Evaluating the suitability of a pH-dependent pore former in a sustained release film-coating formulation

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INTRODUCTION

Since the development of polymers for enteric coating in the late 1950's [1], numerous investigations have illustrated the application of these functional excipients such as poly(methacrylic acid-co-ethyl acrylate). Also mixtures with other polymers like poly(vinyl acetate) have already been well described [2 – 4].

The combination of an insoluble and an enteric polymer allows the alteration of the drug release rate of a coated dosage form during its passage through the gastro intestinal tract of the human body. This allows for instance to achieve a constant release pattern for weak basic drugs. While solubility of basic drugs is high in acid media (gastric passage), the permeation through the coat is restricted by the enteric pore former. As soon as pH-value increases (dosage form enters the intestines), the permeation rate increases due to the solubility of the enteric polymer in this milieu. Hence, the decreasing solubility of the drug is balanced [5, 6].

The aim of the present investigations was the evaluation of poly(methacrylic acid-co-ethyl acrylate) as pH-dependent pore former in a poly(vinyl acetate) based coat. Of particular challenge was the incompatibility of the two polymer dispersions, disabling a direct formulation of the two components as polymer mixture. In order to gain a homogeneous coat consisting of both polymers in the required ratio, the two dispersions were applied simultaneously in a fluid bed coating process by combining bottom and top spray technology.

MATERIALS AND METHODS

Materials and formulations

Pellets consisting of 90% theophylline and 10% carrageenan were provided from the Heinrich Heine University Düsseldorf. As coating material poly(vinyl acetate) dispersion (Kollicoat® SR 30 D, BASF SE) and poly(methacrylic acid-co-ethyl acrylate) dispersion (Kollicoat® MAE 30 DP, BASF SE) were used in combination with the plasticiser triethyl citrate (TEC, Merck KGaA). As spin probe for ESR measuring 4-Hydroxy-TEMPO (Tempol, ABCR GmbH & Co KG) at a purity grade of 98% was added to dedicated formulations.

Film-coating application

The coating trials were conducted in a GPCG 3.1 (Glatt GmbH). Due to the incompatibility of the two dispersions polymers were applied separately. In order to allow this, bottom and top spray nozzles were installed.

Five different polymer ratios were investigated. The ratio was altered by varying the polymer concentration of the top spray dispersion (Table 1). This method of varying solid matter content was regarded as being more precise compared to the alternative of altering the polymer ratio by adjusting the spray rates with the peristaltic pumps.

Table 1. Formulations tested.

Ratio MAE:SR		1:9	2:8	3:7	4:6	5:5
Solid matter content of the dispersion	MAE	4%	8%	12%	16%	20%
	SR	20%	20%	20%	20%	20%

After pre-heating of equipment and pellets, the Wurster column was set to a height of 3 cm above the distribution plate. All coating processes were conducted with the same parameters (Table 2). In order to investigate different coating levels, samples were taken every 10 to 15 minutes processing time. After finishing the spraying process, the batch was finally dried directly in the fluid bed coater.

Table 2. Process settings and parameters.

Parameter	Setting	Mean value	Standard deviation
Inlet air temperature	40°C	40.3°C	0.1 K
Inlet air volume	120 m³/h	117.3 m³/h	13.3 m³/h
Atomisation air pressure	1.5 bar	1.5 bar	0.0 bar
Spray rate (MAE)	5-6 g/min	5.5 g/min	0.6 g/min
Spray rate (SR)	5-6 g/min	5.5 g/min	0.7 g/min
Product temperature	-	31.3°C	1.0 K
Exhaust air temperature	-	29.2°C	1.1 K
Relative exhaust air humidity	-	30.2%	4.8%
Batch size	1,000 g	1,000.1 g	0.1 g

Dissolution tests

A standard USP Dissolution Apparatus 2 (Paddle) from ERWEKA, equipped with continuous on-line UV measuring (Agilent 8453) was used (50 rpm, 37°C ±0.5 K). The dissolution test was conducted with samples having a total pellets weight of 120 mg ±1 mg (n=5) at pH 1.0 (HCl, 1 M; volume 750 mL). After 120 minutes the pH-value was altered to 6.8 by adding 250 mL of a tri-sodium phosphate buffer solution (0.2 M).

NMR spectroscopy

With the intention to gain a strong signal, a total sample weight of 300 to 600 mg pellets (corresponding to about 60 mg MAE) were tested at a proton resonance frequency of 400 MHz. Mestrec was used as analysis software [7].

EPR spectroscopy

This analysis was conducted with an EPR spectroscope L-Band (Magnettech). As spin probe 4-Hydroxy-TEMPO (Tempol) was used. This tracer was incorporated into dedicated coating formulations (applied via bottom spray nozzle) and applied during the coating process.

Tempol shows a paramagnetic moment. Fractions of mobilised Tempol molecules can be utilised as quantitative indicator for the extent of water influx. Tracing the release of the spin probe over time delivers information on the water influx into the coat as a precondition for the subsequent mobilisation [8 – 11].

