Liquid Fill of Hard Gel Capsules – Investigating the Effect of Matrix-Excipients on the Release Characteristics

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Introduction

Filling liquid formulations (e.g. two component mixtures) into hard gelatin capsules combines the benefit of soft gel capsules with the efficient and economic process of hard gel capsule filling. [1]

Various dissolution characteristics can be addressed with the selected matrix excipients:

1. Instant release: For instant release formulations, the benefits focus on 'simplification' (ideally only three components need to be formulated and declared) and a high content uniformity (eg. for low dose drugs) can be achieved by filling solutions or dispersions into the shell.

2. Sustained release: Modified release functionality can easily be achieved by the use of e.g. ceraceous substances in combination with release enhancing compounds as per the desired release pattern. Requirements of the food/dietary supplement market can be easily addressed.

3. Solubility enhancement: This formulation approach offers advantages in the field of solubility enhancement. For example, lipid based drug delivery systems or self-emulsifying drug delivery systems can be formulated as per the respective requirements and administered in capsules. With a simple downstream processing, further formulation challenges can be avoided.

The selected, commonly used matrix-excipients offer a divers toolbox for easy and quick formulation development.

Objective

The aim of this study was to evaluate the impact of matrix - excipients – found to be suitable for liquid hard gel capsule filling – on the dissolution pattern of three model drugs. [1] Caffeine fine powder was tested in combination with the listed matrix-excipients as a rather soluble model drug. Ibuprofen was tested as a representative of drugs with pH-dependent solubility. Fenofibrate is a BCS class II component. This active was used as a model active to evaluate whether solubility enhancement could be gained by the liquid fill formulation approach.

Materials and Methods

Table 1. List of excipients screened in the realm of this study.

Compendial name	Brandname	Supllier
Triacetin	Kollisolv® GTA	BASF SE
Triglycerides medium-chain	Kollisolv® MCT 70	BASF SE
Cocoyl caprylocaprate	Kollicream® 3C	BASF SE

Cetyl palmitate 15	Kollicream® CP15	BASF SE
Decyl oleate	Kollicream® DO	BASF SE
Oleyl alcohol	Kollicream® OA	BASF SE
Octyldodecanol	Kollicream® OD	BASF SE
Macrogol cetostearyl ether 12	Kolliphor® CS12	BASF SE
Macrogol cetostearyl ether 20	Kolliphor® CS20	BASF SE
Macrogolglycerol ricinoleate 35	Kolliphor® EL	BASF SE
Macrogol 15 hydroxystearate	Kolliphor® HS15	BASF SE
Poloxamer 188	Kolliphor® P188	BASF SE
Poloxamer 407	Kolliphor® P407	BASF SE
Macrogolglycerolhydroxystearate 40	Kolliphor® RH40	BASF SE
Vitamin E polyethylene glycol succinate (TPGS)	Kolliphor® TPGS	BASF SE
Cetyl alcohol	Kolliwax® CA	BASF SE
Cetosteryl alcohol	Kolliwax® CSA50	BASF SE
Glycerol monostearate 40-55 (typ II)	Kolliwax® GMS II	BASF SE
Castor oil hydrogenated	Kolliwax® HCO	BASF SE
Myristyl alcohol	Kolliwax® MA	BASF SE
Stearyl alcohol	Kolliwax® SA	BASF SE
Stearic acid 50	Kolliwax® S	BASF SE

Model drugs were: caffeine fine powder (Siegfried AG); Ibuprofen (BASF SE) and Fenofibrate powder (Pfannenschmidt Hamburg).

