mm sieve, dried in a fluidized bed granulator and fractionated. The 0.7 – 1.4 mm fraction was then used for film coating. The formulation of the active ingredient pellets is given in Table 85.

Table 85: Formulation of carbamazepin active ingredient pellets (50 %)

Components	**Amount**
I Carbamazepin (Farchemia FIS)	50.0 g
Microcrystalline cellulose	47.5 g
Kollidon VA64	2.5 g
II Water	As required

500 g of the rounded pellets with 50 % active ingredient were coated with the colourless coating formulation listed in Table 86 in an Aeromatic Strea-1 fluidized bed granulator. To prepare the spray suspension, plasticizer 1,2-propylene glycol was mixed with water and Kollicoat SR 30D was stirred in. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 86: Spray suspension and spraying conditions for carbamazepin pellets (Aeromatic Strea-1)

Spray suspension	**Amount**
Kollicoat SR 30D	60.5 %
1,2-Propylene glycol	1.8 %
Water	37.6 %
Spraying conditions	**Settings**
Batch size (active ingredient pellets)	500 g
Inlet air temperature	60 °C
Outlet air temperature	35 °C
Pellet temperature	36 °C
Spray pressure	1.0 bar
Spray rate	11.5 g/min
Subsequent drying	3 min/40 °C
Amount applied	1 mg/cm^2

Measurement of the release of active ingredient carbamazepin from the pellets was carried out under the following conditions:
0 – 24 h in an aqueous solution of 1 % sodium lauryl sulphate at 37 °C and 75 rpm. Active ingredient release was over a period of more than 24 h (Fig. 64). Release of the active ingredient was compared with that from uncoated pellets.

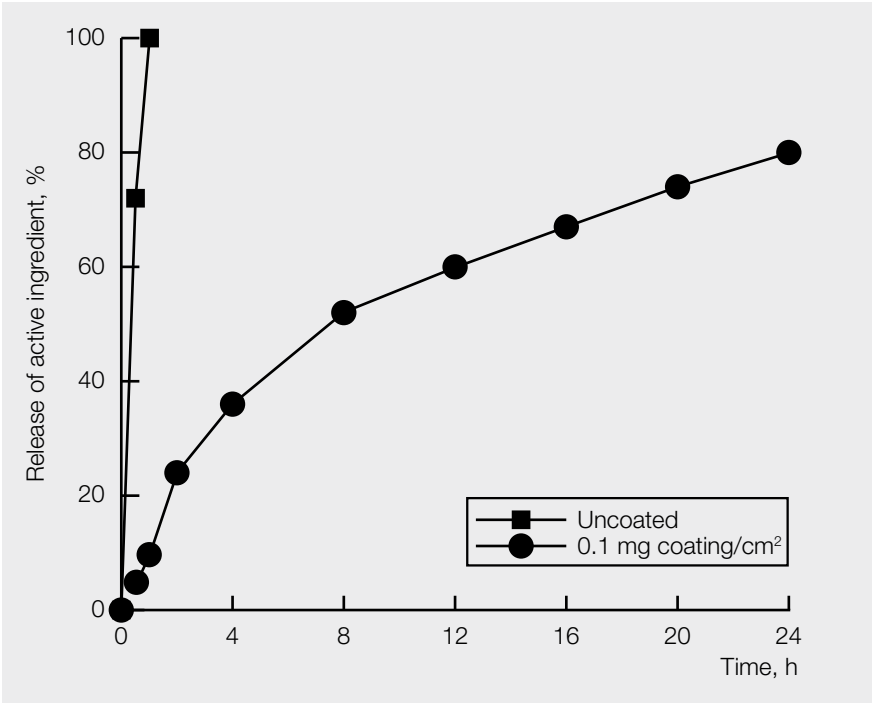


Fig. 64: Release from carbamazepin sustained release pellets

4.3.5 Sustained release matrix tablets prepared by compression of SR pellets with Kollicoat SR 30D

4.3.5.1 Introduction

As tablets are the most popular and best accepted drug form, sustained release pellets can also be compressed to tablets instead of being filled into hard gelatine capsules. This is possible using the procedure described in chapter 4.3.2 for the compression of sustained release granules. However, in the case of pellets, the plasticity of the coating is even more important as these rounded particles have to be deformed even more in order to produce tablets with a sustained release matrix and no hollow spaces.
Thus, it is not possible to compress sustained release pellets coated with the popular ethyl cellulose to tablets. Even if 25 % triethyl acetate is added to the ethyl cellulose, the release profile is significantly altered due to the mechanical stress of compression. Fig. 65 illustrates this using the example of propranolol sustained release pellets coated with a film comprising 20 % ethyl cellulose (Aquacoat ECD) and subsequently compressed to tablets using medium compression force (15 kN) in a mixture containing 50 % microcrystalline cellulose [10]. The loss of sustained release effect brought about by compression is disproportionately high and hence unacceptable in practice.

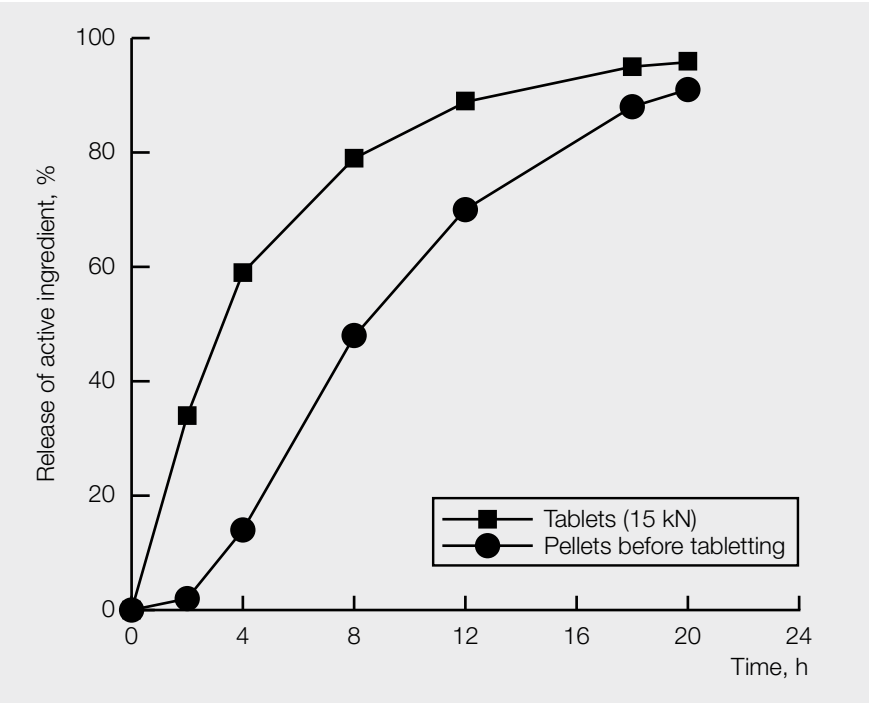


Fig. 65: Release of propranolol-HCl from sustained release pellets containing ethyl cellulose before and after compression to tablets (0.1 N hydrochloric acid, 37 °C, 100 rpm) [10]

If the same propranolol pellets are coated using the same amount of Kollicoat SR film containing only 10 % instead of 25 % of triethyl acetate plasticizer instead of ethyl acetate and if these are subsequently compressed in the same way to tablets at a medium compression force of 15 kN in a mixture of 50 % microcrystalline cellulose, the following is observed: the release effect is not reduced as a result of the mechanical stress of compression (see chapter 4.3.5.2, Fig. 66). Electron microscopic photos show that the pellets in this case are not destroyed but only deformed [10]. For this reason, Kollicoat SR 30D can be regarded as an excellent film former for the technology of preparing tablets from sustained release pellets.

The sustained release pellets can be compressed to tablets with various fillers; however, release is not always uniform as the pores and dissolution speeds tend to vary. Based on experience gained, the differences are not very great [10]. Strongly swelling or strongly hydrophilic excipients such as micronised crospovidone (e.g. Kollidon CL-M) accelerate release. In the case of sparingly soluble active ingredients such as theophylline or carbamazepin, hydrophilic fillers like lactose monohydrate in pure or granule form (Ludipress LCE) or even Kollidon CL-M are perhaps more suitable. For readily soluble active ingredients, microcrystalline cellulose could be the substance of choice.

4.3.5.2 Propranolol sustained release matrix tablets prepared from pellets

Propranolol sustained release pellets were produced using the "SR-coating of drug layered nonpareilles" technology. Placebo pellets were coated with a 10 % soluble HPMC film containing active ingredient propranolol-HCl. 800 g of the pellets were coated with a white Kollicoat SR sustained release film in a fluidized bed coater CPGC1 (Glatt) according to the formulation and spraying conditions given in Table 87. 10 % triethyl acetate, based on the solid Kollicoat SR, was added to the formulation; this provided the necessary plasticity for subsequent compression to tablets.

To prepare the spray suspension, the plasticizer was mixed with water and Kollicoat SR 30D was stirred in. Separately, talcum was suspended in water and homogenised in a colloid mill. The talcum suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 87: Spray suspension and spraying conditions for propranolol sustained release pellets (Glatt CPCG1)

Spray suspension	**Amount**
I Kollicoat SR 30D	533 g
Triethyl citrate	16 g
Water	433 g
II Talcum	56 g
Water	100 g
Spraying conditions	**Settings**
Batch size (pellets with a coating of active ingredient)	800 g
Inlet air temperature	50 – 55 °C
Outlet air temperature	29 – 32 °C
Air flow	35 – 40 °C
Spray nozzle	90 m^3/h
Spray pressure	1.2 mm
Spray rate	1.2 bar
Spraying duration	4.5 g/min
Subsequent drying	220 min
Amount applied	15 min/40 °C
	20 % solids

250 g of the sustained release pellets thus produced of size of 850 – 1000 µm were mixed with 250 g of microcrystalline cellulose and 2.5 g of magnesium stearate. These were sieved and compressed to biplanar tablets of 10 mm diameter, a hardness of approx. 100 N and a weight of 400 mg using medium- and high compression forces of 15 and 25 kN respectively. Release was achieved that was not accelerated by the mechanical stress caused by compression so that there was no decrease in the sustained release effect (Fig. 66) as was the case when using ethyl cellulose (see Fig. 65)

[10]. Rather, due to the compression process, strong local warming could possibly bring about a certain sintering effect on the part of the polymer and hence some slowing down of the release rate. The release shown in Fig. 66 was measured in the same way as that in Fig. 65 in 0.1 N hydrochloric acid at 37 °C and 100 rpm.

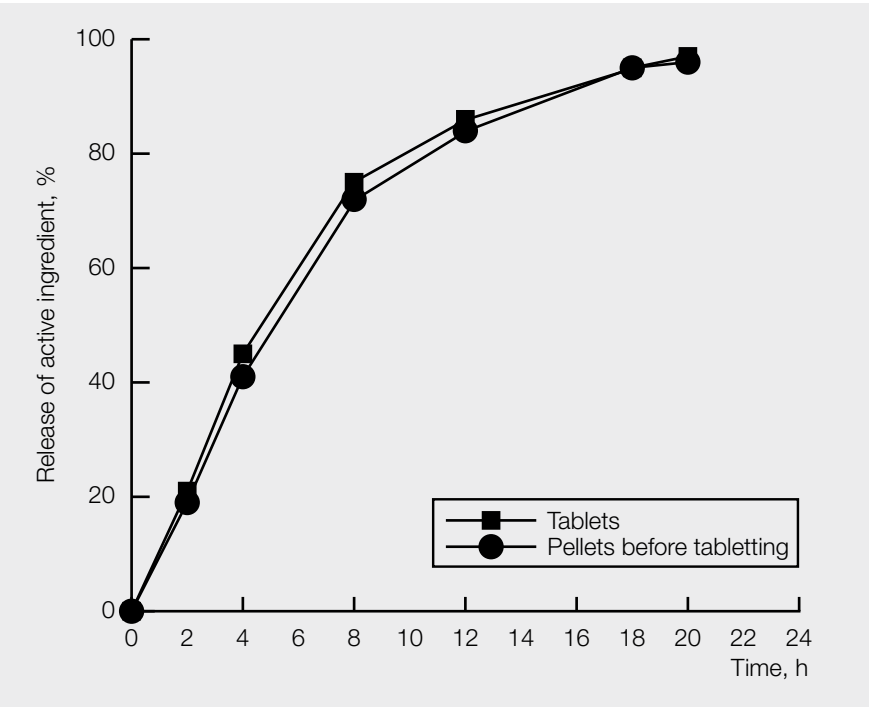


Fig. 66: Release of propranolol-HCl from Kollicoat SR sustained release pellets before and after compression to tablets (compression force 15 kN) [10]

4.3.5.3 Ambroxol sustained release matrix tablets prepared from pellets

The ambroxol sustained release pellets as described in chapter 4.3.4.3, with coatings of 10 and 20 %, were compressed to biplanar tablets using direct tabletting technology in the formulation given in Table 88. Medium compression force of 15 kN was used and the tablets had a weight of 400 mg and a diameter of 10 mm. The hardness of the tablets produced was between 92 and 116 N.

Table 88: Formulation of ambroxol sustained release tablets from pellets

Components	**Amount**
Ambroxol-HCl sustained release pellets with Kollicoat SR 30D (as described in chapter 4.3.4.3)	250 g
Microcrystalline cellulose	250 g
Magnesium stearate	2.5 g

The release of ambroxol-HCl from the sustained release tablets thus produced was not quite as linear as the sustained release pellets prior to compression (c.f. chapter 4.3.4.3); however, they produced release of active ingredient over a period of 24 h. The curve of the tablets made from pellets with 20 % coating was somewhat flatter than that with 10 % (Fig. 67).

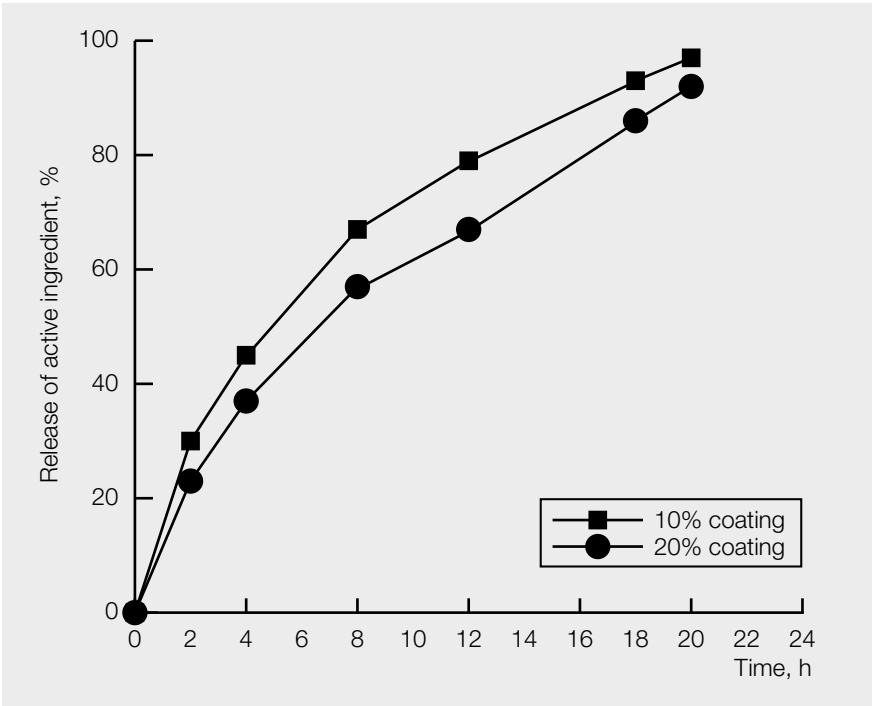


Fig. 67: Release of ambroxol sustained release tablets produced from pellets with 10 and 20 % Kollicoat SR coating

4.3.6. Taste masking of granules and tablets with Kollicoat SR 30D

4.3.6.1 Introduction

Kollicoat SR 30D films are suitable for masking the taste of crystals or instant release tablets of bitter or unpleasantly tasting active ingredients such as the sympatho-mimetic pseudo-ephedrine, the anti-hypertonic agent ramipril or several of the analgesics. However, in these applications, a compromise has to be found between the insolubility of the film former or its taste masking effect and the required speed of release. This is all the more important when analgesics are involved, e.g. with the bitter active ingredients tramadol, acetaminophen (paracetamol) or ibuprofen, where the pain-relieving effect should occur as soon as possible after taking the drug.
Such a compromise is often a balance act; it can best be achieved by adding precisely calculated amounts of soluble or swelling pore formers such as povidone, micronised crospovidone, microcrystalline cellulose, copovidone etc. Pore formers such as Kollidon 30, Kollicoat IR or Kollidon VA64 that are also film formers are the agents of choice if their concentrations in the film is high, as in the formulation with acetaminophen (chapter 4.3.6.2). The effect of the pore former can be seen in Fig. 68; here, for the active ingredient acetaminophen, uncoated crystals are compared with crystals with a coating of Kollicoat SR 30D without a pore former and a coating with a formulation as described in chapter 4.3.6.2 with pore former Kollidon 30. The coated taste-masked crystals with pore former show practically the same release as uncoated crystals whereas the crystals without pore former result in significant slowing down of release.

It has to be taken into account that only so much coating should be applied that the taste masking just covers the period when the crystals or tablets are normally in the mouth.

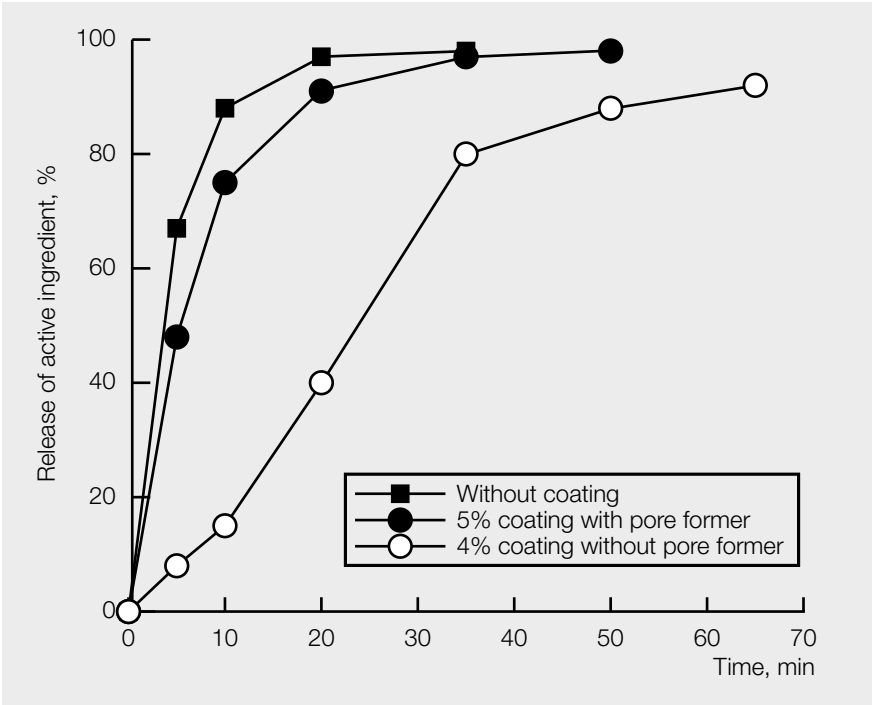


Fig. 68: Influence of pore former Kollidon 30 on the release of acetaminophen crystals coated with Kollicoat SR polymer for taste masking

It is a well-known fact that the particle size of the active ingredient can influence taste masking due to the different surface areas of the particles. This also applies to crystals coated with Kollicoat SR 30D. If fine crystals are being used, the surface area is greater and hence the taste is all the more intensive. For this reason, the same effect of taste masking cannot be achieved with the same coating amount as with coarser crystals. Table 89 illustrates this with three different coating thicknesses and two sizes of crystal of acetaminophen, the formulation given in chapter 4.3.6.2 being used (4 parts solid Kollicoat SR + 3 parts Kollidon 30). Tasting was carried out subjectively using several persons present in the laboratory.