RESULTS AND DISCUSSION

Process optimisation

In addition to the fact that both dispersions are prone to coagulation as soon as they are combined in a liquid state, a process related problem needed to be considered as well. The assembling of bottom and top spray configuration at the same time went along with a noticeable increase of spray losses, appearing as deposited polymer mainly at the upper opening of the Wurster column.

Particularly challenging was the top spray application. This presumption was confirmed by two experiments where poly(methacrylic acid-co-ethyl acrylate) dispersion (MAE) was applied: firstly, via top spray and secondly, via bottom spray configuration. In both trials water was sprayed through the second nozzle to simulate the actual coating process. Eventually, a spray loss of 76% was found for the top spray approach whereas the bottom spray method did not cause any spray losses at all. However, the process could be improved while increasing batch size from 1 to 3 kg. Distinctive spray losses of 30% could still be seen, though (Figure 1).

Even with an optimised coating process, the originally intended polymer rations could still not be applied precisely. Therefore, NMR analysis was conducted to determine the precise composition of the coat [4]. This was important to allow the correlation of dissolution data with the actually applied coating formulation.

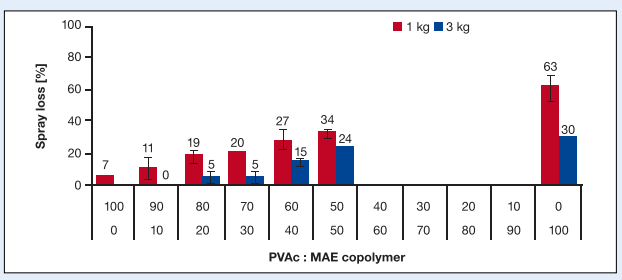

Figure 1. Comparison of the resulting spray losses for different coating formulations (polymer ratios) and batch sizes (1 and 3 kg) indicating that top spray (MAE) was more crucial.

Evaluating a suitable coating level

An appropriate coating level should provide delayed as well as prolonged drug release which is to correspond with the average gastro-intestinal passage time of the dosage form in the human body. From an economical point of view, high coating levels (which would lead to a distinct delay in drug release) come along with huge polymer consumptions and long process times and are therefore expensive. In contrast, dosage forms bearing lower coating level are cheaper, but they are more prone to damages and bear the inherent risk of a burst release. In order to serve both processing and economical aspects, weight gains/coating levels of 4%/1.2 mg/cm² (Figure 2), 6%/1.8 mg/cm² (Figure 3) and 11%/3.3 mg/cm² (Figure 4) were evaluated.

According to general recommendations, enteric coats should be used with a coating level of 3 to 5 mg/cm². The level of MAE applied in these trials was fairly below these recommended values. Therefore, gastric resistance could not be expected.

The release characteristics of the pellets bearing a weight gain of 6.0% (Figure 3) were found to be in an applicable range with 100% drug release within 20 hours. This was in accordance with the aim of a prolonged release during the gastro-intestinal passage. Furthermore, the coating level appeared to be reasonable in regard to economic aspects and product safety. A weight gain of 6.0% offers a high probability of a pellet's surface completely covered with polymer eliminating the risk of a burst release.

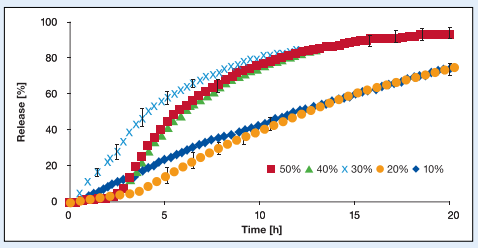

Figure 2. Dissolution profiles of theophylline pellets as function of different MAE contents in the coat, weight gain 3.5 to 4.4%.

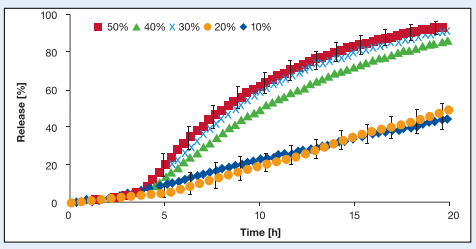

Figure 3. Dissolution profiles of theophylline pellets as function of different MAE contents in the coat, weight gain 6.0%.

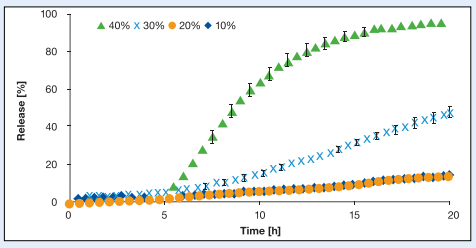

Figure 4. Dissolution profiles of theophylline pellets as function of different MAE contents in the coat, weight gain 10.0 to 12.0%.

Drug release characteristics

Firstly, each individual polymer was coated onto the theophylline pellets as a single film-former. The resulting dissolution profiles were plotted into the following diagrams for comparison reasons.