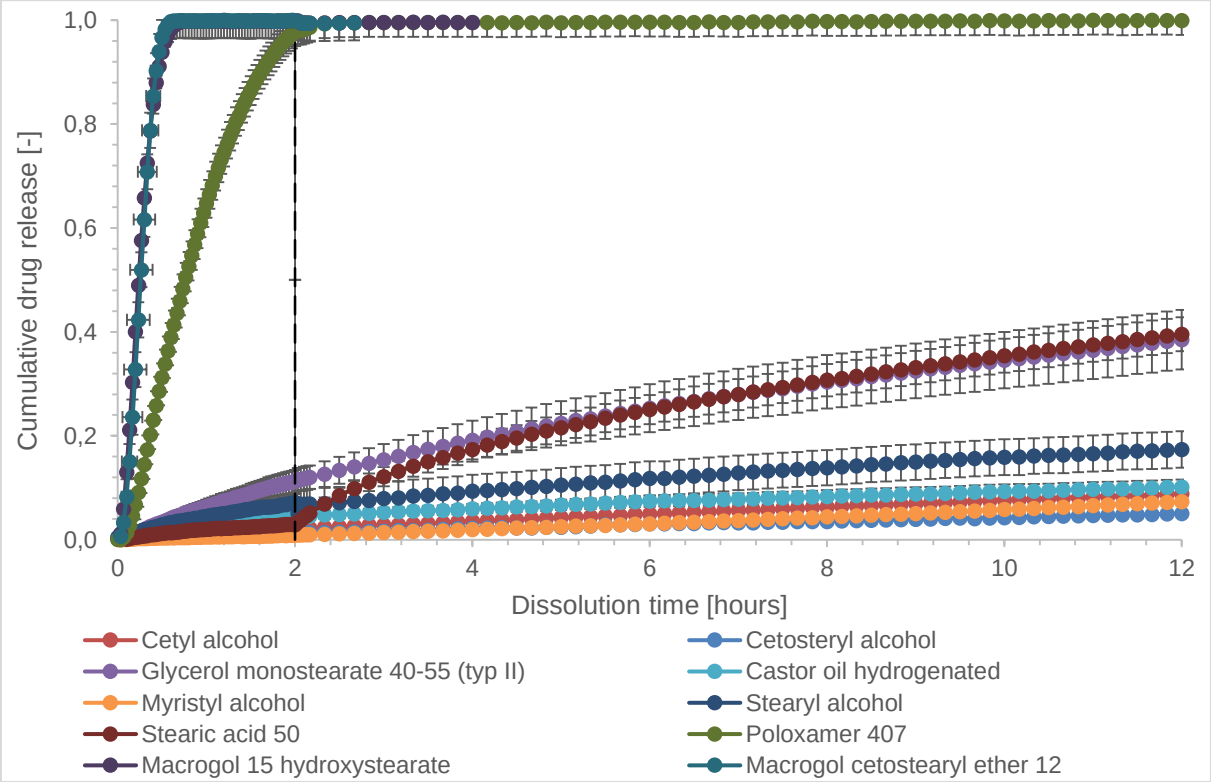
The respective formulations (two component mixtures) were prepared and filled into capsules manually. Excipients being solid at room temperature (RT) were molten upfront at their respective melting temperature (TM). The dissolution patterns were recorded using an Erweka DT 700/720 USP dissolution apparatus with continuous on-line UV measurement (Agilent 8453). The formulations were tested 2 hours in an 0.08 mol/L HCL buffer until the dissolution media was changed to a pH 6.8 phosphate buffer and tested for further 10 hours.

Results and Discussion

Caffeine:

For most of the matrix-excipients tested, hardly any differences in the dissolution pattern of caffeine was found. Basically, all rather hydrophilic formulations provided immediate release functionality. With a distinctly reduced drug release rate Poloxamer 407 was the only exception. In contrast, macrogol 15 hydroxystearate and macrogol cetostearyl ether 12 offered the quickest release of caffeine (see Figure 1). Even though triacetin, triglycerides medium chain and octyldodecanol could be tested in hard gel capsules, both excipients leaked out and thus cannot be recommended as single matrix component. However, at a later stage it might be interesting to use these excipients in multiple component formulations to alter either viscosity, API solubility or disintegration. The lipophilic nature of cetyl alcohol, cetosteryl alcohol, glycerol monostearate 40-55 (typ II), castor oil hydrogenated, myristyl alcohol, stearyl alcohol and stearic acid 50 affected the drug release characteristics of caffeine tremendously. The pure components led to such a low drug release rate that it is recommended to formulate these excipients with a release enhancer, to achieve more appropriate drug release patterns with soluble APIs.

Figure 1. Selected dissolution profiles of Caffeine - change of pH-value 1.1/6.8 after 2 hours' dissolution time.