Table 89: Influence of coating amount on taste masking using different particle sizes of acetaminophen crystals

Type of crystal	Coating (4 parts solid Kollicoat SR + 3 parts Kollidon 30)	Duration of masking effect
Small crystals	8.75 %	12 sec
	17.50 %	24 sec.
	26.25 %	48 sec.
Large crystals ("granules")	8.75 %	62 sec.
	17.50 %	96 sec.
	26.25 %	> 120 sec.

4.3.6.2 Taste masking of acetaminophen crystals and tablets

In this formulation example, the influence of the compression of taste-masked crystals to tablets was investigated in relation to the release of active ingredient.

300 g of acetaminophen crystals were coated with a spray suspension which, in addition to Kollicoat SR 30D, also contained Kollidon 30 as a film forming pore former. The ratio of solid Kollicoat SR to Kollidon 30 was 4:3. As a coating of 8.75 % (5 % Kollicoat SR + 3.75 % Kollidon 30) proved to be inadequate for taste masking (see Table 89), twice and three times the amounts respectively according to formulations 1 and 2 in Table 90 were sprayed onto the crystals in a fluidized bed granulator using the "top-spray" method.

Table 90: Formulation of the spray suspension and spraying conditions in an Aeromatic Strea-1 for the taste masking of 300 g of acetaminophen crystals

Spray suspension	Amount Formulation 1	Formulation 2
Kollicoat SR 30D	100 g = 10 %	150 g = 15 %
Kollidon 30	22.5 g = 7.5 %	33.75 g = 11.25 %
Water	140 g	210 g
Spraying conditions	**Settings**	
Batch size (crystals)	300 g	300 g
Inlet air temperature	60 °C	60 °C
Outlet air temperature	33 – 35 °C	33 – 35 °C
Spray nozzle	0.8 mm	0.8 mm
Spray pressure	1.2 bar	1.2 bar
Subsequent drying	5 min/40 °C	5 min/40 °C
Total amount applied	17.5 %	26.3 %
Amount applied (solid Kollicoat SR)	**10 %**	**15 %**

The coated crystals thus produced were compressed to biplanar tablets of 400 mg weight and 16 mm diameter using the direct tabletting procedure. The tablet formulation is shown in Table 91.

Table 91: Tablet formulation of taste-masked acetaminophen

Components	**Amount (%)**	**Amount (mg)**
Coated acetaminophen (acc. to Table 90)	37.91	400
Sorbitol (Karion Instant)	28.44	300
Kollidon VA64	9.00	95
Microcrystalline cellulose	14.22	150
Kollidon CL	9.48	100
Magnesium stearate	0.95	10

The release from taste-masked tablets of acetaminophen coated with 10 and 15 % solid Kollicoat SR (formulations 1 and 2) was compared to that of the coated crystals prior to compression in 0.1 N hydrochloric acid at 50 rpm. Fig. 69 shows that compression slows down release somewhat; however, 90 % of the active ingredient is released within 60 minutes.

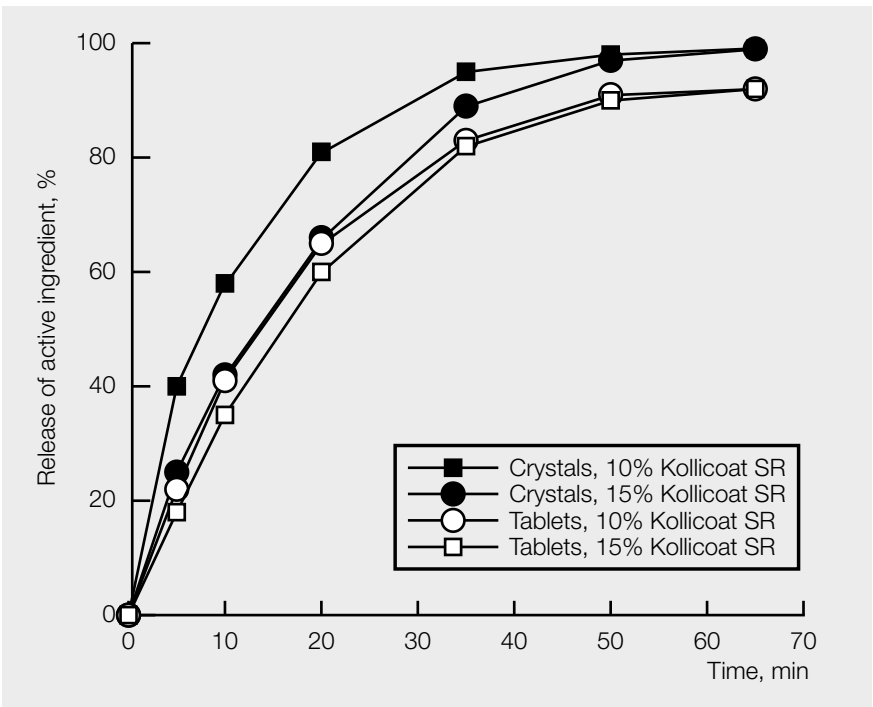


Fig. 69: Release of acetaminophen from taste-masked crystals and the tablets made from these

4.3.6.3 Taste masking of ibuprofen granules and tablets

In this formulation example, two pore formers with different action mechanisms were compared.

300 g ibuprofen type DTP (BASF) containing 97 % active ingredient were coated with a spray suspension that, apart from Kollicoat SR 30D, also contained Kollidon 30 (formulation A) or Kollidon CL-M (formulation B) as film former or swelling pore former respectively (Table 92). The coating amount of solid Kollicoat SR, based on the active ingredient, to that of pore former was 3:1 and 4:1 in formulations A and B respectively.
Both formulations (Table 92) were sprayed onto the active ingredient in a fluidized bed granulator using the "top-spray" method.

Table 92: Formulations of the spray suspension and spraying conditions in an Aeromatic Strea-1 for the taste masking of 300 g of ibuprofen

Spray suspension	**Amount**	
	Formulation A	**Formulation B**
Kollicoat SR 30D	150 g = 15 %	150 g = 15 %
1,2-Propylene glycol	4.5 g	4.5 g
Kollidon 30	15.7 g = 5.2 %	--
Kollidon CL-M	--	11.2 g = 3.7 %
Water	156 g	138 g
Spraying conditions	**Settings**	
Batch size (ibuprofen DTP)	300 g	300 g
Inlet air temperature	40 °C	40 °C
Outlet air temperature	20 – 22 °C	20 – 22 °C
Spray nozzle	0.8 mm	0.8 mm
Spray pressure	1.2 bar	1.2 bar
Subsequent drying	5 min/40 °C	5 min/40 °C
Total amount applied	21.7 %	20.2 %
Amount applied (solid Kollicoat SR)	15 %	15 %

The active ingredient granules thus obtained from formulation B with Kollidon CL-M as pore former were compressed to biplanar tablets with 400 mg coated active ingredient and 16 mm diameter. The direct tabletting procedure was used in conjunction with a low compression force (6.5 kN). The tablet formulation is shown in Table 93.

Table 93: Tablet formulations of taste-masked ibuprofen

Components	Amount (%)	Amount (mg)
Ibuprofen granulate (Formulation B)	37.91	400
Sorbitol (Karion Instant)	28.44	300
Kollidon VA64	9.00	95
Microcrystalline cellulose	14.22	150
Kollidon CL	9.48	100
Magnesium stearate	0.95	10

The release from the taste-masked tablets made from the ibuprofen granules produced according to formulation B was compared to that of the uncompressed granules of formulations A and B respectively in phosphate buffer of pH 7.2 and at 50 rpm. Fig. 70 shows that in the case of the uncompressed granules, Kollidon 30 is more effective than Kollidon CL-M as a pore former. This is no doubt because of the higher amount of Kollidon 30 used.
On the other hand, in the case of swelling pore former Kollidon CL-M, the release of ibuprofen is not slowed down as a result of the low compression force used.

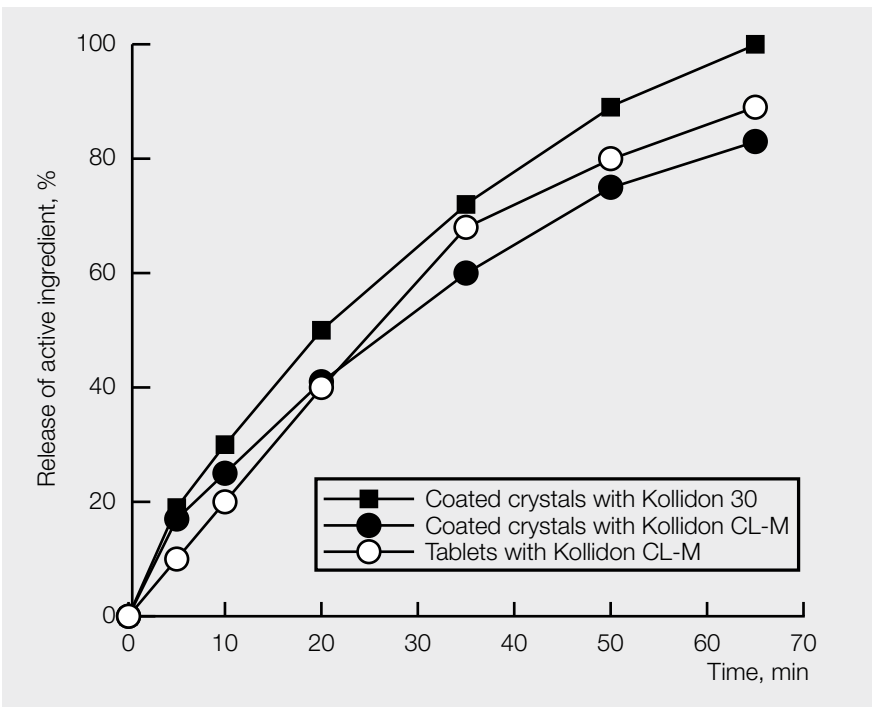


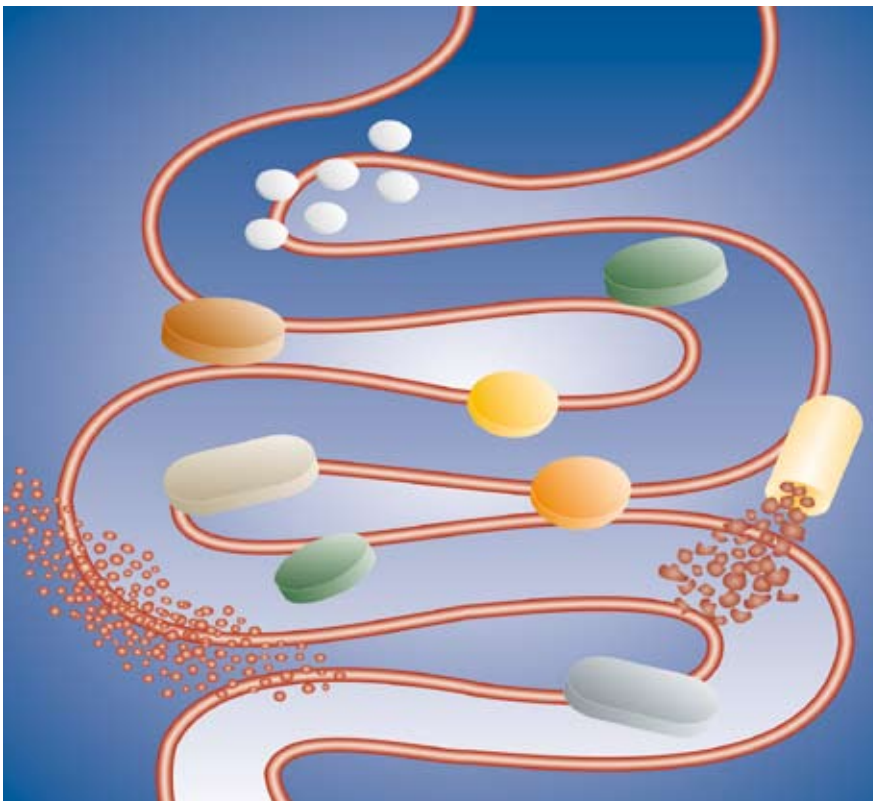
Fig. 70: Release of coated ibuprofen with Kollidon 30 and Kollidon CL-M as pore formers before and after compression (6.5 kN)

4.3.7 Cleaning the machines after processing with Kollicoat SR 30D

When processing with coating spray suspensions, residues of polymer, pigment and other excipients often collect on the inside walls of the machine and in the tubing and spraying systems. As long as the films are in a fresh condition and capable of swelling, they can be mechanically removed with relative ease. Subsequent to longer drying periods, however, the films tend to harden. This renders cleaning somewhat more difficult.

As polyvinyl acetate is insoluble in water, acid and alkali, residues cannot simply be removed with aqueous solutions. However, they can be soaked in hot water until they swell and then removed with high-pressure or hot water cleaners or mechanically with brushes and conventional cleansers. The smaller machine parts such as nozzles and tubing are best cleaned by soaking overnight in cleansers. If the residues prove to be difficult to remove, brushes or plastic scrapers can be used.

As polyvinyl acetate is soluble in ethanol and 2-propanol, these alcohols can also be used. This is of particular interest for the cleaning of smaller apparatus parts such as nozzles and tubes.



5. Kollicoat EMM 30D

5.1 Structure, composition, packaging

5.1.1 Chemical structure, composition

Kollicoat EMM 30D is an aqueous dispersion of a neutral co-polymer made up of the monomers ethyl acrylate and methyl methacrylate and with a solid content of 30 %. The ratio of the two monomers is 2:1. The weight average molecular weight (Mw) is approximately 800,000. The chemical structure of the co-polymer is shown in Fig. 71.

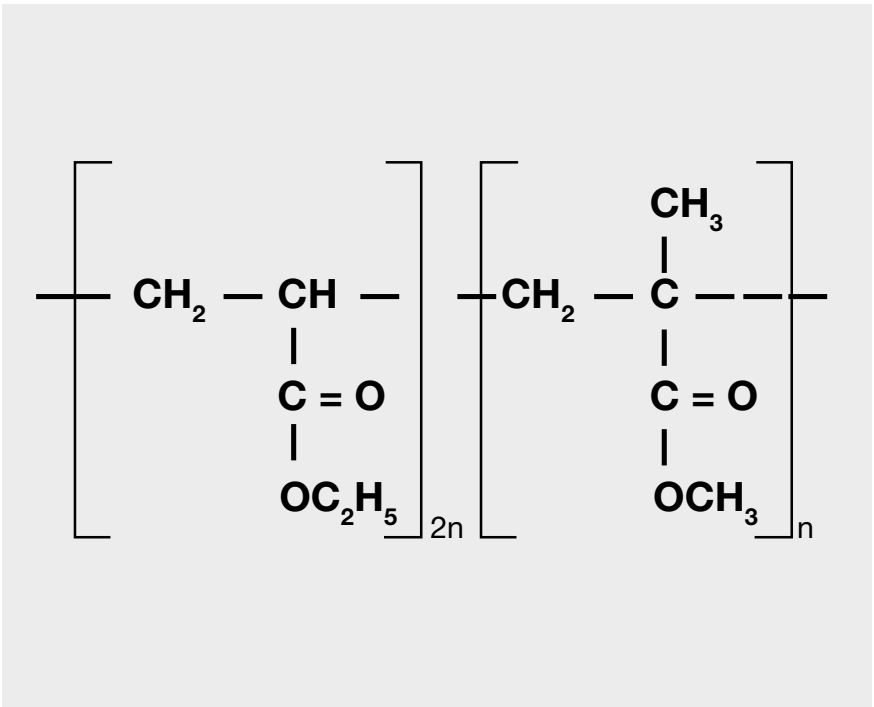


Fig. 71: Chemical structure of the Kollicoat EMM copolymer

To prevent sedimentation of undissolved particles in the dispersion during storage, the emulsifier nonoxinol 100 is added; the precise amount is listed in Table 94. The emulsifier also increases the wettablitiy of Kollicoat EMM 30D films in gastric juice and intestinal fluid.

Table 94: Precise composition of the Kollicoat EMM 30D dispersion

Components	Content
Ethyl acrylate-methyl methacrylate co-polymer 2:1	28.5 %
Nonoxinol 100	1.5 %
Water	70.0 %

Kollicoat EMM 30D has the BASF article number 50893449 (25 kg) and the PBG number 10213678.

5.1.2 Packaging

Standard Kollicoat EMM 30D dispersions are packaged in 25-kg polyethylene drums (packaging no. 67000739). Larger packages are available upon request.

Kollicoat EMM 30D is somewhat sensitive to microbiological contamination. This means that opened packages should be used up immediately if possible; if this is not possible, preservatives should be added for further storage.

5.2 Product properties

5.2.1 Description

As it is produced in Ludwigshafen, Germany according to cGMP, Kollicoat EMM 30D is of high pharmaceutical quality. The suspension has a milky white-to-yellow appearance and has a slight characteristic odour.

5.2.2 Specifications, pharmacopoeias

Kollicoat EMM 30D is described in several pharmacopoeial monographs and corresponds to these. The main monographs are “POLYACRYLATE dispersion 30 per cent” of the European Pharmacopoeia Ph.Eur. and “ETHYL ACRYLATE AND METHYL METHACRYLATE COPOLYMER DISPERSION” of the Japanese Pharmaceutical Excipients JPE.

The added excipient nonoxinol 100 is also of pharmaceutical quality.

The current specifications of Kollicoat EMM 30D are listed in Table 95. The methods are those contained in the European Pharmacopoeia Ph.Eur. Several methods have been specifically developed by BASF AG for this product and can be obtained upon request. The actual specifications are listed in the current technical data sheet.

Table 95: Specifications of Kollicoat EMM 30D

Parameter	Limit	Method
Identity	Corresponds	Ph. Eur.
Film formation	Corresponds	See below
Relative density	1.045 – 1.065	Ph. Eur.
Viscosity	Max. 100 mPa·s	See below
Agglomerates	Max. 0.5 %	See below
Solid content	28.5 -31.5 %	Ph. Eur.
Sulphated ash	Max. 0.5 %	Ph. Eur.
Heavy metals	Max. 20 ppm	Ph. Eur.
Arsenic	Max. 2 ppm	USP
Monomers	Max. 100 ppm	Ph. Eur.
Microbiological status	Corresponds to category 3	Ph. Eur.

Film formation is carried out using the following test procedure:
10 g of Kollicoat EMM 30D is spread on a glass plate and allowed to dry.
A colourless film is formed.

The viscosity is measured with a Brookfield rotation viscosimeter at 23 °C and a shear of 250 sec^{-1} according to DIN EN ISO 3219.

The proportion of agglomerates can be measured using the following method:
100 g of Kollicoat EMM 30D is passed through a 90-µm sieve. The residue is dried to constant weight at 105 °C and weighed.

