Investigating the effect of partial neutralisation of the polymer on the dissolution characteristics of Kollicoat® MAE 100-55 based coats

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INTRODUCTION

Various active pharmaceutical ingredients (APIs) are either aggressive to the stomach's mucosa or vulnerable to the acidic nature of the gastric juice. Solid oral dosage forms carrying one of these APIs thence require gastric resistant functionality. Poly(methacrylic acid-co-ethyl acrylate) based coats are most frequently applied to introduce this functionality [1].

The polymer is available in three different grades (Ph.Eur.):

- Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent (e.g. Kollicoat® MAE 30 DP)
- Methacrylic acid - ethyl acrylate copolymer (1:1), Type A (e.g. Kollicoat® MAE 100-55)
- Methacrylic acid - ethyl acrylate copolymer (1:1), Type B (Kollicoat® MAE 100 P)

Formulations based on the aqueous dispersion Kollicoat® MAE 30 DP can be prepared directly. In contrast, type A powder grade Kollicoat® MAE 100-55 requires a partial neutralisation of its functional groups to gain redispersability in water. The type B powder grade Kollicoat® MAE 100 P is inherently partially neutralised (6 mol%) and can be readily redispersed in water directly. Consequently, the type A grade requires the additional incorporation of an alkaline material (e.g. NaOH) for its preparation in aqueous media.

OBJECTIVE

The aim of this study was the investigation of the effect of partial neutralisation on the release characteristics of a solid oral dosage form. Particular focus was put on the dissolution characteristics at intermediate pH-values. Intermediate pH-values occur in a stomach's fed state and typically range between pH 4 and 5. Tablets carrying coats of a varying grade of pre-neutralisation were evaluated.

MATERIALS AND METHODS

Tablet cores (round [Ø=9 mm], convex, no engravement) consisting of the following ingredients: Caffeine, gran. 0.2 – 0.5 (Siegfried), Ludipress® LCE (BASF), Kollidon® VA 64 (BASF), Kollidon® CL-F (BASF), and magnesium stearate (Bärlocher), were used for this investigation (Table 1). The tablets had an average mass of 350 mg and a crushing strength of about 130 N.

In a first coating step, a Kollicoat® IR (BASF) based sub-coat was applied carrying 2.3% thymol blue (parameters Table 2). This colourant is pH sensitive and was used as a tracer, indicating acid permeation in the subsequent functionality testing of the enteric release coat.

Table 1.
Tablet core formulation.

Ingredient	Quantity	Functionality	Brand name (manufacturer)
Caffeine	15.5%	API	Caffeine, gran. 0.2 – 0.5
Lactose, agglomerated	74.0%	Filler	Ludipress® LCE
Copovidone	5.0%	Dry binder	Kollidon® VA 64
Crospovidone	5.0%	Disintegrant	Kollidon® CL-F
Magnesium stearate	0.5%	Lubricant	MG Siel 1

Table 2.
Process settings (side vented pan coater) for application of sub- and top-coat.

Configuration	Settings for applying: Sub-coat	Top-coat
Equipment	BOSCH Manesty XL Lab 01	
Nozzle	OptiCoat	
Nozzle orifice	1.2 mm	0.8 mm
Drum	Ø=610 mm	Ø=406 mm
Drum speed	6 rpm	13 rpm
Batch size	30 kg	2 kg
Inlet air quantity	350 m³/h	350 m³/h
Inlet air temperature	50°C	50°C
Product temperature	35°C	40°C
Spray rate	30 g/min	13 g/min
AA/PA pressure	1.2/1.2 bar	1.0/1.0 bar

In a second step, a Kollicoat® MAE 100-55 (BASF) based top-coat was applied (parameters Table 2), formulated with 15% triethyl citrate (based on polymer) [2]. The grade of pre-neutralisation was varied (4, 6, 8 mol%, with respect to the carboxylic acid groups within the polymer).

Drug release was determined in a standard USP Dissolution Apparatus 2 (Paddle) from ERWEKA, equipped with continuous on-line UV measuring (Agilent 8453). The initial dissolution test was conducted for 2 hours at pH 1.1 (HCl, 0.08 mol/L; volume 700 mL), subsequently followed by adding 15.9 mL of concentrated potassium phosphate buffer to adjust a pH-value of 6.8. Additionally, dissolution was tested in phosphate and acetate buffer (700 mL) at pH-values of 4.0, 4.5, and 5.0. All tests were conducted with a paddle speed of 50 rpm at 37°C ±0.5 K (n=6).

RESULTS AND DISCUSSION

A pH-indicator (colourant) was used to determine the coating level of the Kollicoat® MAE 100-55 based top-coat required for providing protective functionality (Figure 1). Even though, drug liberation was prevented with a comparatively low coating level (3 mg/cm²), acid could still permeate the coat leading to a reddish discolouration of the sub-coat. To prevent acid permeation completely, a coating level of at least 6 mg/cm² was required.

Figure 1.
Images indicating: acid permeation at a coating level of 3 mg/cm² (upper row), and no acid permeation at a coating level of 6 mg/cm² (lower row), and the respective effect on the disintegration features after alteration of pH-value (blue boxes).

The degree of partial neutralisation of the Kollicoat® MAE 100-55 polymer had no impact on the dissolution characteristics determined at the standard testing conditions pH 1.1/pH 6.8 (Figure 2).