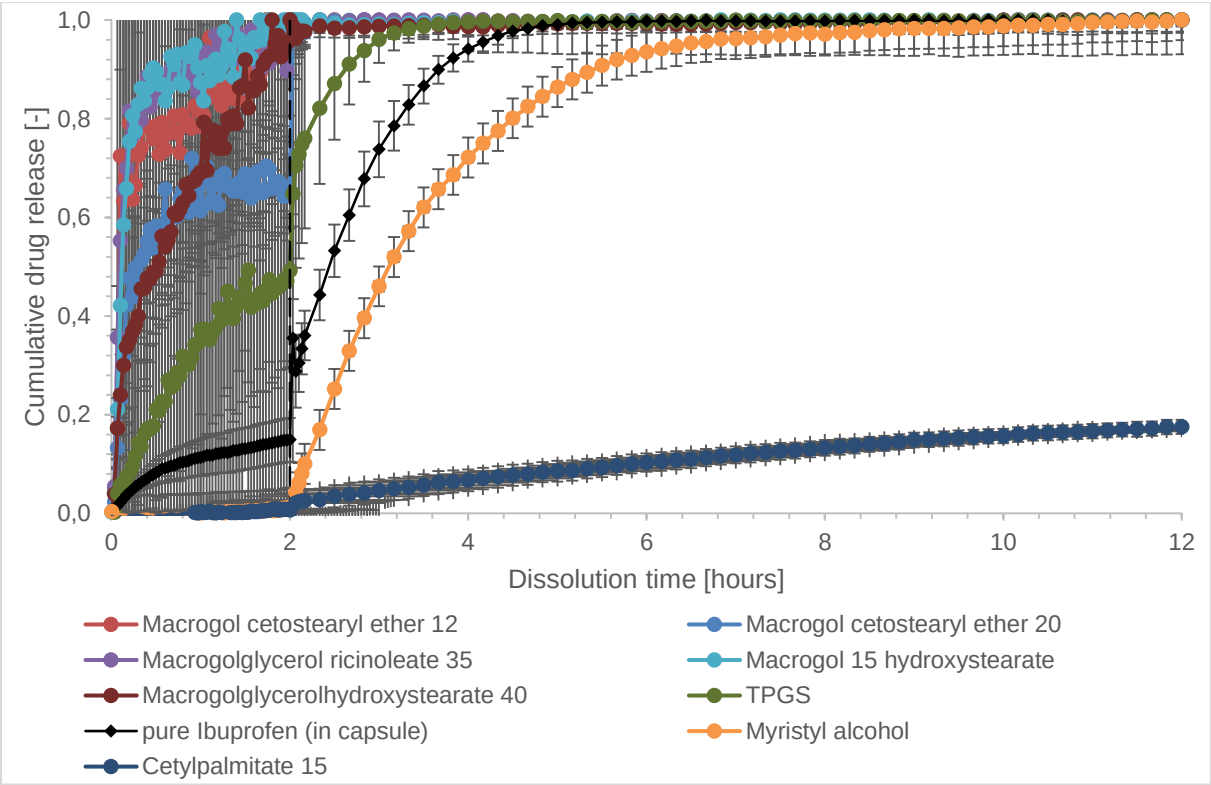


Ibuprofen:

Due to the rather poor solubility of Ibuprofen in acidic media (about 20% release in the first two hours), hardly any further drug release could be measured during the first period of dissolution testing (pH 1.1), even though the capsules were fully disintegrated. However, macrogol cetostearyl ether 12, macrogol cetostearyl ether 20, macrogolglycerol ricinoleate 35, macrogol 15 hydroxystearate, macrogolglycerolhydroxystearate 40 and TPGS acted as solubiliser for Ibuprofen in acidic media (see Figure 2). Even though the standard deviation during this phase of dissolution testing is tremendously high, it can be assumed that – with some optimization - the up-take of Ibuprofen (by the human body) improves. In contrast, myristyl alcohol even prevented the dissolution of Ibuprofen in acetic media completely,

although the release profile in phosphate buffer showed an immediate release pattern (see Figure 2). In case of Ibuprofen, myristyl alcohol delivers a kind of enteric protection which could be true for some other APIs as well. The use of cetyl palmitate 15 resulted in a sustained release pattern. The poor solubility of Ibuprofen in acidic media in combination with the lipophilic character of the cetyl alcohol, cetosteryl alcohol, glycerol monostearate 40-55 (typ II), castor oil hydrogenated, stearyl alcohol and stearic acid 50, led to hardly any drug release during the first two hours of dissolution testing. Even after altering the pH-value to 6.8 a rather slow drug release was found. One exception is myristyl alcohol, providing a rather quick dissolution pattern (see Figure 2).