5.2.3 Solubility, miscibility

Kollicoat EMM 30D is miscible with water in any ratio whereby it does not lose its milky appearance. If mixed with ethanol, 2-propanol or acetone in the ratio of 1:5, a slightly opalescent solution of increased viscosity results.
On adding less hydrophilic organic solvents, the polymer first precipitates but dissolves again on adding further solvent.
Kollicoat EMM 30D is insoluble in dilute acids or bases and retains its typical appearance in their presence.

5.2.4 Viscosity

The viscosity of Kollicoat EMM 30D is always less than 100 mPa·s. For this reason, it is practically always possible to use the dispersion in a higher concentration or even undiluted for spraying purposes. The viscosity can be lowered a little by warming.
Addition of ethanol or 2-propanol increases the viscosity.

5.2.5 Particle size

The dispersed latex particles in Kollicoat EMM 30D usually have a mean diameter of approximately 150 nm (typical value). They are thus so fine that, under normal conditions, no sedimentation occurs. However, temperatures of over 35 °C, frost and too high a shear force brought about by vigorous stirring with the formation of too much foam should be avoided otherwise agglomerates can form that make spraying impossible. Several other factors can also cause agglomeration, e.g. the addition of high concentrations of fine pigments, radical adjustment of the pH or the addition of organic solvents.

5.2.6 Properties of Kollicoat EMM films

5.2.6.1 Dissolution, adsorption of water

Kollicoat EMM 30D films dissolve neither in dilute acid nor dilute alkali, e.g. artificial gastric juice or intestinal fluid. For this reason, they are excellently suited for use as sustained release coatings as they enable active ingredient to be released, controlled by diffusion, over a longer period of time. The release depends on the coating thicknesses, solubility of the active ingredient and any pore formers added.

Kollicoat EMM 30D films can adsorb up to 60 % of their own weight of water. In doing so they swell somewhat but do not dissolve. In addition, the water can also slowly penetrate through the film.

5.2.6.2 Plasticity, minimum film-forming temperature

The very high degree of plasticity and elasticity of Kollicoat EMM films is reflected in the elongation at break value of 600 % at room temperature [6]. For this reason, plasticizers are not required in any of the Kollicoat EMM 30D applications.

However, not only plasticity and elongation at break are relevant for application as a film former; the minimum film-forming temperature (MFT), related to a certain extent, also plays a role. This is an important parameter as only a completely closed film guarantees reproducible sustained release of the active ingredient. In the case of Kollicoat EMM 30D, the MFT is approximately 5 °C [12]; hence, film formation, as shown in Fig. 72, is possible at room temperature. Initially, after spraying, the individual latex particles on the pellet or tablet surface are still in a layer of water. In a second stage, the water evaporates; however, the latex particles remain unchanged in position next to each other. With Kollicoat EMM 30D, the final stage of film formation, where the particles coacervate, takes place very quickly. This process is photographically illustrated in chapter 3.3.1.

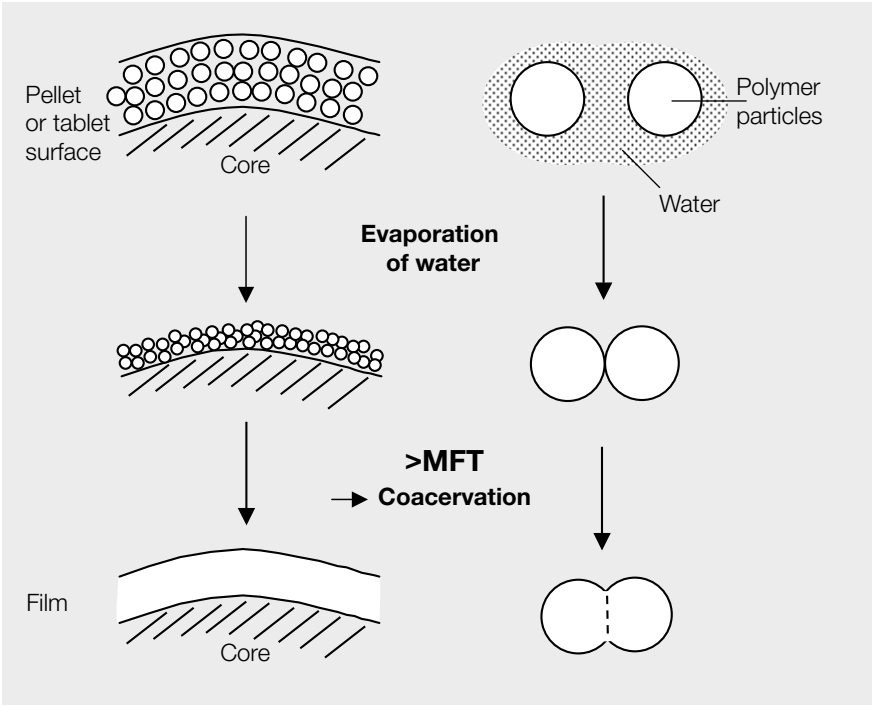


Fig. 72: Schematic illustration of film formation on a pellet or tablet surface

5.2.6.3 Tackiness

The one disadvantage of Kollicoat EMM 30D as a film former is its tackiness. For this reason, practically all formulations must include an anti-tack agent. The most widely used agent of this type is talcum; however, microcrystalline cellulose (MCC), hypromellose and simethicon are also suitable. However, these all have some influence on the sustained release effect of the polymer. This is schematically illustrated in Fig. 73. In the case of hypromellose 2910, type 3 mPa·s (HPMC), this side-effect is strongest; for, as fast as the tackiness decreases with increase in concentration, the more the sustained release effect of Kollicoat EMM decreases due to its pore forming effect. In the case of microcrystalline cellulose (MCC), the sustained release effect is not so strongly reduced but its influence on tackiness is considerably less than in the case of hypromellose. The fact that talcum in concentrations normally used has practically no effect on the sustained release effect explains why it is the most widely used anti-tack agent.

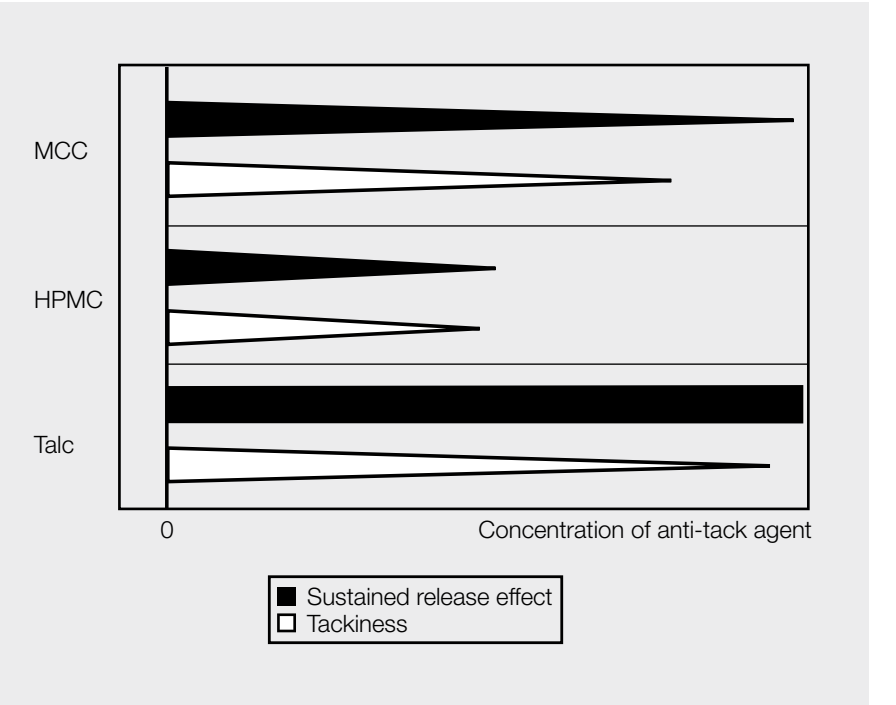


Fig. 73: Influence of anti-tack agents on the tackiness and the sustained release effects of Kollicoat EMM films as a function of the concentration of the anti-tack agent.

Table 96 shows that hypromellose (HPMC 2910, type 3mPa·s) has a stronger anti-tack effect than microcrystalline cellulose (MCC). In this case, the tackiness was quantified using the Hoessel method [1]. A scale of 0 to 5 proved adequate, whereby tackiness was registered between the fingers at a value of about 1.4 and above. In the case of microcrystalline cellulose, more than double the concentration, based on the polymer, was required than with HPMC to bring the Hoessel value for tackiness subjectively under 1.4. If the influence on sustained release is to be reduced to a minimum, both excipients may be combined.

Table 96: Tackiness of Kollicoat EMM films with MCC and HPMC as anti-tack agents (Hoessel method)

Anti-tack agent	Concentration, based on the polymer	Tackiness (Hoessel)
Microcrystalline cellulose (MCC)	0 %	4.0
	20 %	3.0
	30 %	2.5
	40 %	1.5
	50 %	1.0
Hypromellose (HPMC)	10 %	2.0
	20 %	0.5
MCC + HPMC	30 % + 5 %	0.5

The anti-tack effect of talcum can be enhanced in the case of Kollicoat EMM 30D films by combining with simethicon (see chapter 5.3.1).

5.2.7 Stability, storage

An unopened dispersion of Kollicoat EMM 30D can be kept for more than 18 months at room temperature providing the valid specifications given in chapter 5.2.2 are fulfilled.

Kollicoat EMM 30D should be stored at room temperature in unopened original packs. As in the case of other aqueous polymer dispersions, temperatures over 30 °C and under 0 °C should be avoided as under these conditions agglomeration can take place. Too vigorous shaking accompanied by the formation of foam has a similar effect. Agglomerates can block the spray nozzles, hence making the product unsuitable for this application. As the product is sensitive to microbiological contamination, opened packs should be used up as soon as possible.

5.3 Applications of Kollicoat EMM 30D

5.3.1 Overview and general information

The various film forming functions of Kollicoat EMM 30D can be used in a variety of drug dosage forms (see Table 97). The most important applications are those enabling controlled release of the active ingredient such as in sustained release pellets, that can be marketed in their own right or filled into hard gelatine capsules, and sustained release matrix tablets. It can, however, also be used for taste masking in standard release crystals or granules or as a protective coating. A completely different application is as a film in trans-dermal systems.
Typical examples of formulations for the most important of these applications are shown further below in the chapter.

Table 97: Overview of the applications of Kollicoat EMM 30D

Dosage form	**Manufacturing technology**
Sustained release pellets and granules	Film coating of pellets of active ingredient or granulation of the active ingredient with Kollicoat EMM 30
Sustained release hard gelatine capsules	Film coating of pellets of active ingredient with Kollicoat EMM 30 and filling into hard gelatine capsules
Sustained release matrix tablets	Granulation of the active ingredient with Kollicoat EMM 30 and subsequent compression to tablets
Masking of odour and taste of standard granules and tablets	Granulation of the active ingredient with Kollicoat EMM 30 and pore formers (and subsequent compression)
Tablets with protective coatings/ sub-coatings	Film coating of tablet cores
Trans-dermal systems	Film coating using special machines

Formulations containing Kollicoat EMM 30D, due to their high degree of plasticity and low minimum film-forming temperature (see chapter 5.2.6.2), require neither a plasticizer nor curing subsequent to spraying. A flexible film is formed immediately under standard spraying conditions and does not alter during subsequent storage.

The amounts of Kollicoat EMM film applied to sustained release pellets or matrix tablets or for use in taste masking should not be below a certain minimum; this ensures a uniform, closed and stable coating and a closed matrix. The amounts required for controlled release of the active ingredient are dependent mainly on the following parameters:
- The solubility of the active ingredient
- The particle size of the active ingredient
- The required release profile.

The most important factor for the adjustment of release is the amount of sustained release polymer applied. This is illustrated using the example of theophylline sustained release matrix tablets as shown in chapter 5.3.3.2. If the active ingredient is insoluble or only slightly soluble as e.g. in the case of theophylline, one or more pore formers should be added. The influence of pore formers on active ingredient release is described in chapters 5.3.2.2 and 5.3.2.4 using the examples of theophylline and verapamil sustained release pellets. Hydrophilic but also swelling substances such as microcrystalline cellulose, hypromellose, povidone (e.g. Kollidon 30), normal or granulated lactose (e.g. Ludipress LCE) or even micronised crospovidone (e.g. Kollidon CL-M) have also proven suitable for the purpose.

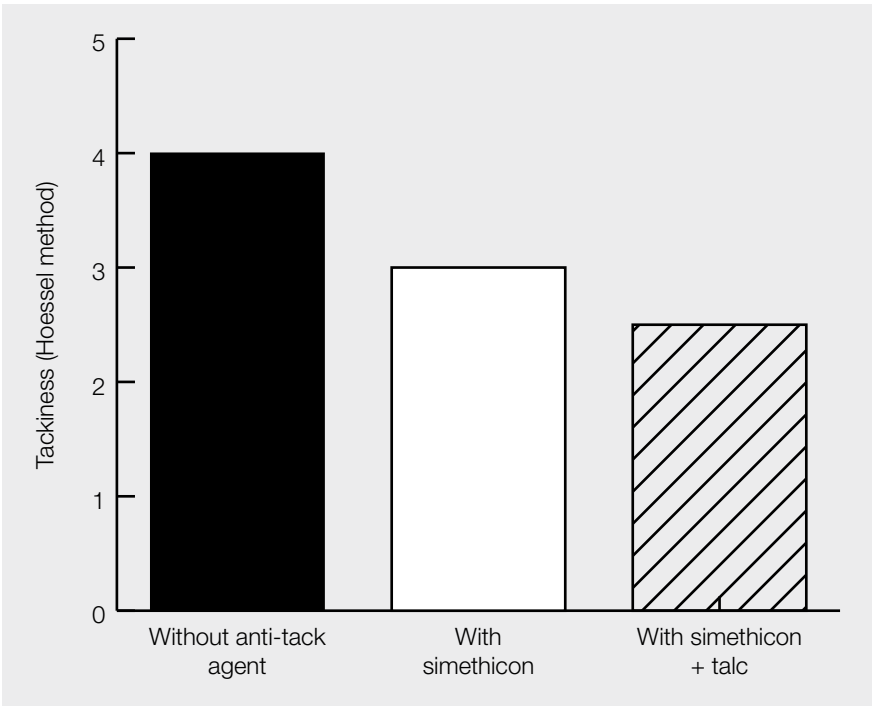


Fig. 74: Tackiness of Kollicoat EMM 30D films with and without simethicon and simethicon+ talcum as anti-tack agents (Hoessel method)

In order to solve the problem of the tackiness of Kollicoat EMM films, supplementary investigations were carried out to those described in chapter 5.2.6.3 on coated propranolol sustained release pellets. It was shown that the anti-tack effect of talcum could be increased by the addition of simethicon. The Hoessel method was again used to establish tackiness [1]. Fig. 74 shows how the combination of simethicon (Pharsil 21046VP) with talcum enhances the latter's effect in reducing the tackiness of Kollicoat EMM 30D films. The major advantage of this combination is that no influence on the release of the active ingredient was observed (see Fig. 75).

Films of Kollicoat EMM 30D result in release behaviour that is independent of pH and the ionic status. This was also checked using a number of other formulations.

Incompatibility in the form of agglomeration between individual excipients and the polymer as is known from other acrylates such as e.g. Kollicoat MAE 30DP was observed less frequently in formulations with Kollicoat EMM 30D; however, this is still possible. Strong foam formation brought about by too vigorous stirring, milling in a colloid mill or the addition of organic solvents should in any case be avoided as these can lead to agglomeration.

5.3.2 Sustained release pellets prepared by coating with Kollicoat EMM 30 D

5.3.2.1 Introduction

Sustained release pellets can be marketed as such or filled into hard gelatine capsules. There are several possibilities for manufacturing coated pellets with sustained release properties. Two of these are schematically illustrated in chapter 4.3.4.1 (sustained release pellets with Kollicoat SR 30D). These two alternatives – "SR-coating of drug layered nonpareilles" and "SR-coating of drug pellets" – can of course be used with Kollicoat EMM 30D. In the first method, a placebo pellet is coated with the active ingredient and a soluble film former and then with the sustained release coating. In the second method, a pellet of active ingredient rounded in a spheronizer is provided with a sustained release coating.

To adjust the release of active ingredient, the thickness of the sustained release coating can be varied (see caffeine sustained release pellets in chapter 5.3.2.3). Pellets containing soluble active ingredients require a thicker sustained release coating than insoluble active ingredients (see Table 98). In the latter case, the addition of a pore former is recommended to accelerate release. The coating amount applied in Kollicoat EMM films should not be below a certain minimum amount; this ensures a uniform, closed and stable coating. In the case of pellets, this amount is approx. 1.5 mg/cm^2.

Typical amounts of Kollicoat EMM polymer required for release over a period of 24 h are shown in Table 98. The data given are based on the weight of pellets.

Table 98: Typical amounts of Kollicoat EMM polymer as a function of the solubility of the active ingredient in sustained release pellets

Solubility of the active ingredient	**Typical amount of polymer used as pellet coating**
Insoluble (< 1 %)	7.5 %
Sparingly soluble (< 10 %)	10 %
Soluble (> 10 %)	12 %
Readily soluble (> 20 %)	15 %

However, anti-tack agents such as hypromellose and microcrystalline cellulose that are also pore formers can influence release of the active ingredient in some formulations (see verapamil sustained release pellets, chapter 5.3.2.4). The only anti-tack agents that, in normal concentrations, do not have any effect on release are talcum and simethicon. This is illustrated in Fig. 75 using the example of propranolol-HCl sustained release pellets with and without the addition of simethicon (Pharsil 21046VP). For this reason, most of the formulation examples given below contain these two excipients.

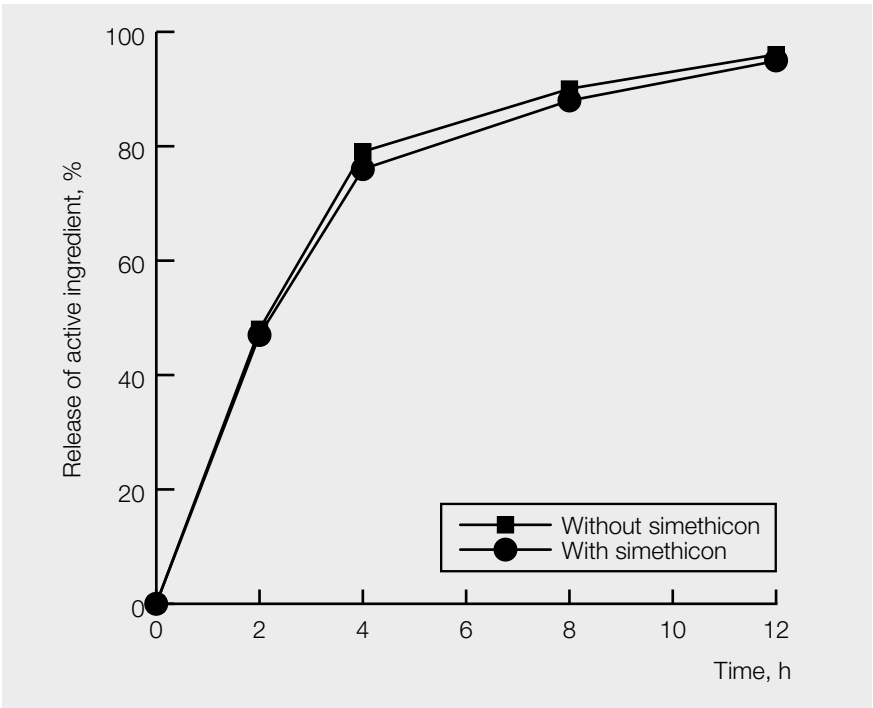


Fig. 75: Release from propranolol sustained release pellets containing Kollicoat EMM 30D as a function of the addition of anti-tack agent simethicon

Curing of the coated pellets has no effect on release as the minimum film-forming temperature of Kollicoat EMM films is considerably below 10 °C. For the manufacture of sustained release pellets with Kollicoat EMM 30D, fluidized bed granulation is recommended as this ensures optimal homogeneous coating. Comparison of various fluidized bed machines for coating pellets shows that there are no significant differences with respect to release of active ingredient. The two coaters tested were the "top spray" systems from Niro (Strea-1™ and MP-1). On comparing the Strea-1™ with the Hüttlin "Kugelcoater", type HKC5, however, there were some significant differences.