Delayed release

USP 31 demands for delayed-release dosage forms that no individually tested dosage form exceeds 10% drug release within 120 minutes of dissolution testing in an acidic media. This requirement could be fulfilled for each coated pellet formulation tested, regardless of the polymer ratio applied (Figure 5). There was no significant difference in the relative release of theophylline between the investigated polymer mixtures. A tendency of faster drug release with decreasing MAE contents could be observed, though.

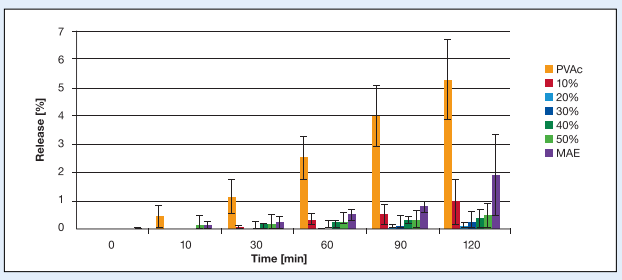

Figure 5. Drug release during acid stage with regard to time and MAE content (3 kg batch, n≥5).

Prolonged release

A general trend could be found that an increasing amount of MAE in the coating formulation led to a faster drug release. However, between 10 and 20% MAE content seemed to be a critical concentration. Conversely, while using MAE below this concentration, a slowing down of the drug release rate could be observed (Figure 6).

Investigating water up-take by means of EPR spectroscopy

Three samples with varying MAE contents were investigated. An increasing mobility of Tempol could be seen within two hours testing time at a pH-value of 2 (Figure 7). The curves were fitted to a growing exponential function with a relative error of 0.02.

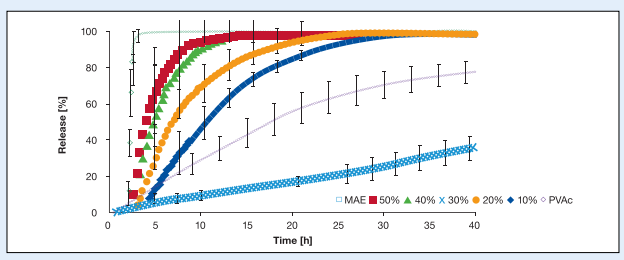

Figure 6. Release curves of 3 kg-batches with different contents of pore former (n=3).

During the first minutes the signal jumped to an initial value which can be explained by the mobilisation of Tempol molecules being situated in the outer coating layer. However, a lag-phase of 15 to 25 minutes could be seen before obtaining reliable results. This was due to the time needed to obtain an equilibrated state of homogeneously wetted pellets, which is essential for gaining a constant signal [4]. Interestingly, even though both polymers are insoluble in water at a pH-value of 2 differences in the water influx could be determined. This indicated the higher permeability of poly(vinyl acetate) (PVAc) compared to MAE.

Furthermore while considering the results of the dissolution testing, a tendency of poorer permeability with increasing MAE contents could be stated. This thesis was confirmed by means of EPR spectroscopy. Two hours after wetting the pellets (pH 2.0), 39% ±2% of the added Tempol were mobilised in the MAE coat, while 56% ±2% of the spin probe were mobilised in the coat containing 10% MAE. The value for 40% MAE content was at 48% ±2% and herewith reasonably in-between the two previously mentioned values.

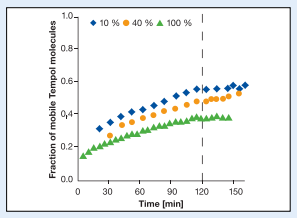

Figure 7. Increasing mobilisation of spin probe at pH 2 at different MAE contents.

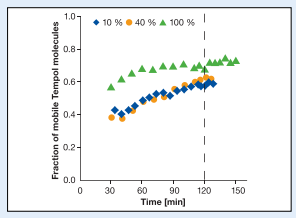

Figure 8. Increasing mobilisation of spin probe at pH 6.8 at different MAE contents in pellet coat.

In contrast, permeability was inverted at a pH-value of 6.8 (Figure 8). After two hours 62% ±2% of Tempol molecules were mobilised in the MAE coat, in comparison to 57% ±2% in the coat containing 10% MAE. Yet, the coat with 10% and 40% MAE hardly showed any difference. This means, a coat consisting of MAE only still has 32% of immobilised Tempol molecules left after two hours of testing time, although it easily dissolves at a pH >5.5. An entire dissolution of the polymer should result in the release of the whole amount of spin probe. One could suppose that, in spite of the good stability of the NO radical, it interacted in some way with the polymer – resulting in the loss of its paramagnetic characteristic.

CONCLUSION

It was possible to apply two incompatible dispersions in parallel by means of facilitating both bottom and top spray modification of a fluid bed coater simultaneously. However, some distinctive spray losses of the dispersion applied via the top spray nozzle occurred in spite of the conducted process optimisation. A careful consideration of this fact was necessary to learn about the final composition of the applied coat.

When combining the functionality of the two polymers, a delayed and extended drug release can be achieved. Thus, the enteric polymer acts as a pH-dependent pore former. With variations in the ratio of the two polymers in the coat, the release rate and dissolution characteristics can be altered respectively.

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