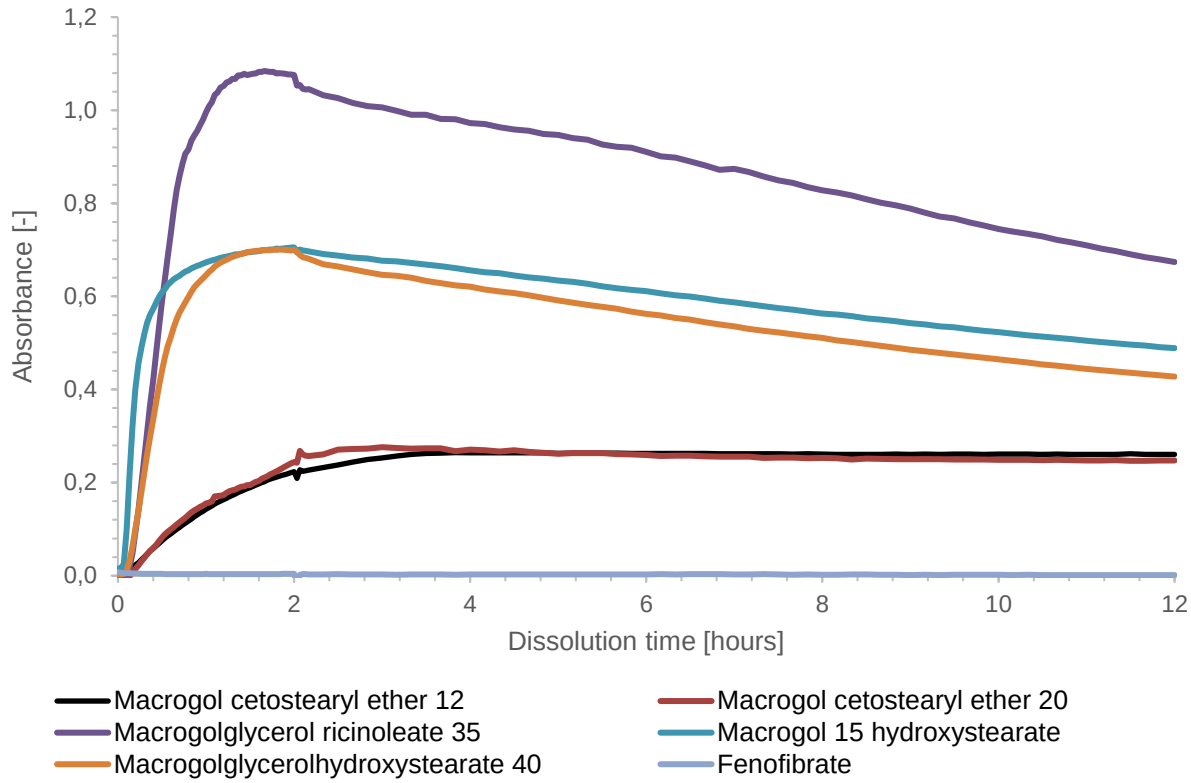
Figure 2. Selected dissolution profiles of Ibuprofen - change of pH-value 1.1/6.8 after 2 hours' dissolution time.



Fenofibrate:

In case of Fenofibrate the absorbance was plotted as function of dissolution time. Most of the excipients tested, didn't provide any advantage in terms of solubility enhancement. No test indicated any dissolved Fenofibrate. However, macrogol cetostearyl ether 12, macrogol cetostearyl ether 20, macrogolglycerol ricinoleate 35, macrogol 15 hydroxystearate, macrogolglycerolhydroxystearate 40 and TPGS provided some promising results and can be considered for further studies on fenofibrate formulations (see Figure 3).

Figure 3. Selected absorbance profiles of Fenofibrate - change of pH-value 1.1/6.8 after 2 hours' dissolution time.



Conclusion

Most matrix-excipients tested are suitable of beeing used as liquid fill of hard gelatin capsules. Depending on the nature of the API, this approach is suitable to address all desired dissolution characteristics (e.g. instant release or modified release) with a rather simple formulation approach. Further solubility enhancement can be demonstrated.

References

1. Rottmann N. et al., Liquid Fill of Hard Gel Capsules – Screening of Suitable Excipients, PBP World Meeting 2018, Granada, Spain

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