The conditions and settings of the machines used for pellet coating with aqueous spray suspensions of Kollicoat EMM 30D are within the normal ranges used, e.g.:
- Inlet air temperature 30 – 65 °C
- Outlet air temperature 20 – 35 °C
- Product temperature 25 – 35 °C

The higher the concentration of anti-tack agent and pore former in the spray suspension, the higher the inlet temperature can be set. In this way process times can be shortened.

Should the uncoated pellets contain an active ingredient that is sensitive to hydrolysis so that contact with water should be avoided, a sub-coating comprising a 10 % ethanolic solution of copovidone (Kollidon VA64) [3] is recommended prior to coating with the aqueous sustained release spray suspension of Kollicoat EMM 30D.

5.3.2.2 Theophylline sustained release pellets with red coating

In this formulation example, the influence of the amount of anti-tack agent and pore former hypromellose on the release of the active ingredient was investigated.

Pellets containing 60 % theophylline active ingredient ("drug pellets") were prepared by granulating with water in a mixer granulator. They were placed in a 1.5 mm sieve, rounded for 10 minutes in a spheronizer and subsequently dried at 70 °C in a fluidized bed granulator. The 0.7 – 1.4 mm fraction was then used for film coating. The formulation of these instant release pellets is given in Table 99.

Table 99: Formulation of theophylline active ingredient pellets (60 %)

Components	Amount (%)
I Theophylline (BASF)	60.0
Microcrystalline cellulose	37.5
Kollidon VA64	2.5
II Water	As required

1 kg of these pellets, rounded in a spheronizer and containing 60 % active ingredient, were coated with formulations 1 and 2 as listed in Table 100 in an Aeromatic MP-1 fluidized bed granulator. The difference between

the two formulations was the amount of anti-tack agent and pore former hypromellose 2910, type 3 mPa·s used.

To prepare the spray suspension, the hypromellose was first dissolved in water; microcrystalline cellulose and then Kollicoat EMM 30D were subsequently stirred into the solution. Separately, Kollidon 30 was dissolved in water, iron oxide, simethicon and talcum suspended under vigorous stirring and the mixture homogenised in a colloid mill. The pigment/talcum suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension obtained was continuously stirred.

Table 100: Spray suspensions and spraying conditions for theophylline pellets (Aromatic MP-1)

Spray suspension	**Amount (%)**	
	Formulation 1	**Formulation 2**
I Kollicoat EMM 30 D	32.5	32.5
Hypromellose 2910, type 3 mPa·s	0.5	1.0
Microcrystalline cellulose	4.5	4.5
Water	33.4	32.9
II Kollidon 30	0.5	0.5
Talcum	0.5	0.5
Sicovit red iron oxide	5.9	5.9
Simethicon	3.9	3.9
Water	18.3	18.3
Solids content	21.56 %	22.06 %
Polymer content	9.75 %	9.75 %
Spray conditions	**Settings**	
Batch size (active ingredient pellets)	1 kg	
Inlet air temperature	40 – 45 °C	
Outlet air temperature	28 – 30 °C	
Spray pressure	1.0 bar	
Spray rate	7 – 11 g/min	
Subsequent drying	5 min/45 °C	
Amount of solid applied	2.6 mg/cm^2	
Amount of polymer applied	1.2 mg/cm^2	

Measurement of the release of active ingredient theophylline from the pellets was carried out under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Fig. 76 shows that release was over more or less 24 h, whereby it can be seen that the anti-tack and pore former hypromellose has a significant effect on release. On doubling the concentration of hypromellose (formulation 2), the release of active ingredient was accelerated significantly due to enhanced pore formation.

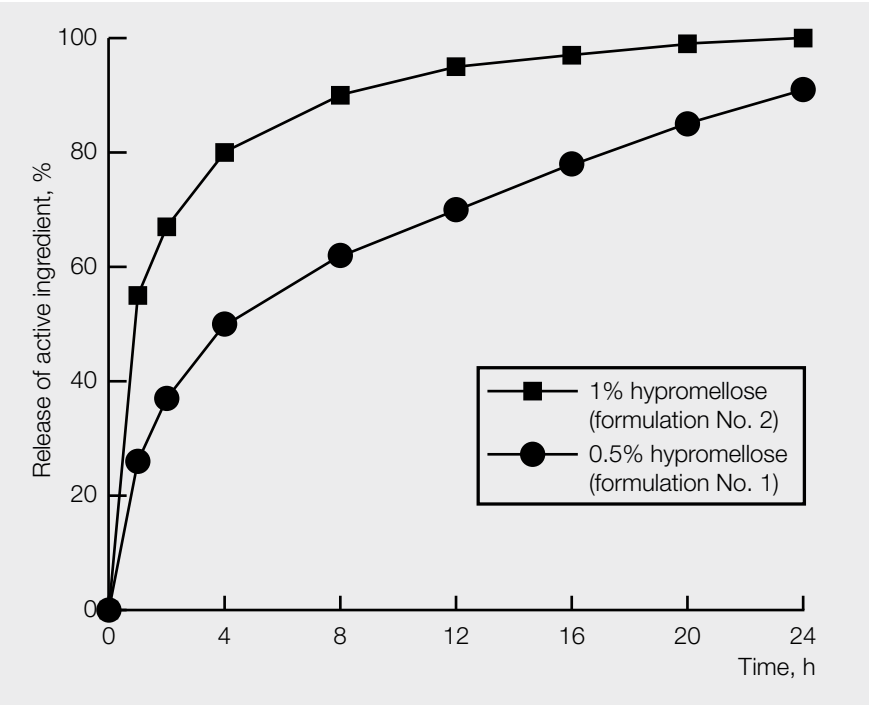


Fig. 76: Release from theophylline sustained release pellets as a function of the concentration of pore former hypromellose

5.3.2.3 Caffeine sustained release pellets with a coloured coating

In this formulation example, the influence of the amount of coating on release of the active ingredient was investigated.

Pellets containing 10 % caffeine active ingredient were prepared by granulating with water in a mixer granulator ("drug pellets"). They were placed in a 1.5 mm sieve, rounded for 10 minutes in a spheronizer and subsequently dried in a fluidized bed granulator. The 0.7 – 1.4 mm fraction was then used for film coating. The formulation of these instant release pellets is given in Table 101.

Table 101: Formulation of caffeine active ingredient pellets (10 %)

Components	Amount (%)
I Caffeine (BASF)	10.00
Microcrystalline cellulose	43.75
Lactose monohydrate	43.75
Kollidon VA64	2.50
II Water	As required

0.5 kg of the pellets, rounded in a spheronizer and containing 10 % active ingredient, were coated with the formulation listed in Table 102 in an Aromatic Strea-1 fluidized bed granulator.
To prepare the spray suspension, the anti-tack agent simethicon was mixed with water and Kollicoat EMM 30D stirred into the mixture. Separately, talcum was suspended in water and homogenised in a colloid mill. The talcum suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 102: Spray suspension and spraying conditions for caffeine pellets (Aeromatic Strea-1)

Spray suspension	**Amount (g)**	**Amount (%)**
I Kollicoat EMM 30 D	198.72	41.66
Simethicon	0.12	0.025
Water	170.84	35.815
II Talcum	59.63	12.5
Water	47.69	10.0
Total	477.0	100.0
Solids content	119.37	25.0
Polymer content	56.64	11.9

Spray conditions	**Settings**
Batch size (active ingredient pellets)	0.5 kg
Inlet air temperature	45 °C
Outlet air temperature	25 °C
Spray pressure	1.0 bar
Spray rate	16 g/min
Spray duration	30 min
Subsequent drying	3 min/45 °C
Amount of solid applied	1 – 4 mg/cm^2
Amount of polymer applied	0.5 – 2 mg/cm^2

Measurement of the release of active ingredient caffeine from the pellets was carried out under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

As can be seen in Fig. 77, release of active ingredient is over a period of approx. 12 h with a coating amount of up to 3 mg/cm^2. Only in the case of a coating amount of 4 mg/cm^2 was release over approx. 24 h. The example clearly shows how release can be controlled by the amount of coating applied.

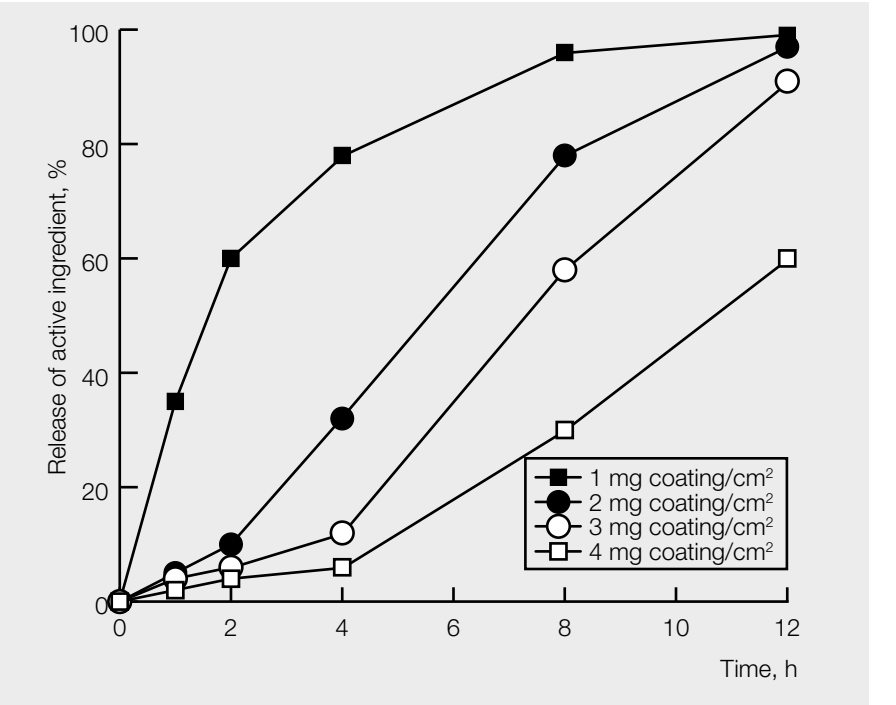


Fig. 77: Release of caffeine sustained release pellets as a function of the amount of coating

5.3.2.4 Verapamil sustained release pellets with red coating

In this formulation example, the influence of the amount of anti-tack agent and pore former hypromellose on the release of the active ingredient was investigated.

Pellets containing 48 % verapamil hydrochloride active ingredient were prepared by granulating with water in a mixer granulator ("drug pellets"). They were passed through a 1.5 mm sieve, rounded in a spheronizer for 10 minutes at 300 – 400 rpm and subsequently dried at 70 °C in a fluidized bed granulator. The 0.7 – 2.5 mm fraction was then used for film coating. The formulation of these instant release pellets is given in Table 103.

Table 103: Formulation of verapamil active ingredient pellets (48 %)

Components	Amount (g)
I Verapamil-HCl (BASF)	480
Microcrystalline cellulose	300
Kollidon VA64	20
Aerosil 200	25
Talcum	175
II Water	400

1 kg of these pellets, rounded in a spheronizer and containing 48 % active ingredient, were coated with formulations 1 and 2 as listed in Table 104 in an Aeromatic MP-1 fluidized bed granulator. The difference between the two formulations was the addition of anti-tack agent and pore former hypromellose 2910, type 3 mPa·s. Only formulation 2 contained this excipient. To prepare the spray suspension, the hypromellose was first dissolved in water; microcrystalline cellulose and then Kollicoat EMM 30D were subsequently stirred into the solution. Separately, Kollidon 30 was dissolved in water, iron oxide, simethicon and talcum suspended under vigorous stirring and homogenised in a colloid mill. The pigment/talcum suspension was then stirred into the polymer suspension. During the entire spraying process the spray suspension thus obtained was continuously stirred.

Table 104: Spray suspensions and spraying conditions for verapamill sustained-release pellets (Aeromatic MP-1)

Spray suspension	**Amount (%)** **Formulation 1**	**Formulation 2**
I Kollicoat EMM 30 D	32.5	32.5
Hypromellose 2910, type 3 mPa·s	--	0.7
Microcrystalline cellulose	4.5	4.5
Water	35.8	35.1
II Kollidon 30	0.5	0.5
Talcum	0.5	0.5
Sicovit red iron oxide	5.9	5.9
Simethicon	3.9	3.9
Water	16.4	16.4
Solids content	21.1 %	21.7 %
Polymer content	9.75 %	9.75 %
Spraying conditions	**Settings**	
Batch size (active ingredient pellets)	1 kg	
Inlet air temperature	40 – 45 °C	
Outlet air temperature	28 – 30 °C	
Spray pressure	1.0 bar	
Spray rate	7 – 11 g/min	
Subsequent drying	5 min/45 °C	
Amount of solid applied	2.4 mg/cm^2	
Amount of polymer applied	1.1 mg/cm^2	

Measurement of the release of active ingredient verapamil hydrochloride from the pellets was carried out under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Fig. 78 shows that release was over at least 24 h, whereby the significant influence of the amount of pore former and anti-tack agent hypromellose can be seen; it is in fact necessary if release is to be over a period of 24 h.

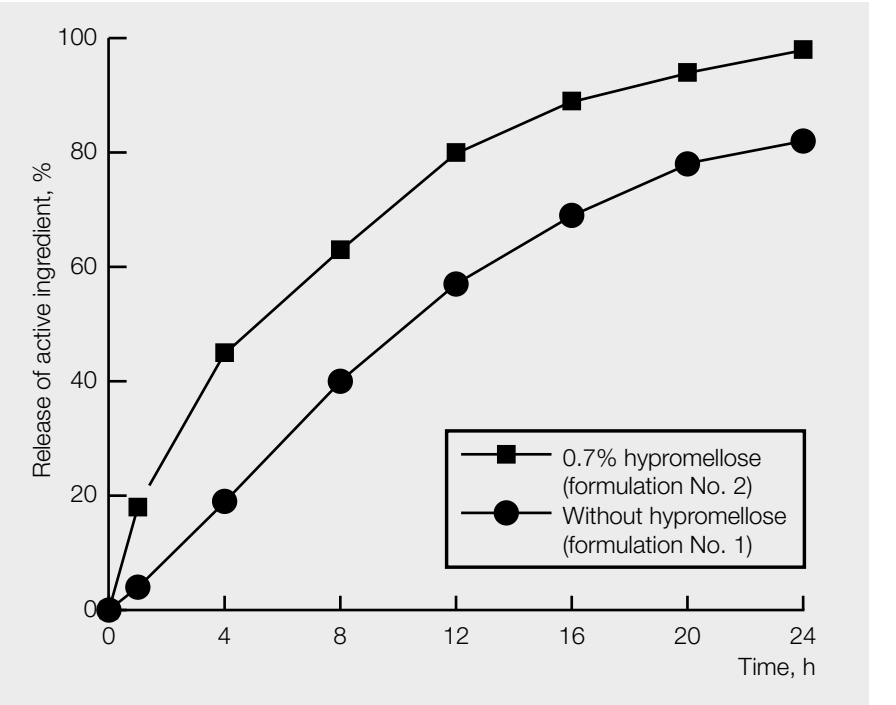


Fig. 78: Release from verapamil sustained release pellets as a function of the concentration of pore former hypromellose

5.3.2.5 Propranolol sustained release pellets with red coating

Pellets containing 20 % propranolol hydrochloride active ingredient were prepared by granulating with water in a mixer granulator ("drug pellets"). They were passed through a 1.5 mm sieve, rounded in a spheronizer at 200 – 400 rpm and subsequently dried at 70 °C in a fluidized bed granulator. The fraction over 0.7 mm was then used for the coating formulation. The formulation of these instant release pellets is given in Table 105.

Table 105: Formulation of propranolol active ingredient pellets (20 %)

Components	Amount (g)
I Propranolol-HCl	200
Microcrystalline cellulose	517
Lactose monohydrate	258
Kollidon VA64	25
II Water	500

1 kg of the pellets, rounded in a spheronizer and containing 20 % active ingredient, were coated with the formulation listed in Table 106 in an Aeromatic MP-1 fluidized bed granulator.

To prepare the spray suspension, Kollicoat EMM 30D was first diluted with water. Separately, the suspension stabiliser Kollidon 30 was dissolved in water and iron oxide, simethicon and talcum suspended in this solution under vigorous stirring. The suspension was then homogenised in a colloid mill. The pigment/talcum suspension was then stirred into the polymer suspension. During the entire spraying process the suspension thus obtained was continuously stirred. On completion of the spraying process another anti-tack suspension (1 g Aerosil 200 in 60 g water) was sprayed onto the pellets. Drying was then carried out for a period of 5 minutes at 45 °C.

Table 106: Spray suspension and spraying conditions for propranolol pellets (Aeromatic MP1)

Spray suspension	**Amount (g)**
I Kollicoat EMM 30 D	393.0
Water	221.3
II Kollidon 30	5.0
Talcum	47.2
Sicovit red iron oxide	5.0
Simethicon	70.9
Water	257.6
Solids content	246 (= 24.6 %)
Polymer content	11.2 %

Spray conditions	**Settings**
Batch size (active ingredient pellets)	1 kg
Inlet air temperature	40 – 45 °C
Outlet air temperature	28 – 30 °C
Product temperature	28 – 31 °C
Spray nozzle	0.8 mm
Air flow	100 – 120 m^3/h
Spray pressure	1.0 bar
Spray rate	7 – 11 g/min
Subsequent drying	5 min/45 °C
Amount of solid applied	2.4 mg/cm^2
Amount of polymer applied	1.1 mg/cm^2

Measurement of the release of active ingredient propranolol hydrochloride from the sustained release pellets was carried out under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.
As can be seen in Fig. 79, active ingredient release was over a period of 24 h. In the case of the active ingredient propranolol-HCl, no pore former was added in order to achieve continuous release over this period.
The S-formed curve obtained was probably caused by the fact that the water required some time to enter the coating without pore former and, on swelling, to penetrate it and dissolve the active ingredient.