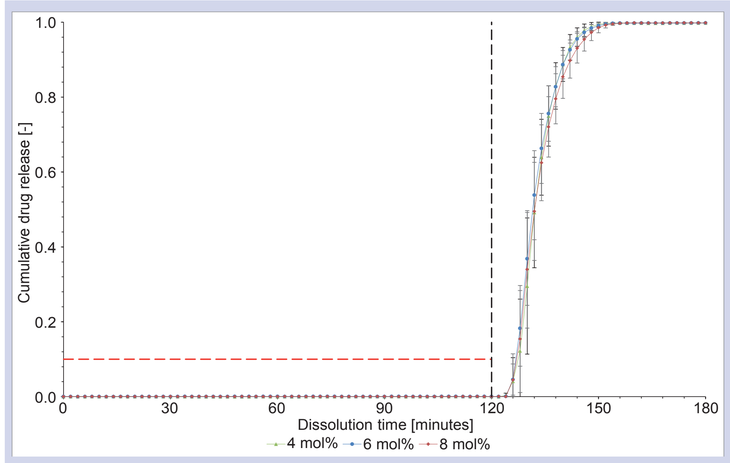

Figure 2.
Drug release pattern in pH 1.1 (HCl), with change to pH 6.8 (phosphate buffer) after 2 hours testing time. The mol% refer to the degree of neutralisation of the carboxylic acid groups within Kollicoat® MAE 100-55.

At intermediate pH-values, functionality clearly depended on the degree of pre-neutralisation and buffer medium in which dissolution was tested. In phosphate buffer (Figure 3), no drug liberation was found at all intermediate pH-values for the polymer pre-neutralised with 4 mol%. In contrast, 6 and 8 mol% led to 100% drug liberation with in the first 60 minutes of dissolution testing, even at a pH-value of 4.0.

Interestingly, the results found for acetate buffer were different (Figure 4). Even though, there is a tendency for a better performance of the coat being pre-neutralised with 4 mol% (in particular at pH 4.5), the results are much more alike. Nevertheless, it is recommended to use the lowest possible rate of pre-neutralisation required for redispersion, to affect the opening pH-value of the polymer to the least possible extent.

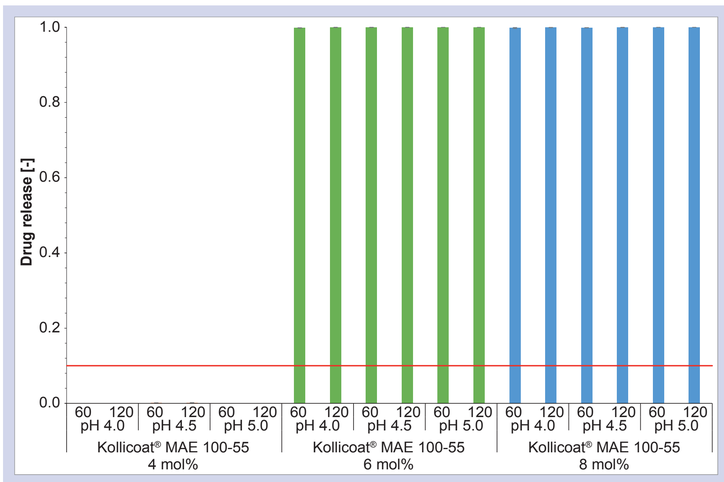

Figure 3.
Drug released in phosphate buffer as function of time (60/120 minutes), pH-value (4.0, 4.5, 5.0), and grade of pre-neutralisation (4, 6, 8 mol%) [mean values, ±SD, n=6].

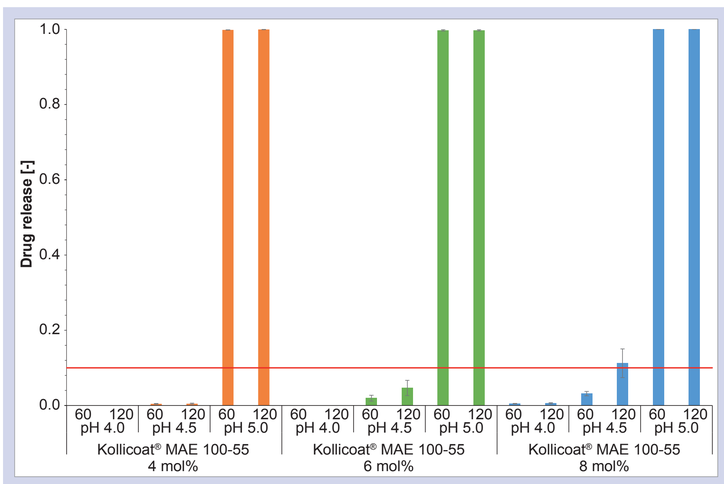

Figure 4.
Drug released in acetate buffer as function of time (60/120 minutes), pH-value (4.0, 4.5, 5.0), and grade of pre-neutralisation (4, 6, 8 mol%) [mean values, ±SD, n=6].

CONCLUSION

Dissolution testing at pH 1.1 for 2 hours, subsequently followed by a pH-value alteration to 6.8 indicated the same drug release patterns for all formulations investigated.

Testing at intermediate pH-values provided a very different picture, though. The poly(methacrylic acid-co-ethyl acrylate) being partially pre-neutralised with 4 mol% only, provided the most reliable gastric resistant functionality (in particular in phosphate buffer). Increasing the grade of pre-neutralisation distinctively reduces the opening pH-value of the coat, suggesting a high risk for food effects.

Consequently, it is recommended to use the lowest possible grade of pre-neutralisation (4 mol%) to redisperse methacrylic acid - ethyl acrylate copolymer (1:1), type A in water to provide the best functionality possible.

REFERENCES

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