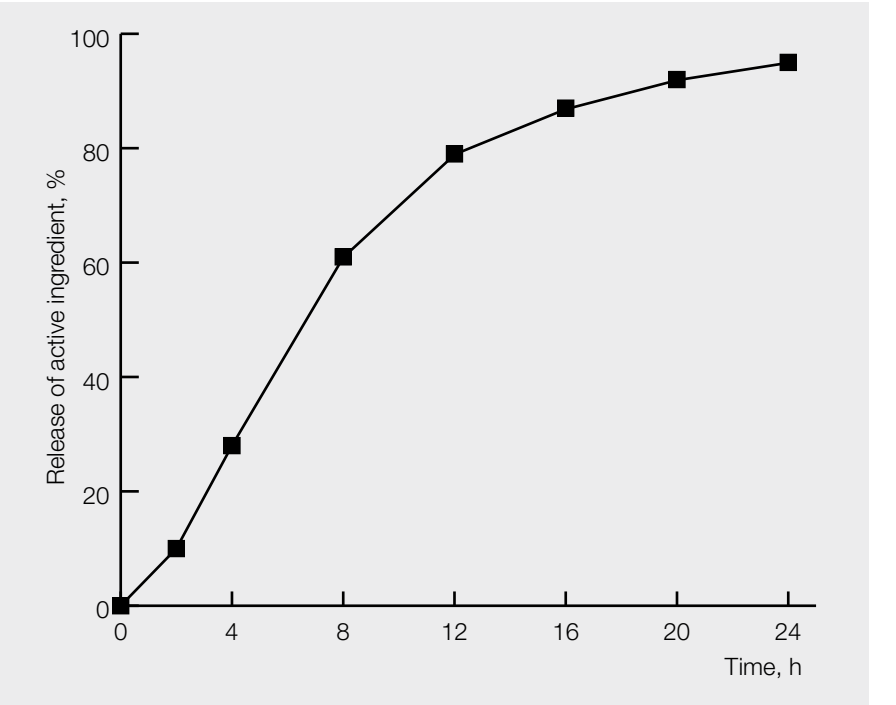


Fig. 79: Release of propranolol-HCl from sustained release pellets

5.3.3 Sustained release matrix tablets prepared by granulation with Kollicoat EMM 30D

5.3.3.1 Introduction

Using this technology, the active ingredient, with or without intra-granular filler, is granulated with Kollicoat EMM 30D and an anti-tack agent. After adding further excipients such as microcrystalline cellulose or granulated lactose (Ludipress LCE) as filler, the mixture is compressed to controlled release matrix tablets. When using the standard amounts of sustained release polymer of 5 – 25 %, a matrix structure is formed on compression that encloses the particles of active ingredient. Subsequent to penetration by gastric juice or intestinal fluid into the matrix, the active ingredient is slowly dissolved and then diffuses through the matrix at a controlled speed. Fig. 80 shows a scanning electron microscope image of the typical acrylate matrix structure of a tablet subsequent to dissolution of the active ingredient [6].

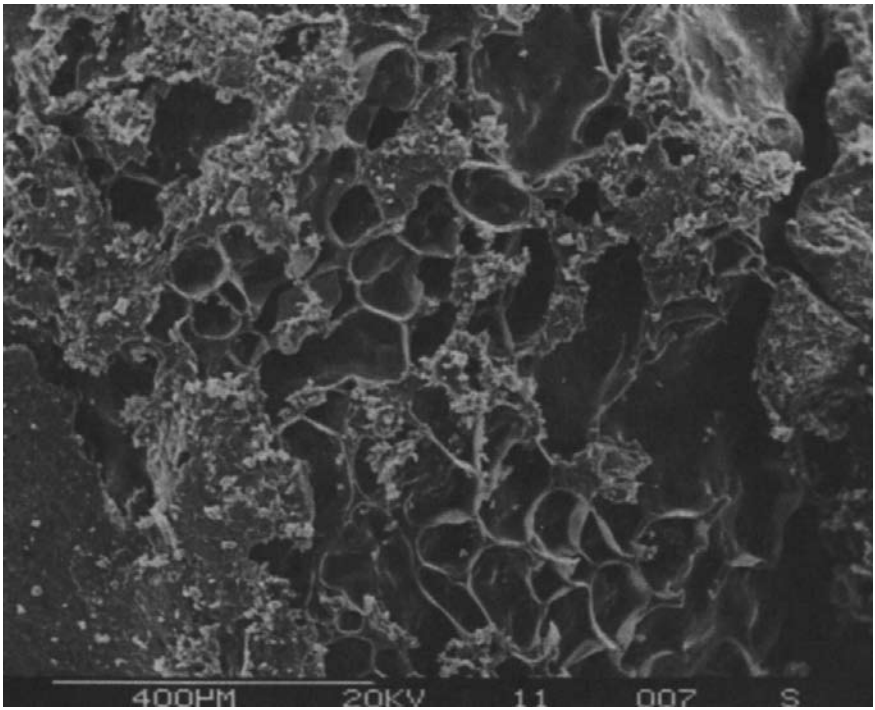


Fig. 80: Typical acrylate matrix structure of a tablet subsequent to partial dissolution of the active ingredient [6].

The sustained release effect of Kollicoat EMM 30D is very high and significantly stronger than that of Kollicoat SR 30D. To demonstrate this, the active ingredient release was directly compared using the two polymers in theophylline sustained release matrix tablets. It was shown that the release level with 7.5 % Kollicoat SR polymer between 12 and 24 h was approx. 20 % higher and thus quicker than with the same amount of Kollicoat EMM polymer (Fig. 81). Comparison of the curves of Kollicoat SR 30D in Fig. 81 with the release shown in Fig. 83 (chapter 5.3.3.2), shows that the curve with 5 % Kollicoat EMM polymer is identical to that with 7.5 % Kollicoat SR polymer.

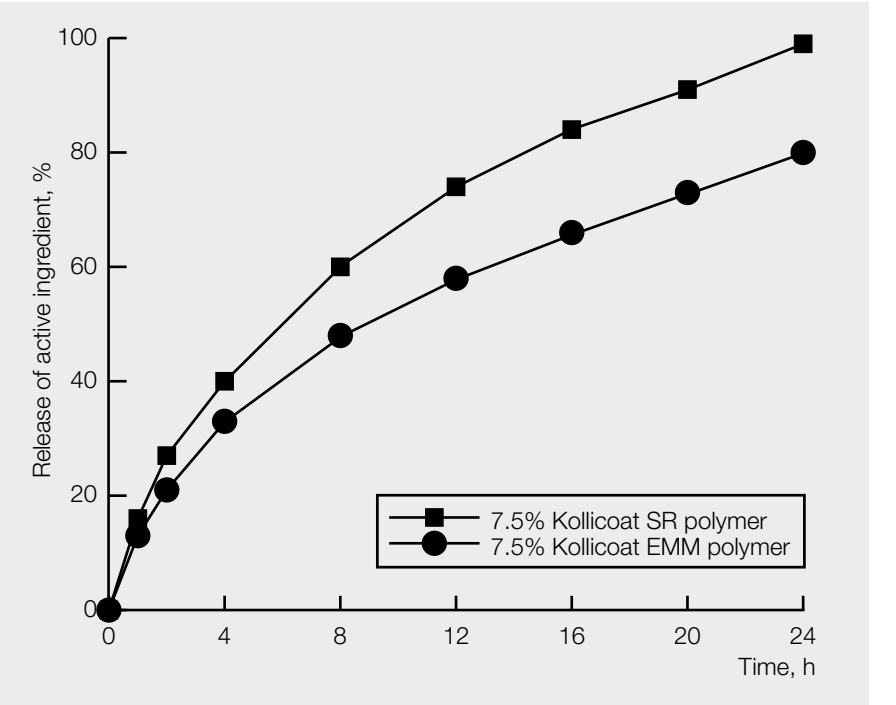


Fig. 81: Comparison of the sustained release effect of Kollicoat SR 30D with Kollicoat EMM 30D in theophylline sustained release matrix tablets

In general, the necessary amount of Kollicoat EMM polymer required for controlled release of the active ingredient from sustained release matrix tablets is dependent on the solubility and the particle size of the active ingredient. In tablets, the particle size of the active ingredient can be more important than in the case of pellets. To adjust the release in the case of sparingly or insoluble active ingredients, the amount of polymer (see chapter 5.3.3.2, Fig. 83) and the addition of pore formers are the main parameters used.

Typical amounts of Kollicoat EMM polymer required for release over a period of 24 h are shown in Table 107. The data are based on the weight of the granules. However, the tackiness of the coatings often restricts the use of higher concentrations of Kollicoat EMM polymer.

Table 107: Typical amounts of Kollicoat EMM polymer in the granules as a function of the solubility of the active ingredient in sustained release matrix tablets

Solubility of the active ingredient	**Typical amount of polymer**
Insoluble to sparingly soluble	5 – 12 %
Soluble to readily soluble (> 20 %)	15 – 25 %

Fluidized bed granulation is also the preferred technology for the granulation of active ingredients for the preparation of sustained release matrix tablets. However, comparative studies have shown that granulation can also be carried out in a conventional mixer granulator. In this case though, a higher consumption of Kollicoat EMM 30D has to be accepted if the same release is to be obtained. This is clearly shown in Fig. 82 with the example of theophylline sustained release matrix tablets containing 5 % Kollicoat EMM polymer and 50 % active ingredient. The reason for this difference is probably that, in the case of fluidized bed granulation, there is a more uniform and complete coating of the crystals than in the case of conventional granulation. Formulation examples for both technologies are given in the following two chapters 5.3.3.2 and 5.3.3.3.

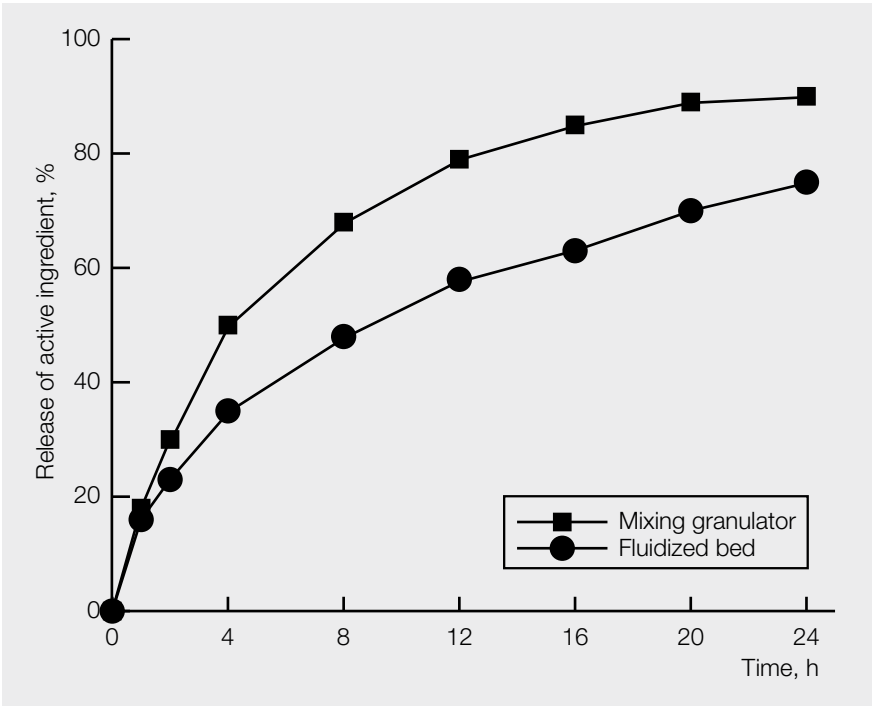


Fig. 82: Influence of granulation technology on release from theophylline sustained release matrix tablets

The type of intra-granular filler that may be necessary in the case of low dosages of active ingredients to obtain the required granulate or tablet weight as well as an adequate matrix has a minor effect on active ingredient release (see chapter 5.3.3.3) although it alters the porosity significantly in a variety of ways.

5.3.3.2 Theophylline sustained release matrix tablets (400 mg) containing Kollicoat EMM 30D

One of the goals of this formulation development was to demonstrate how, by varying the amount of Kollicoat EMM polymer, the release profile of the active ingredient can be influenced.

The active ingredient theophylline was mixed with a filler and this mixture sprayed with 5.0, 7.5 and 10 % solid Kollicoat EMM, based on the weight of granulate, directly in an Aeromatic Strea-1 fluidized bed granulator. The dry granules were mixed with magnesium stearate lubricant and flowability agent Aerosil 200 for 10 minutes and then sieved. The mixture was compressed to 19 x 8.5 mm oblong tablets of approx. 800 mg weight with an active ingredient of approx. 400 mg using a compression force of 18 kN. The three formulations and the granulation conditions are summarised in Table 108.

Measurement of release of the active ingredient took place under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Table 108: Formulations and granulation conditions for theophylline sustained release matrix tablets containing Kollicoat EMM 30D

Formulation	**No. 1 (5.0 %)**	**No. 2 (7.5 %)**	**No. 3 (10.0 %)**
I Theophylline powder (BASF)	400 mg	400 mg	400 mg
Lactose monohydrate	360 mg	340 mg	320 mg
II Kollicoat EMM 30 D	133 mg (= 40 mg solids)	200 mg (= 60 mg solids)	267 mg (= 80 mg solids)
III Magnesium stearate	4 mg	4 mg	4 mg
Aerosil 200	4 mg	4 mg	4 mg
Tablet weight	808 mg	808 mg	808 mg
Granulation settings (fluidized bed granulator, "top-spray" method)			
Inlet air temperature	55 °C		
Outlet air temperature	22 – 27 °C		
Nozzle diameter	0.8 mm		
Spray rate	approx. 10 g/ml		
Spray pressure	2 bar		

The amount of Kollicoat EMM 30D required is very low due to the insolubility of theophylline if no pore former is used. As can be seen in Fig. 83, for the particle size of theophylline (powder, BASF) used, the amount of solid Kollicoat EMM of 5 %, based on the weight of granulate, is just right for release

of active ingredient over a period of 24 h. This amount should if at all possible not be smaller as it might prevent the formation of the right matrix structure.

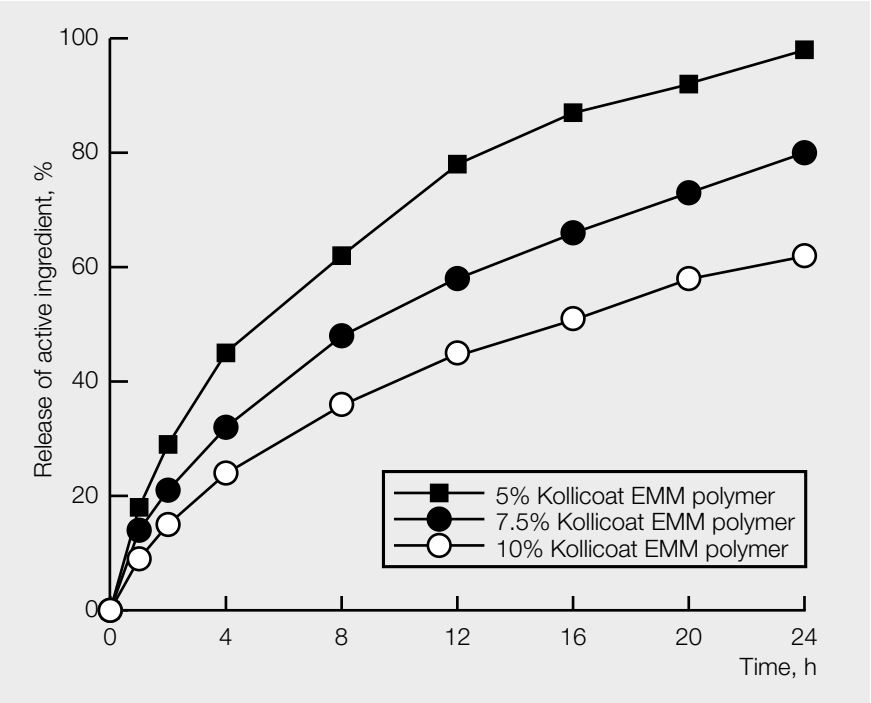


Fig. 83: Influence of the amount of Kollicoat EMM on the release of theophylline sustained release matrix tablets

5.3.3.3 Sustained release matrix tablets of propranolol (160 mg) prepared by granulation with Kollicoat EMM 30D

One of the goals of this experiment was to show the influence of various intra-granular fillers on the release of active ingredients. In addition, it was to be demonstrated that conventional mixer granulation technology can also be used for the manufacture of granules.

The readily soluble active ingredient propranolol hydrochloride was mixed with three different fillers and 20 % solid Kollicoat EMM, based on the weight of granulate, was sprayed onto the mixture in a mixer granulator (Stephan). The sieved and dried granules were mixed with magnesium stearate lubricant and flowability agent Aerosil 200 for 10 minutes, sieved and compressed to diplanar tablets of 10 mm diameter, approx. 320 mg weight and with an active ingredient content of 160 mg using a compression force of 18 kN. The granulation conditions for the three formulations are summarised in Table 109.

Measurement of release of the active ingredient took place under the following conditions: 0 – 2 h in 0.08 M hydrochloric acid, 2 – 24 h in phosphate buffer of pH 6.8, 37 °C and 50 rpm.

Table 109: Formulations and granulation conditions for propranolol sustained release matrix tablets containing Kollicoat EMM 30D

Formulation	**No. 1**	**No. 2**	**No. 3**
I Propranolol-HCl	160 mg	160 mg	160 mg
Lactose monohydrate	96 mg	--	--
Microcrystalline cellulose	--	96 mg	--
Dicalcium phosphate	--	--	96 mg
II Kollicoat EMM 30 D	213 mg (= 64 mg solids)	213 mg (= 64 mg solids)	213 mg (= 64 mg solids)
III Magnesium stearate	1.6 mg	1.6 mg	1.6 mg
Aerosil 200 (	1.6 mg	1.6 mg	1.6 mg
Tablet weight	323 mg	323 mg	323 mg
Granulation settings (Stephan mixer)			
Batch size	0.5 kg		
Pre-mix	400 rpm		
Granulation	550 rpm		
Granulation time	5 min		
Sieving	500 µm,		
Drying	16 h at room temperature		

Due to the excellent solubility of propranolol-HCl, the required amount of 20 % Kollicoat EMM 30D is quite high in all three formulations. The various intra-granular fillers all had a significant influence on the porosity of the tablets. This is illustrated in Table 110 using the example of three different compression forces of 10, 18 and 25 kN.

Table 110: Influence of intra-granular fillers and compression forces (KN) on the porosity of propranolol sustained release matrix tablets

Filler	**Porosity**		
	10 kN	**18 kN**	**25 kN**
Lactose monohydrate	4.5 %	1.6 %	2.0 %
Microcrystalline cellulose	6.9 %	4.9 %	2.7 %
Dicalcium phosphate	19.0 %	16.0 %	16.8 %

It is interesting to note that in Fig. 84, the three intra-granular fillers, in spite of having a substantial influence on porosity, exercise no significant influence on the release of propranolol-HCl. Only in the case of microcrystalline cellulose are the values at 8 and 12 h a little higher than the other two fillers. This is all the more surprising as this result does not correlate with the porosities shown in Table 110; here, it is dicalcium phosphate and not microcrystalline cellulose that produces the greatest degree of porosity.

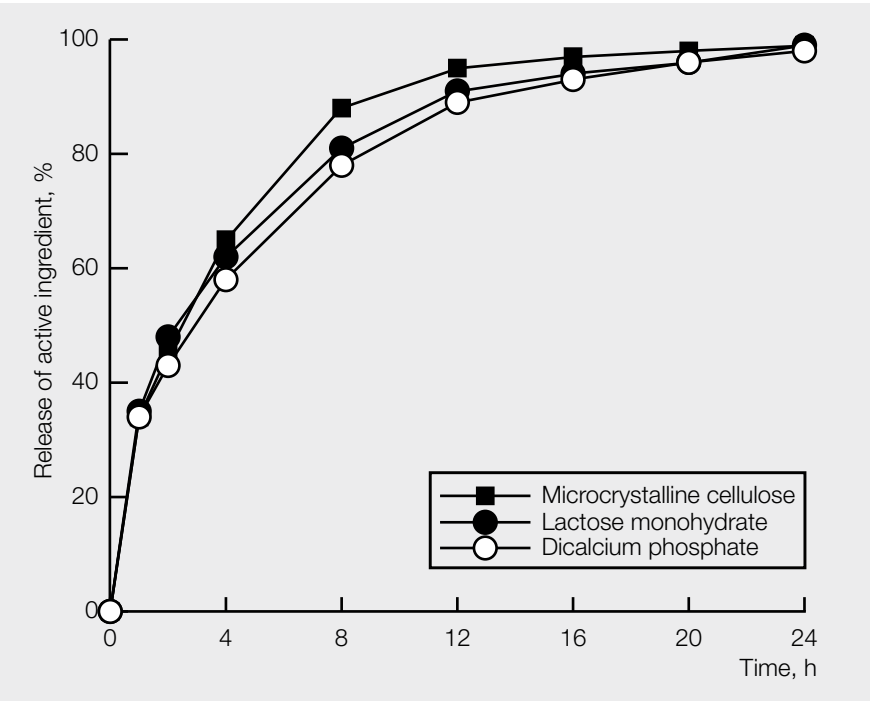


Fig. 84: Influence of intra-granular fillers on release from propranolol sustained release matrix tablets (compression force 18 KN)

5.3.4 Taste masking of granules and tablets containing Kollicoat EMM 30D

5.3.4.1 Introduction

Kollicoat EMM 30D films are suitable for masking the taste of bitter or unpleasantly tasting active ingredients such as the sympathomimetic pseudoephedrine or the analgesics tramadol, acetaminophen (paracetamol) and ibuprofen. However, in these applications, one has to find a compromise between the insolubility of the film-former, its associated taste masking properties and the required speed of release. This is all the more important in the case of analgesics as here pain relief should optimally occur as quickly as possible after ingestion.
Such a compromise, however, is difficult to accomplish. It can best be achieved by adding precisely calculated amounts of soluble or swelling pore

formers such as povidone, micronised crospovidone, microcrystalline cellulose, copovidone etc. Pore formers such as Kollidon 30, Kollicoat IR or Kollidon VA64, which are also film formers, are preferred, especially if their concentrations in the film is very high, as is the case with acetaminophen (see next chapter 5.3.4.2).
Care should be taken that just enough coating should be applied for taste masking to cover the period when the crystals or tablets are normally in the mouth.

The particle size of the active ingredient also normally influences taste and taste masking. This also applies to crystals coated with Kollicoat EMM 30D. If fine crystals are used, the surface area is greater and hence the taste all the more intensive. For this reason, the same taste masking effect cannot be achieved with the same coating amount as with coarser crystals.

5.3.4.2 Taste masking of acetaminophen crystals and tablets

500 g of acetaminophen (type: granules) were coated with a spray suspension which, in addition to Kollicoat EMM 30D, also contained Kollidon 30 as a film forming pore former. The ratio of solid Kollicoat EMM to Kollidon 30 was 4:3.
The spray suspension was sprayed onto the crystals using a “top spray” Aeromatic Strea-1 sprayer (Table 111).

Table 111: Formulation of the spray suspension and the spray conditions for the taste masking of acetaminophen in the Aeromatic Strea-1

Spray suspension	**Amount (g)**	**(%)**
Kollicoat EMM 30 D	142.87	38.10
Kollidon 30	32.13	8.57
Water	200.00	53.33
Total	375.00	100.00
Spraying conditions	**Settings**	
Batch size (acetominophen)	500 g	
Inlet air temperature	60 °C	
Outlet air temperature	33 – 35 °C	
Spray nozzle	0.8 mm	
Spray pressure	1.2 bar	
Subsequent drying	5 min/60 °C	
Total amount applied	15 %	
Amount of polymer applied	8.1 % Kollicoat EMM +6.4 % Kollidon 30	

5.3.5 Application of Kollicoat EMM 30D in trans-dermal systems

The low resorption capacity of the human skin is often utilized to obtain controlled percutaneous bioavailability of active ingredients. Here, so-called trans-dermal systems or trans-dermal therapeutic systems (TTS) are used that guarantee continuous percutaneous resorption of active ingredient over a longer period of time. The advantages and goals of such a TTS are summarised in Table 112.

Table 112: Advantages and goals of trans-dermal therapeutic systems

- Avoidance of incompatibility of the active ingredient with the mucous membranes of the stomach and intestine
- Avoidance of “first-pass” effects
- Longer application intervals
- No degradation of the active ingredient within the gastro-intestinal tract
- Improved acceptance by the patient

A trans-dermal therapeutic system comprises various layers, a carrier film, a matrix film containing a reservoir of active ingredient and a removable cover film, e.g. made of aluminium. Sometimes, an intermediate adhesive layer can be inserted between the active ingredient matrix film and the cover film in order to improve adhesion to the skin.

As Kollicoat EMM 30D forms neutral, adhesive and insoluble polyacrylate films that swell in water and are to some extent permeable to water and active ingredients, it is excellently suited to applications in TTS as an active ingredient matrix layer. As it also contains no functional groups, there is normally no interaction with active ingredient groups. A further advantage of the aqueous dispersion Kollicoat EMM 30D is that organic solvents need not be used. In a similar way to matrix tablets, a high concentration of active ingredient can be used.

The speed of active ingredient release from polyacrylate films is dependent on the solubility of the active ingredient and, especially, on its concentration in the polymer and the thickness of the polymer layer. Fig. 85 shows the correlation between concentration and matrix film thickness for initial active ingredient concentrations of 0.5 – 2.0 mg/cm^3 and film thicknesses of 100 – 500 µm based on in-vitro experiments [6]. Should the percutaneous resorption be slower than the release from the matrix film, the skin becomes the speed-determining factor for bioavailability. Should release from the matrix film be too slow, resorption enhancers such as pore formers or emulsifiers can be added.

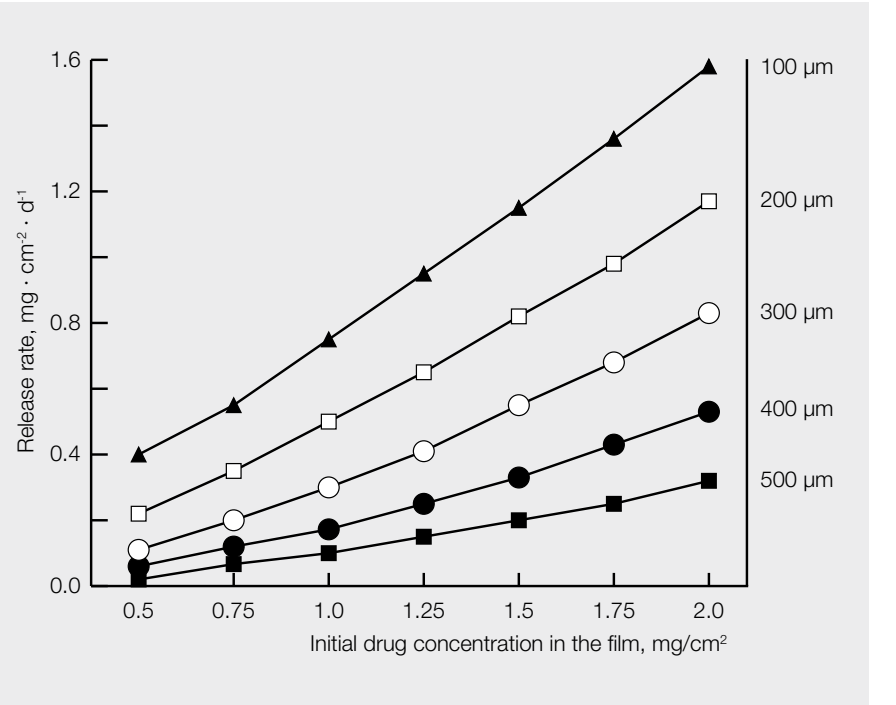


Fig. 85: Active ingredient release from polyacrylate films in trans-dermal systems as a function of film thickness (100 – 500 µm) and active ingredient concentration in the film [6]

For the manufacture of matrix film containing active ingredient, the active ingredient is suspended or dissolved in dilute aqueous Kollicoat EMM 30D. If required, the viscosity can be adjusted by adding a thickener such as Aerosil 200. Alternatively, other excipients such as emulsifiers can be added. Plasticizers are not required. The continuous manufacture of TTS usually takes place using the so-called blade coating process schematically illustrated in Fig. 86. The dispersion of active ingredient and Kollicoat EMM 30D is applied to the carrier film as a product layer and dried. It is then applied to the film side of the matrix and covered with a film (e.g. aluminium). Using this process, matrix films up to 0.5 mm thickness can be applied.

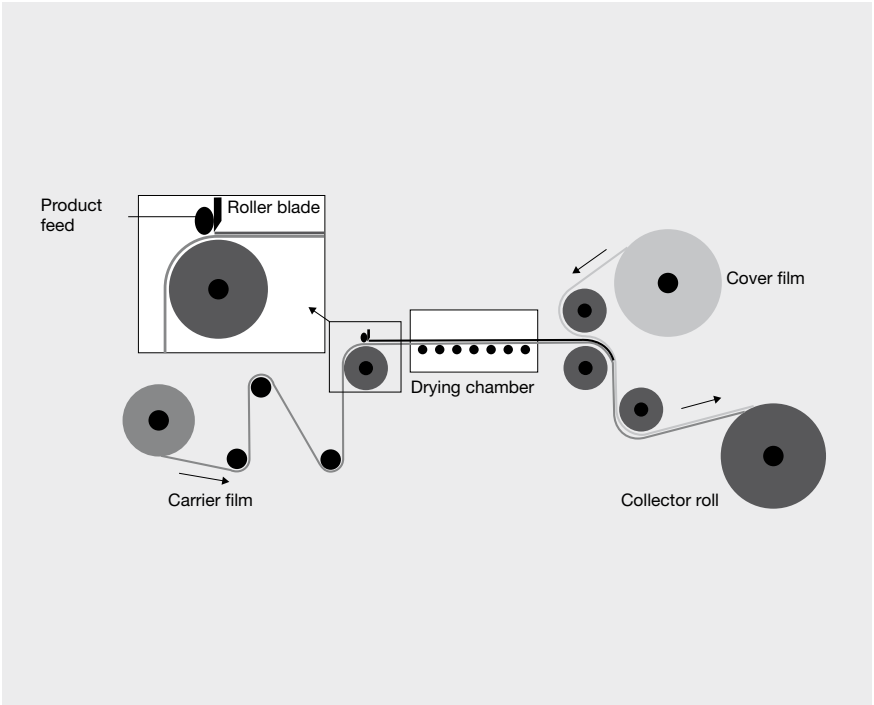


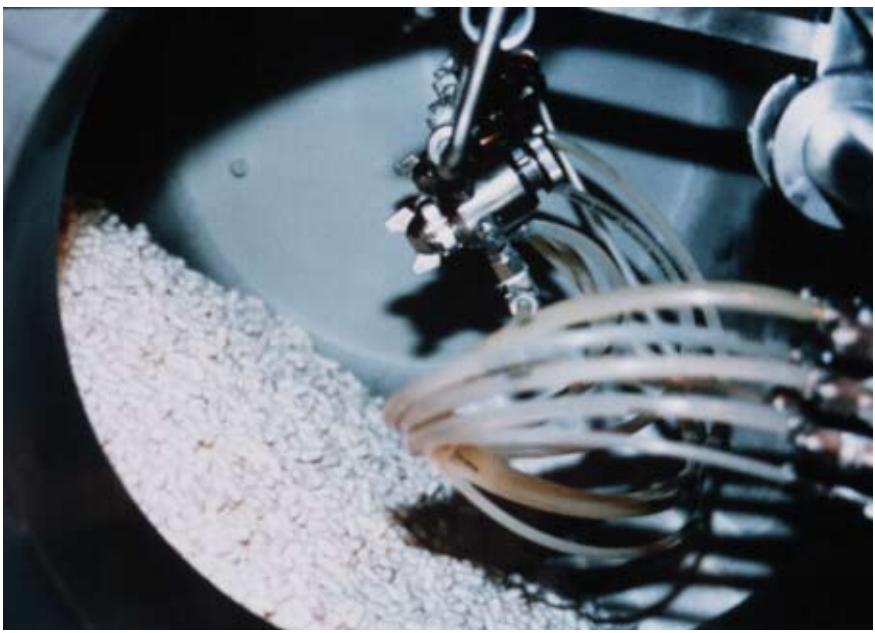
Fig. 86: Schematic of the TTS blade coating process

5.3.6 Cleaning the machines after processing with Kollicoat EMM 30D

When processing film coating formulations, residues of polymer, pigment and other excipients often collect on the inside walls of the machine and in the tubing and spray systems. As long as the films are in a fresh condition and still capable of swelling, they can be mechanically removed with relative ease. Subsequent to longer drying periods, however, the films tend to harden. This renders cleaning somewhat more difficult.

As the Kollicoat EMM copolymer is insoluble in water, acid and alkali, film residues cannot simply be removed by using aqueous solutions. However, using acid or alkaline washing solution, the residues can be softened and made to swell; they can then be removed with a high-pressure hot water cleaner or mechanically removed with brushes. The smaller machine parts such as nozzles and tubing are best cleaned by soaking overnight in cleaners. If the residues prove to be difficult to remove, brushes or plastic scrapers can be used.

As the copolymer of Kollicoat EMM 30D is soluble in a mixture of ethanol and water in the ratio of 1:1, this mixture can also be used for cleaning. While organic solvents normally present a health and safety risk, such a water/ethanol mixture, due to its higher flash point, is not regarded as being a fire risk. Instead of ethanol, 2-propanol can also be used.



6. The influence of machine settings and formulations on film coatings

6.1 General

Today, almost exclusively, aqueous formulations are used in the film coating of tablets and pellets; thus, besides the formulation of the spray suspension itself, water is the most important direct or indirect factor. Thus, the art is to use the available machine settings for the coating process to determine how long the water remains on the product to be coated and to adjust to the optimal speed of evaporation. This, together with uniform coating of the spray suspension, influence on film formation, appearance of the film, the physical stability of the coating and other factors, including the chemical stability of the active ingredient.

Defects in the films can often be attributed to the water. If the water remains too long on the surface of the tablet cores or pellets, the water can penetrate and cause damage, either immediate or longer term. Such damage can take the form of the cores sticking to each other, the films rupturing or even loss of stability through hydrolysis of the active ingredient. If the water remains on the surface for too short a time, film formation will be incomplete and the appearance will suffer. All of these situations can be caused by the machine settings, e.g. the distance of the spray nozzle from the surface, the temperature, the spray rate and the air flow used.

As machine settings are important for optimal application of the Kollicoat grades, chapter 6.2 gives an overview of the various setting parameters used in film coating and the coating defects that can result from these. Within the scope of this book, however, it is not possible to go into great detail concerning specific machines. As the film coating of tablets today is normally no longer carried out by traditional pan-coating but rather with a perforated drum system, the following data will refer to this latter type of machine.

Apart from the machine settings, in some cases the formulation of the spray suspension or the tablet cores may cause problems. The properties of the cores can also be relevant for the coating process. These aspects will be looked at in more detail in chapter 6.3.

The parameters described here for the coating of tablet cores are also essentially applicable for the coating of pellets. The various influences that are of relevance in coating pellets and tablets cannot be regarded in isolation; they are all part of the whole in this respect.

If in certain cases a particular problem cannot be optimally solved by adjusting the machine settings (e.g. swelling of cores containing disintegrant), a sub-coating comprising a 10 % ethanolic solution of Kollidon VA64, with the same machine, is recommended.

6.2 Influence of machine settings on tablet film coatings

6.2.1 Temperature of inlet air, cores and outlet air

The right setting for inlet air temperature is a very important parameter as this exerts most influence on the speed of evaporation of the water. As the inlet air temperature also essentially controls the temperature of the cores, it can have a certain influence on the stability of active ingredients that are sensitive to heat or hydrolysis. Of course, the effects of inlet air temperature should never be regarded in isolation; the spray rate and the distance and angle of the spray nozzle(s) e.g. also directly influence whether the cores are too moist or too dry. Also, if there is poor adhesion on the tablet surface in conjunction with too high product temperature, blisters may appear in the film. Table 113 lists the effects of wrongly set inlet air and core temperatures.

Table 113: Possible influences of inlet air and core temperature on the film coating

Temperature setting	Possible effects
Too low	- No film formation (below MFT) - Cores stick together - Picking and cratering on the film surface (see Fig. 87) - Bridging effect (see Fig. 91) - Swelling of cores containing disintegrant - Hydrolysis of the active ingredient
Too high	- Blockage of the spray nozzle through drying out - Formation of blisters and wrinkles on the film - Film takes on a rough, “orange skin” appearance (see Fig. 88) - Cracking and splitting of the film (see Fig. 89) - Peeling and flaking at the edge of the tablet (see Fig. 90) - Pitting on the film surface in the case of cores containing stearic acid at a product temperature > 65 °C (see Fig. 92)

In contrast to inlet air temperature, the outlet air temperature is not a fixed parameter but rather a function of inlet air temperature, amount of air involved, spray rate and spray pressure. These are normally set in such a way that the outlet air temperature is within the range 30 – 55 °C. If this is too low with respect to the inlet air temperature, the cores will be too moist. If it is too high, they will be too dry.

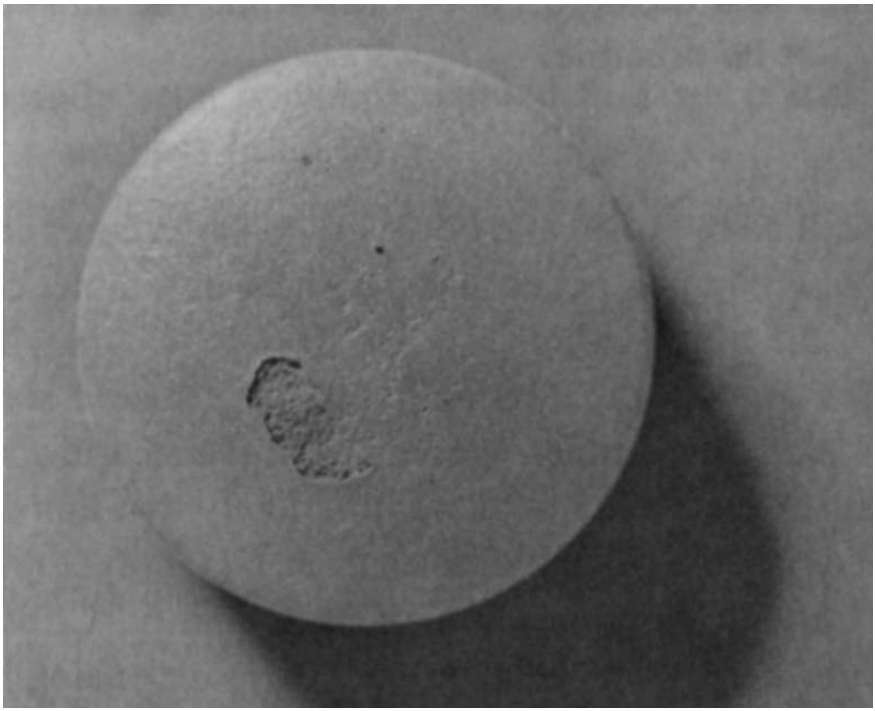


Fig. 87: Picking and cratering on the tablet surface

6.2.2 Distance and angle of the spray nozzle

Whether a single or several spray nozzles are used, the distance from the bed of tablet cores and the angle must be precisely set prior to the spraying process. These two parameters have a similar effect to inlet air and product temperature as they directly influence the moistness of the tablet surface.
If the nozzle is nearer to the core bed or if the angle is more direct, the tablet cores being sprayed will be wetter than if the settings are the opposite. Table 114 shows the influence of these two parameters on the results obtained.
Normally, the nozzle(s) is (are) 20 – 25 cm from the core bed. The nozzle angle(s) should be set in such a way that the spray is directed neither to the edge of the moving bed of cores nor to the centre but to the upper area – about two-thirds of the height of the moving bed.
If several nozzles are being used, the distance between the individual nozzles also has to be adjusted. Normally, the distance is 15 cm. It should always be ensured that all of the nozzles spray uniformly. Thus, they should regularly be adjusted, controlled and cleaned.

Table 114: Possible influences of distance and angle of the spray nozzle(s) on the film coating

Setting of the nozzle(s)	Possible effects
Distance from tablets too small or angle too small (= too direct)	- Non-uniform colour distribution on core bed - No film formation - Picking and cratering in the film (see Fig. 87) - Swelling of cores containing disintegrant - Hydrolysis of the active ingredient
Distance from tablets too great or angle too wide or too oblique	- Coating layer too thin - Loss of spray suspension due to spray-drying effect - Film takes on a rough, "orange skin" appearance (see Fig. 88)
Distance between nozzles incorrect	- Non-uniform colour distribution on core bed - Some cores too rough (Fig. 88) - Picking and cratering on the core surface (Fig. 87)

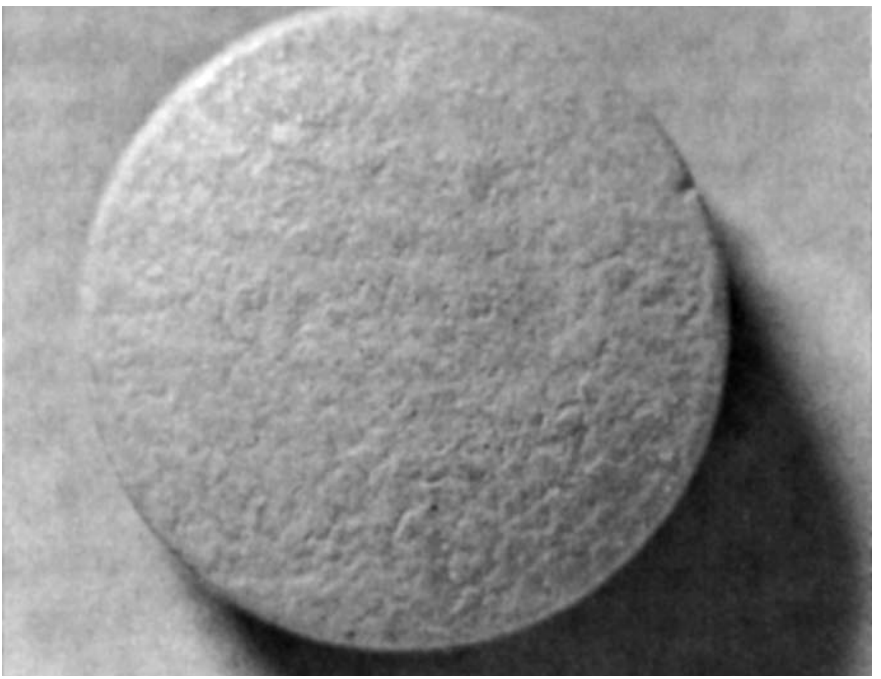


Fig. 88: Rough "orange skin" film surface

6.2.3 Spray rate

As the spray rate also influences the amount of water in the coating, there is often a connection between this parameter and/or the inlet air temperature and the setting of the spray nozzle. However, the spray rate also determines the amount of solid applied and can thus cause other negative effects if wrongly set. It can be a cost-determining factor in film coating; for this reason, it is normally set as high as possible. Table 115 lists the effects that can be caused by varying the spray rate. Normally, the spray rate is set to 80 – 150 ml/min per nozzle.

If a low spray rate is set, the spray suspension will move slowly within the tube linking tank and nozzle. Thus, the tube should be as short as possible and be free of unnecessary curves. The diameter of the tube should also be as small as possible. In this way, sedimentation can be prevented by the rapid movement of the spray suspension in the tube.

Table 115: Possible influences of spray rate on film coating

Spray rate setting	Possible effects
Too low	- Sedimentation of the suspension in the tube - Peeling and flaking at the edge of the tablet (see Fig. 90)
Too high	- Non-uniform colour distribution on core bed - Picking and cratering on the film (see Fig. 87) - Cores stick together - Cracking and splitting of the film (see Fig. 89) - Bridging effect (see Fig. 91) - Swelling of the cores - Hydrolysis of the active ingredient

Fig. 89: Cracking and splitting on the tablet surface

6.2.4 Spray pressure, diameter of the spray nozzle, pattern air

The spray pressure and, to a certain extent, the diameter of the spray nozzle determine the size of the drops of suspension applied to the surface of the tablet cores. The smaller the diameter and the higher the spray pressure, the finer the drops. The drops should not be too large otherwise the cores will become too moist; but they should also not be too small otherwise a spray drying effect will occur so that the water evaporates before it reaches the surface of the cores. Thus, the spray pressure can exert a number of influences on film coating; these are summarised in Table 116.
In those machines used in the laboratory, a spray pressure of 2 – 4 bar was applied and spray nozzles of 0.8 – 1.0 mm diameter employed.

Due to the evaporation of the water immediately on leaving the nozzle, slight residues and crusts tend to form; these can cause non-uniform spraying or even block the nozzle. Thus, the nozzles should be regularly checked during the coating process and if necessary cleaned with a brush.

Table 116: Possible influences of spray pressure on film coating

Spray pressure	Possible effects
Too low	- Picking and cratering due to the film being too wet (see Fig. 87) - Cracking and splitting of the film (see Fig. 89) - Bridging effect (see Fig. 91)
Too high	- Coating layer too thin - Loss of spray suspension due to spray-drying effect - Rough film surface (see Fig. 88)

In many spray systems, the pattern air is fixed and can thus not be altered. In others, it can be set independently of the pressure of the spray or nebulizer air. The pattern air is important in so far that it flattens the nebulized spray cone into a more elliptical form.

If the pattern air pressure is set too high, there is a risk that the tablet cores will become too moist; in such a case similar effects will occur as with a too low spray pressure (see Table 116). If the pattern air pressure is too low, the solids in the coating may be non-uniform, especially in the case of multiple nozzles.

6.2.5 Amount of inlet air (air flow)

The amount of air flowing through the machine also influences the drying and hence the wetness of the film on the surface of the core. The possible effects of too little and too much air flow are summarised in Table 117.

Table 117: Possible influences of the amount of air on film coating

Inlet air setting	Possible effects
Too low	- Picking and cratering on the film (see Fig. 87) - Swelling of cores containing disintegrant - Hydrolysis of the active ingredient
Too high	- Coating layer too thin - Loss of spray suspension - Formation of blisters and wrinkles on the film

6.2.6 Drum speed

Normally, the rotational speed of the coating drum is not decisive; however, due to its movement and mixing effect on the core bed, it does exert a certain influence on the homogeneity of colour distribution as well as on the contact time between the individual cores. This latter aspect is important when a coating polymer with a certain degree of tackiness is applied. Table 118 list the few influences of this parameter.

Table 118: Possible influences of drum speed on film coating

Drum speed	Possible effects
Too low	- Non-uniform colour distribution on core bed - Cores stick together - Picking and cratering due to cores sticking together (see Fig. 87)
Too high	- Peeling and flaking at the edge of the tablet (see Fig. 90)

Fig. 90: Peeling and flaking at the edge of the tablet

6.2.7 Stirring speed and suspension flow rate

The stirring speed in the spray suspension tank is an important parameter; this is because only a homogeneous suspension maintained throughout the entire coating process can guarantee good results in the form of uniform tablet coating. In addition, an adequate stirring speed prevents the pigment particles from agglomerating. The precondition, however, is that the spray suspension is well homogenised and shows no interaction with the polymer as can occur e.g. with methacrylic acid-ethyl acrylate copolymers. Table 119 lists the possible negative effects that can occur through too slow stirring and/or the agglomerate formation that can result thereof.

In the numerous formulations possible, it has to be taken into account that both the stirring speed and the shear force of the pump are not too high; too high shear forces can bring about agglomeration of the polymers and pigments.

Table 119: Possible influences of stirring speed and agglomeration in the spray suspension on film coating

Settings	Possible effects
Too low stirring speed	- Sedimentation of the spray suspension in the tank - Sedimentation in the tube - Blocked nozzle - Rough “orange skin” film surface (see Fig. 88) - Non-uniform colouring of individual tablets
Too high shear force caused by too vigorous stirring	- Formation of agglomerates with sedimentation - Blocked nozzle

It is also important that the spray suspension does not sediment or agglomerate in the tube between the tank and the nozzle. Thus, the tube should always be of uniform, small diameter, as this results in higher flow rates. It should also not be too long and have no curves. Also, the spray rate should not be too low to maintain the flow rate through the tubes at a high level.

6.3 Influence of formulations on the film coating

6.3.1 Viscosity and solid content of the spray suspension

The viscosity of the spray suspension is especially important when the polymer to be processed is in solution (e.g. Kollicoat IR or hypromellose). Viscosity is principally determined by the polymer. The solid content of the spray suspension is determined by the polymer content but also, strongly, by the concentrations of pigment and talcum it contains.
Viscosity and solid content are the main factors that determine the cost of the coating process as these limit the speed of the process. Thus, they are normally set at a high level to save overall cost. Both parameters exert similar influences on the process of film coating and on the appearance of the films. Details are given in table 120.

Table 120: Possible influences of viscosity and solid content of the spray suspension on film coating

Settings	Possible effects
Viscosity and/or solid content too low	- Coating process is too long - Costs are too high
Viscosity too high	- Passage through the nozzle is restricted - Rough “orange skin” film surface (see Fig. 88) - Bridging effect (see Fig. 91)
Solids content too high	- Rough “orange skin” film surface (see Fig. 88) - Cracking and splitting of the film (see Fig. 89) - Peeling and flaking at the edge of the tablet (see Fig. 90)

Fig. 91: Bridging effect (cross-section of a tablet)

6.3.2 Content of titanium dioxide in the spray suspension

The white pigment titanium dioxide guarantees uniform distribution of the dye of the colour lake or pigment on the surface of the tablet core. If the content of titanium dioxide is too low, the resulting coated tablet may not have the same colour intensity.

6.3.3 Plasticizers and the plasticity of the polymer in a spray suspension

The plasticity of the film is an important precondition for the formation of a stable film that completely covers all edges and for the durability of the tablet coating. It is primarily determined by the plasticity of the polymer used. As this is inadequate in many cases, a plasticizer must be added; the type and concentration of such a plasticizer then determine plasticity and minimum film-forming temperature. However, too high concentrations of plasticizer can lead to undesired side-effects. During storage of the coated tablet e.g., the plasticizer could conceivably migrate from the film to the core, hence altering the plasticity of the coating (formation of cracks etc.) and possibly exerting an influence on the active ingredient. The various possible effects are summarised in Table 121.

Table 121: Possible influences of plasticity or plasticizer on the coating

Settings	Possible effects
Plasticity too low	- Cracking and splitting of the film (see Fig. 89) - Peeling and flaking at the edge of the tablet (see Fig. 90)
Plasticizer concentration too high	- Non-uniform colour distribution on the core surface - Migration of the plasticizer to the core during storage - Loss of plasticity during storage - Change in release behaviour during storage

In order to avoid the negative consequences brought about by lack of plasticity or too high a concentration of plasticizer, either a more flexible polymer can be employed or the cores can be provided with a sub-coating comprising a 10 % ethanolic solution of Kollidon VA64. The latter prevents the migration of plasticizer and increases the adhesion of the film to the core surface.

6.3.4 Formulation and properties of the tablet core

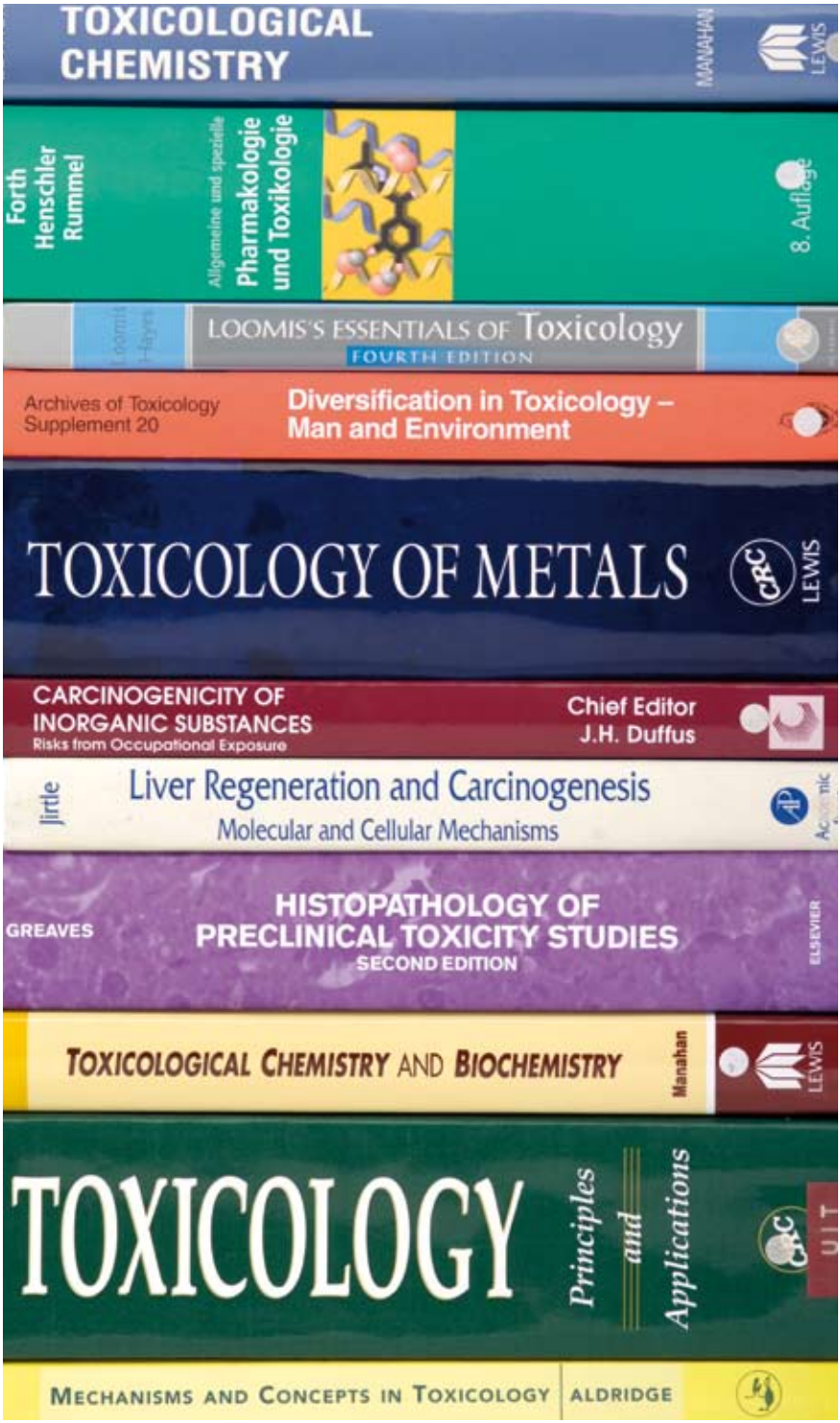
There are a number of ways the formulation and properties of the cores can influence the coating of the tablets. These range from the addition of a swelling disintegrant or the use of stearic acid as a lubricant to the hardness and friability of the tablet core. The possible effects of these parameters are listed in Table 122.

Table 122: Possible influences of the formulation and properties of the cores on film coating

Core parameter	Possible effects
Swelling disintegrant	- Cracking and splitting of the film (see Fig. 89) - Peeling and flaking at the edge of the tablet (see Fig. 90)
Stearic acid as lubricant	- Pitting on the film surface at product temperatures above the melting point of stearic acid (see Fig. 92)
Friability of the cores too high	- Film takes on a rough, "orange skin" appearance (see Fig. 88) - Peeling and flaking at the edge of the tablet (see Fig. 90)
Hardness of the cores too high	- Cracking and splitting on the film due to too little adhesion (see Fig. 89)
Cores not round enough	- Peeling and flaking at the edge of the tablet due to too sharp edges (see Fig. 90) - Sticking together of oblong cores due to too large, even side surfaces

If the core formulation contains an active ingredient susceptible to hydrolysis, the aqueous film coating can have a negative effect on the stability of the active ingredient. In such cases and with all other problems caused by the cores, it can be meaningful to apply, in the same coating machine, a sub-coating comprising a 10 % ethanolic solution of Kollidon VA64 to the cores.

Fig. 92: Pitting in the film caused by stearic acid


TOXICOLOGICAL CHEMISTRY
MANAHAN
LEWIS
Forth
Henschler
Rummel
Allgemeine und spezielle
Pharmakologie und Toxikologie
8. Auflage
LOOMIS'S ESSENTIALS OF Toxicology
FOURTH EDITION
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7. Toxicological and regulatory data

7.1 Summary of the toxicological studies carried out at BASF AG

The information given here refers only to the individual named product of BASF. It is specific for the product and cannot be applied to other products, even if these products are chemically identical.
The data are based on current knowledge and no claims are made regarding completeness. The data do not relieve users from the responsibility of checking the suitability of the product for the intended use and from a risk assessment of their own products.
Our data may only be quoted with BASF's written permission.

7.1.1 Kollicoat IR

The following toxicological studies are also important and relevant to Kollicoat IR White and Kollicoat Protect since Kollicoat IR is the main component of these products.

7.1.1.1 Bioavailability

Result	**Oral bioavailability < 1 %**
Test method	OECD Guideline No. 417 (1984)
Test conditions	
- Species	Rat
- Test substance	^{14}C-Polyvinyl alcohol-polyethylene glycol *graft* copolymer (= Kollicoat IR)
- Route of administration	Oral; gavage
- Dosages	10 and 1 000 mg/kg

7.1.1.2 Acute oral toxicity

Result	**LD_{50} > 2000 mg/kg**
Test method	OECD Guideline No. 423 (1996)
Test conditions	
- Species	Rat
- Observation period	14 days

7.1.1.3 Primary skin irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 404 (1992)
Test conditions	
- Species	Rabbit
- Exposure period	4 h, semi-occlusive dressing
- Observation period	72 h

7.1.1.4 Primary eye irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 405 (1987)
Test conditions	
- Species	Rabbit
- Exposure period	24 h
- Readings	1 h, 24 h, 48 h and 72 h after application

7.1.1.5 Mutagenicity (Ames Test)

Result	**Non-mutagenic**
Test method	OECD Guideline No. 471 (1997)
Test conditions	
- Standard plate test (SPT) and pre-incubation test (PIT), both with and without metabolic activation (S-9 mix)	
- Strains	Salmonella typhimurium TA 1535, TA 100, TA 1537, TA 98, E.coli WP2 uvrA
- Dosage range	20 µg – 5 000 µg/plate (SPT), 20 µg – 5 000 µg/plate (PIT)

7.1.1.6 Cytogenetic study (in vivo) – Mouse Micronucleus Test

Result	**No chromosome damaging (clastogenic) effects and no indications of any impairment of chromosome distribution in the course of mitosis**
Test method	OECD Guideline No. 474 (1997)
Test conditions	
- Species	Mouse
- Number of animals	5 per control group, 5 per test group
- Route of administration	Intra-peritoneal
- Dosage levels	500, 1000, 2000 mg/kg b.w. in purified water; administered twice with a 24 h-interval between administrations

7.1.1.7 Gene mutation test in mouse lymphoma cells (in vitro)

Result	**No mutagenic activity in vitro in the Mouse Lymphoma TK$^{+/-}$ Forward Mutation Assay**
Test method	OECD Guideline No. 476 (1997)
Test conditions	
- System	Thymidine kinase (TK) locus in L5178YTK$^{+/-}$ mouse lymphoma cells with and without metabolic activation (S-9-mix)
- Dose range	**1st experiment:** 0; 312.5; 625; 1 250; 2 500; 5 000 µg/ml (with and without S-9 mix) 0; 312.5; 625; 1 250; 2 500; 5 000 µg/ml (with S-9 mix)

	2nd experiment: 0; 78.125; 156.25; 312.5; 625; 1 250; 2 500; 5 000 µg/ml (without S-9 mix) 0; 312.5; 625; 1 250; 2 500; 5 000 µg/ml (with S-9 mix)

7.1.1.8 Sub-chronic oral toxicity (3 months in drinking water)

Result	**NOEL (no observed effect level): 3 000 ppm (about 300 mg/kg b.w./d in males, about 370 mg/kg b.w./d in females) due to increased water consumption in both sexes.** **NOAEL (no observed adverse effect level): 15 000 ppm (about 1 600 mg/kg b.w./d in males, about 2 200 mg/kg b.w./d in females).** **Clinical examination, clinical chemistry, haematology, urinalysis, macroscopy and histopathology without treatment-related effects**
Test method	OECD Guideline No. 408 (1998)
Test conditions	
- Species	Rat
- Number of animals	20 per control group (10 males, 10 females) 20 per test groups (10 males, 10 females)
- Route of administration	Oral, in drinking water
- Duration of administration	3 months
- Dosages	0; 600; 3 000; 15 000 ppm

7.1.1.9 Prenatal developmental toxicity (rabbit)

Result	**NOAEL (no observed adverse effect level) for maternal and prenatal developmental toxicity:** **1 000 mg/kg b.w./d** **- No signs of maternal toxicity** **- No influence on gestational parameters** **- No signs of developmental toxicity** **- No indications of teratogenic effects**
Test method	Federal Register, Vol. 59, No. 183, pp. 48746 – 48752 (1994)
Test conditions	
- Species	Rabbit
- Number of animals	25 per control group 25 per test group
- Route of administration	Oral, gavage
- Exposure period	Day 6 through day 19 post-insemination
- Dosages	100; 300; 1 000 mg/kg b.w./d (aqueous solution)

7.1.1.10 Prenatal developmental toxicity (Rat)

Result	**NOAEL (no observed adverse effect level) for maternal and prenatal developmental toxicity: 1 000 mg/kg b.w./d** **- No signs of maternal toxicity** **- No influence on gestational parameters** **- No signs of developmental toxicity** **- No indications of teratogenic effects**
Test method	Federal Register, Vol. 59, No. 183, pp. 48746 – 48752 (1994)
Test conditions	
- Species	Rat
- Number of animals	25 per control group 25 per test group
- Route of administration	Oral, gavage
- Exposure period	Day 6 through day 15 post-coitum
- Dosages	100; 300; 1 000 mg/kg b.w./d (aqueous solution)

7.1.1.11 Chronic toxicity (9 months) after oral administration

Result	**NOAEL (no observed adverse effect level) = 30 000 ppm (males: 786 mg/kg bw/day; females: 811 mg/kg bw/day)**
Test method	OECD guideline No. 452 (1981)
Test conditions	
- Species	Dogs
- Number of animals	10 per control group (5 per sex) 10 per test groups (5 per sex)
- Route of administration	Oral, diet
- Dosages	0; 3 000; 10 000 and 30 000 ppm
- Exposure period	9 months, daily.

7.1.2 Kollicoat MAE grades

Since Kollicoat MAE 100P is the same copolymer as in the dispersion Kollicoat MAE 30DP, all toxicolocigal data included in chapter 7.1.2 are valid for Kollicoat MAE 30DP and the dispersions prepared from Kollicoat MAE 100P.

The following additional toxicological studies were carried out with Kollicoat MAE 30DP:

7.1.2.1 Acute oral toxicity

Result	**LD_{50} > 2 000 mg/kg**
Test method	- ECC Directive 92/69, Publication No. L 383A, B.1 (1992) - Acute Toxic Class (ATC) Method, Arch. Toxicol. 66: 455-470 (1992)
Test conditions	
- Species	Rat
- Observation period	14 days.

7.1.2.2 Acute inhalation toxicity

Result	**LC_{50} = 1.03 mg/l/4h**
Test method	- OECD Guideline No. 403 - ECC Directive 92/69 - EPA Guideline
Test conditions	
- Species	Rat
- Exposure period	4 h (liquid aerosol)
- Observation period	14 d

7.1.2.3 Acute intra-peritoneal toxicity

Result	**LD_{50} < 200 mg/kg**
Test method	BASF method
Test conditions	
- Species	Rat
- Observation period	14 d

7.1.2.4 Primary skin irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 404 (1981)
Test conditions:	
- Species	Rabbit
- Concentration	0.5 ml of the unchanged liquid test substance
- Exposure period	4 h, semi-occlusive

7.1.2.5 Primary eye irritation

Result	Non-irritating
Test method	OECD Guideline No. 405 (1987)
Test conditions	
- Species	Rabbit
- Concentration	0.1 ml of the unchanged liquid test substance, one single application (the substance was not washed out)
- Readings	1, 24, 48 and 72 h after application
- Observation period	72 h

7.1.2.6 Sensitization (Buehler Test)

Result	**Non-sensitizing**
Test method	OECD Guideline No. 406 (1992)
Test conditions	
- Species	Guinea pig
- Number of animals	10 per control group, 20 per test group
- Concentration	Induction: 0.5 ml of the undiluted test substance Challenge: 0.5 ml of the test substance (50% in aqua bidest.)
- Induction	Day 0, 7 and 14, percutaneous occlusive

- Challenge	14 days after the 3rd induction; percutaneous occlusive
- Exposure period	Induction: 6 h, challenge: 6 h
- Readings	Induction: 24 h after removal of the patch Challenge: 24 h and 48 h after removal of the patch

7.1.2.7 Mutagenicity (Ames Test)

Result	**Non-mutagenic**
Test method	OECD Guideline No. 471
Test conditions	Standard plate test (SPT) and pre-incubation test (PIT) both with and without metabolic activation (Aroclor-induced rat liver S-9 mix)
- Strains	Salmonella typhimurium TA 1535, TA 100, TA 1537, TA 98
- Dosage range	0 (aqua dest.), 1 250 – 15 000 µg/plate

7.1.3 Kollicoat SR 30D

Further toxicological studies published in the literature are summarized in chapter 7.2.

7.1.3.1 Acute oral toxicity

Result	**LD_{50} > 2 000 mg/kg**
Test method	OECD Guideline No. 423 (1996)
Test conditions	
- Species	Rat

7.1.3.2 Acute skin irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 404
Test conditions	
- Species	Rabbit
- Exposure period	4 h, semi-occlusive dressing

7.1.3.3 Acute eye irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 405
Test conditions	
- Species	Rabbit
- Exposure period	24 h
- Readings	1 h, 24 h, 48 h and 72 h after application

7.1.3.4 Mutagenicity (Ames Test)

Result	**Non-mutagenic**
Test method	OECD Guideline No. 471 (1997)
Test conditions	
- Standard plate test (SPT) and pre-incubation test (PIT) both with and without metabolic activation (S-9 mix)	
- Strains	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, E.coli WP2 uvrA
- Dosage range	20 µg – 5 000 µg/plate (SPT), 20 µg – 5 000 µg/plate (PIT)

7.1.3.5 Cytogenetic study (in vivo) – Mouse Micronucleus Test

Result	**No chromosome damaging (clastogenic) effects and no indications of any impairment of chromosome distribution in the course of mitosis**
Test method	OECD Guideline No. 474 (1997)
Test conditions	
- Species	Mouse
- Route of administration	Intra-peritoneal
- Dosage levels	0, 50, 100, 200 mg/kg b.w.

7.1.3.6 Prenatal developmental toxicity (rat)

Result	**Under the conditions of this toxicity study, the oral administration to pregnant Wistar rats from implantation to one day prior to the expected day of parturition (days 6-19 p.c.) elicited neither maternal toxicity nor were there substance-induced influences on the gestational parameters. There were also no signs of developmental toxicity, especially no substance-induced indications of teratogenicity, up to and including the highest dosage level. NOAEL (no observed adverse effect level) for maternal and prenatal developmental toxicity: 840 mg/kg body weight/day**
Test method	Federal Register, Vol. 59, No. 183, pp. 48746 – 48752 (1994)
Test conditions	
- Species	Rat
- Number of animals	25 per control group; 25 per test group
- Route of administration	oral, gavage
- Dosages	0, 100; 300; 1 000 mg/kg b.w.

7.1.3.7 Sub-chronic oral toxicity

Result	**Under the conditions of this study, the "no observed adverse effect level" (NOAEL) was 50 000 ppm (4493.7 mg/kg body weight/day in males; 5162.7 mg/kg body weight/day in females). The clinical, clinical-chemical and haematological examinations as well as urinalyses did not indicate any treatment-related effects. Finally, no treatment-related changes could be observed by gross pathology and histopathological examinations.**
Test method	OECD Guideline No. 408 (1998)
Test conditions	
- Species	Rat
- Route of administration	Oral, in drinking water
- Duration of administration	3 months
- Dosages	5 000; 20 000; 50 000 ppm

7.1.3.8 Gene mutation test in mouse lymphoma cells (in vitro)

Result	**No mutagenic activity**
Test method	OECD Guideline No. 476 (1997)
Test conditions	
- System	Thymidine kinase (TK) locus in L5178YTK$^{+/-}$ mouse lymphoma cells with and without metabolic activation.

7.1.4 Kollicoat EMM 30D

7.1.4.1 Acute oral toxicity

Result	**LD_{50} > 5 000 mg/kg** (Literature, unpublished result)
Test conditions	
- Species	Rat

7.1.4.2 Primary skin irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 404 (1992)
Test conditions	
- Species	Rabbit
- Concentration	0.5 ml of the unchanged liquid test substance
- Exposure period	4 h, semi-occlusive
- Observation period:	72 h and 14 d

7.1.4.3 Primary eye irritation

Result	**Non-irritating**
Test method	OECD Guideline No. 405 (1987)
Test conditions	
- Species	Rabbit
- Concentration	One single application: 0.1 ml of the unchanged liquid test substance; the substance was washed out with water approx. 24 h after application
- Readings	1, 24, 48 and 72 h after application
- Observation period	72 h

7.1.4.4 Mutagenicity

Result	**Non-mutagenic in bacteria** (literature, unpublished result)

7.1.4.5 Aerobic biodegradation

Result (kinetic)	**21 day(s), ca. 99 %**
Method	ISO DIS 9439 "Ultimate Aerobic Biodegradability-Method by analysis of released carbon dioxide"
Inoculum	Activated sludge, domestic

7.2 Summaries of published toxicological data

7.2.1 Kollicoat SR 30D

As Kollicoat SR 30 D is based on polyvinyl acetate (PVAc), a summary of toxicity studies on this polymer as published in the scientific literature is given here.

After a single oral ingestion, PVAc is practically non-toxic. The oral LD_{50} in rats and mice was found to be > 25 g/kg [15].

It was reported that the oral lethal dose of PVAc formulated as an emulsion dust control material was > 9.7 g/kg for rats [16].

Skin irritation tests on rabbits with this emulsion or the base latex produced moderate to severe irritation on intact and abraded skin [16].
However, in humans no evidence of primary irritation or skin sensitization was observed in any of the 210 volunteers exposed to a film made from two different PVAc emulsions or cotton cloth impregnated with 40 % PVAc resin [17].

After s.c. injection of PVAc into the dorsal skin of rats, the substance was very irritating and produced a strong inflammatory response in the tissue [18].

When PVAc was administered orally for 12 months to rats and mice at a dosage of 250 mg/kg/d, fluctuations in body weight, changes in blood

composition, changes in liver-to-weight ratios, and changes in cholinesterase and catalase activities were observed. As in the publication, no other details were reported; the toxicological relevance of the described findings can thus not be assessed [15].

PVAc was tested for its mutagenic potential in the Ames Test using Salmonella typhimurium strains TA 92, TA 1535, TA 100, TA 1537, TA 94 and TA 98 with metabolic activation. PVAc was not shown to be mutagenic under the conditions of the study [19].
PVAc was also tested in the chromosomal aberration test using a Chinese hamster fibroblast cell line. A metabolic activation system was not used. No chromosomal aberrations were observed [19].

Carcinogenicity studies with oral administration are not available. However, in a limited study, a PVAc powder was implanted (route and amount unspecified) in rats and mice. No local sarcomas were observed within 16–20 months after implantation [20].
In a kinetic study, an aqueous emulsion of PVAc was administered to rabbits by s.c. and i.v. injection [21]. In the s.c. study, the PVAc remained localized at the site of application with little absorption. A small amount of the i.v. injected PVAc was excreted in the urine; the remainder was retained in the body. After i.v. injection of PVAc to pregnant rabbits, the substance was not transferred to the foetus in appreciable amounts.

No studies on the prenatal toxicity or reproductive toxicity of PVAc are available in the scientific literature.

7.3 Pharmacopoeias, registration as drugs

7.3.1 Pharmacopoeias

Most of the Kollicoat grades are either included as monographs in one of the major pharmacopoeias or there are published draft monographs or projects for such. The major pharmacopoeias include the European Pharmacopoeia (PH.Eur.), the United States Pharmacopoeia (USP/NF), the Japanese Pharmacopoeia (JP) and the Japanese Pharmaceutical Excipients (JPE).
The Kollicoat grades fulfil all the requirements of these pharmacopoeias (Table 113).
As these monographs are traditionally cited as proof of quality if an excipient is to be included in a submission for drug registration, there is normally no problem on the part of the regulatory authorities in individual countries if the Kollicoat grades are included in a new or reformulated drug form. The three Kollicoat IR grades, however, are exceptions here as these have been developed over the past few years; they have thus not yet been included as monographs in any of the pharmacopoeias. In addition, there is normally no monograph for mixtures and ready-to-use formulations such as e.g. Kollicoat IR White or Kollicoat Protect. Generally, only those active ingredients and excipients are included in a specific pharmacopoeia if these have already been approved for use in a number of drugs in the country or countries involved. The purpose of a pharmacopoeia is not to introduce new substances but rather to confirm and standardise the quality of those substances already being used in registered drugs.

In the case of Kollicoat MAE 100P and Kollicoat SR 30D, the already published Ph.Eur draft monograph are scheduled for publishing as final monographs in the Supplements 5.7 and 5.8 to the European Pharmacopoeia during the course of 2006.

Table 113: Kollicoat grades included in the various pharmacopoeias (status: end of 2006)

Kollicoat type	Ph.Eur.	USP/NF	JP/JPE
Kollicoat IR grades	NA*	NA*	NA*
Kollicoat MAE 30DP	+	+	+
Kollicoat MAE 100P	+	NA	NA
Kollicoat SR 30D	+	NA	NA
Kollicoat EMM 30D	+	NA	+

NA = No monograph available
* = The other components besides Kollicoat IR fulfil the requirements of the corresponding monographs

The titles of the various monographs are listed in Table 114. Unfortunately, these have not as yet been harmonised in the various pharmacopoeias; there may thus be some confusion.

Table 114: Titles of the various pharmacopoeial monographs where the Kollicoat grades conform

Kollicoat type	Ph.Eur.	USP/NF	JP/JPE
Kollicoat MAE 30 DP	Methacrylic acid-ethyl acrylate co-polymer (1:1), 30 % dispersion	Methacrylic acid co-polymer dispersion	Methacrylic acid co-polymer LD
Kollicoat MAE 100P	Methacrylic acid-ethyl acrylate co-polymer (1:1), type B	NA	NA
Kollicoat SR 30D	Poly (vinyl acetate) dispersion, 30 %	NA	NA
Kollicoat EMM 30 D	Polyacrylate, dispersion, 30 %	NA	Ethyl acrylate and methyl methacrylate copolymer dispersion

NA = No monograph available

7.3.2 Registration in drugs

7.3.2.1 Kollicoat IR grades

Kollicoat IR is a new excipient that has been available to the pharmaceutical industry for a few years only. However, as a number of drugs containing Kollicoat IR have now been registered in Europe (e.g. Germany) and abroad, there should be no difficulties in having other drugs containing Kollicoat IR registered. The necessary information for this process is available from BASF AG.
In the USA, there are Drug Master Files for the Kollicoat IR grades; the respective numbers are listed in Table 115.

Table 115: Drug Master Files for the Kollicoat IR grades in the USA

Product	US DMF No. (Type 4)	US DMF No. (Type 5, toxicological studies)
Kollicoat IR	16886	16885
Kollicoat IR White	18830	
Kollicoat Protect	19184	

7.3.2.2 Kollicoat MAE 30 DP

The 30 % aqueous dispersion of co-polymer methalcrylic acid-ethyl acrylate 1:1 (Kollicoat MAE 30DP) has already been registered for use in drugs in most countries of the world. There are thus no hindrances to the substance being approved.
Kollicoat MAE 30DP has the US DMF No. 14823.

7.3.2.3 Kollicoat MAE 100P

The co-polymer methacrylic acid – ethyl acrylate 1:1 in powder form (e.g. Kollicoat MAE 100P) has also been registered as a component of numerous drugs in all major markets. There are thus no further hindrances to the substance being registered. However, in submitting for registration, the revised monograph of the European Pharmacopoeia (Ph.Eur.) should be referred to. In this monograph, Kollicoat MAE 100P is referred to as type B as previous monographs were valid for the competitive product only.
The revised Ph.Eur. monograph including both types A and B is scheduled to be effective by the end of 2006.

7.3.2.4 Kollicoat SR 30D

Polyvinyl acetate is an excipient that has already been registered in drugs in all major European countries, the USA and in Japan. However, to date, the monograph for the pure powder polyvinyl acetate has been employed as reference. For registration of the aqueous dispersion of Kollicoat SR 30D, that was only developed for use in the pharmaceutical industry a few years ago, the new Ph.Eur. monograph should be referred to. This is scheduled to become effective by the end of 2006.
Kollicoat SR 30D has the US DMF No. 15055.

7.3.2.5 Kollicoat EMM 30 D

The 30 % aqueous dispersion of co-polymer ethyl acrylate and methalcrylic acid 2:1 (Kollicoat EMM 30D) has already been registered in drugs in numerous countries. There are thus no hindrances to the substance being registered.

7.4 Approval for use in foodstuffs

As far as is known, only the polymer polyvinyl acetate as contained in Kollicoat SR 30D has been approved for use in foodstuffs in Europe and Japan.

A submission for approval in foodstuffs has been made for Kollicoat IR in the USA.

The other Kollicoat grades are intended for use in drugs only.


17.4
PHARMEUROPA
The European Pharmacopoeia Forum
edqm
Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms
Second Edition, Revised and Expanded
edited by James W. McGinity
V. Bühler
Polyvinylpyrrolidone Excipients for Pharmaceuticals
Povidone, Crospovidone and Copovidone
Springer
Bauer · Lehmann · Osterwald · Rothgang
Coated Pharmaceutical Dosage Forms
Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials
medpharm Scientific Publishers
CRC
Kollidon
BASF

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