Evaluating the impact of various aspects on the functionality of poly (methacrylic acid-co-ethyl acrylate)

Christine Ertl[1], Thorsten Agnese[1], Florian Bang[1], Thorsten Cech[2], Monika Haberecht[2]

[1]BASF SE, European Application Lab (Pharma Solutions), Ludwigshafen, Germany
[2]BASF SE, Global Technical Marketing & Product Management, Ludwigshafen, Germany

Corresponding author: thorsten.cech@basf.com

BASF
We create chemistry

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) [MAE] based coats are most frequently applied to introduce gastric resistant functionality to a solid oral dosage form [1].

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

- an aqueous dispersion:
  Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent (e.g. Kollicoat® MAE 30 DP),
- a powder grade (non-partly pre-neutralised):
  Methacrylic acid - ethyl acrylate copolymer (1:1), Type A (e.g. Kollicoat® MAE 100-55)
- a powder grade (partly pre-neutralised [6 mol%]):
  Methacrylic acid - ethyl acrylate copolymer (1:1), Type B (Kollicoat® MAE 100 P)

Typically, the polymer is formulated with components such as plasticiser, pigment, and colourant. The aim of this study was, the investigation of various aspects (e.g. temperature, formulation aids) on the stability and functionality of MAE-based aqueous film-coating formulations and making the results visible by means of SEM.

MATERIALS AND METHODS

Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent (Kollicoat® MAE 30 DP, BASF) was investigated in combination with various plasticisers (Table 1), pigments (Table 2), and colourants (Table 3). All formulations varying in additive and solid matter content were prepared in a beaker and stirred for 48 hours, before evaluating potential coagulation by passing the dispersion through a sieve (w=500 µm).

Minimum film-forming temperature [MFFT] was determined on a Kofler heated bench (Coesfeld MFFT 20). The dispersion sample (10 mL) was cast with a layer thickness of ~500 µm on an aluminium foil, and dried with an air flow of 4.3 s.d. and a temperature gradient of 0 to 20°C.

Table 1. List of plasticisers evaluated in this study.

Ingredient	Abbreviation	Source
Triacetin	TAC	BASF
Triethyl citrate	TEC	Jungbunzlauer
Poly(ethylene glycol) 400	PEG 400	BASF
Poly(ethylene glycol) 6000	PEG 6000	BASF
Dibutyl sebacate	DBS	Aldrich Chemistry

Table 2. List of pigments evaluated in this study.

Ingredient	Abbreviation	Source
Microtalc Pharma 8 [d_{50}=2.2 µm]		Mondo Minerals
Microtalc Pharma 50 [d_{50}=12.0 µm]		Mondo Minerals
Talc powder [d_{50}=22.7 µm]		Mondo Minerals
Titanium dioxide	E171	Kronos
Iron oxide red	E171 (30)	BTC Europe
Iron oxide yellow	E171 (10)	BTC Europe

Table 3. List of colourants evaluated in this study.

Ingredient	Abbreviation	Source
Erythrosine 88	E127	BTC Europe
Patent Blue 85	E131	BTC Europe
FD & C Blue No. 1	E133	BTC Europe
Azorubine 85	E122	BTC Europe
Indigotine 85	E132	BTC Europe
Amaranth 85	E123	BTC Europe
Cochineal Red 80	E124	BTC Europe
Yellow Orange 85	E110	BTC Europe
Tartrazine 85	E102	BTC Europe
Quinoline Yellow 70	E104	BTC Europe

RESULTS AND DISCUSSION

Storage conditions

The aqueous latex dispersion of poly(methacrylic acid-co-ethyl acrylate) is thermodynamically stable at temperatures below 30°C. However, freezing of the dispersion must be avoided. During freezing, water forms ice crystals (Figure 1, plane grey areas), increasing the concentration of the latex particles in-between these crystals. Eventually, the particles get in contact and irreversibly coagulate. Consequently, freezing of the dispersion must be avoided.

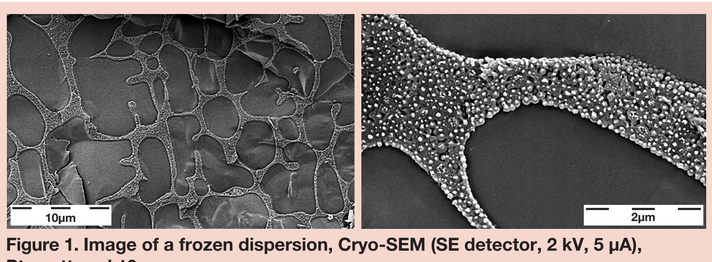

Figure 1. Image of a frozen dispersion, Cryo-SEM (SE detector, 2 kV, 5 µA), Pt sputtered 10 nm.

Plasticisers

Plasticisers are formulation components essentially required to transfer the aqueous dispersion into a homogeneous, defect-free coat. In the absence of a plasticiser, coalescence of the latex droplets is disturbed and cracks are formed, due to a lack of elasticity (Figure 2). Numerous plasticisers can be used to formulate MAE [2]. Hydrophilic plasticisers (e.g. TAC, TEC, PEGs) offer the huge benefit of allowing water to act as an additional plasticiser whereas lipophilic ones (e.g. DBS) displace the liquid carrier leading to elevated MFFTs (Figure 3). At least 10 to 15%, preferably of a hydrophilic plasticiser must be used.

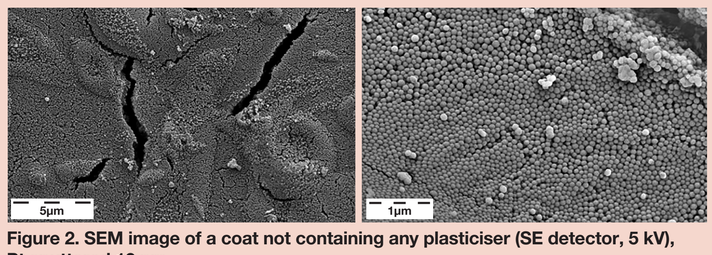

Figure 2. SEM image of a coat not containing any plasticiser (SE detector, 5 kV), Pt sputtered 12 nm.

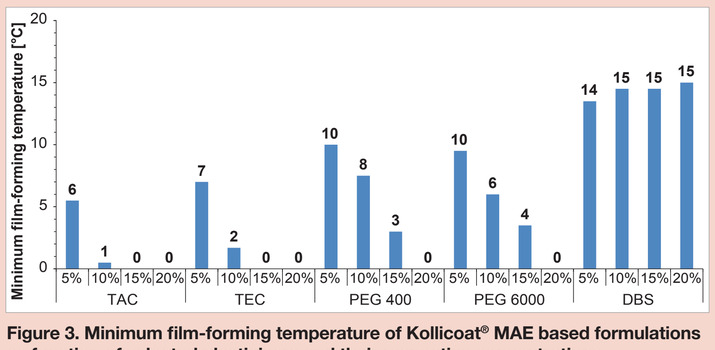

Figure 3. Minimum film-forming temperature of Kollicoat® MAE based formulations as function of selected plasticisers and their respective concentrations.

Pigments

Pigments are insoluble formulation components, which serve various formulation and processing roles. Typically, talc is added in fluid bed processes to prevent tackiness whereas titanium dioxide (E171), or iron oxide (E172) addresses colour appearance. Latex dispersions are prone to destabilisation caused by formulation components, with an increasing risk at elevated solid matter contents. However, adding talc of varying particle size does not cause any problems (Figure 4) whereas some coagulation was seen at high solid matter contents (30%), with dispersions containing either E171 or E172 (Figure 5).

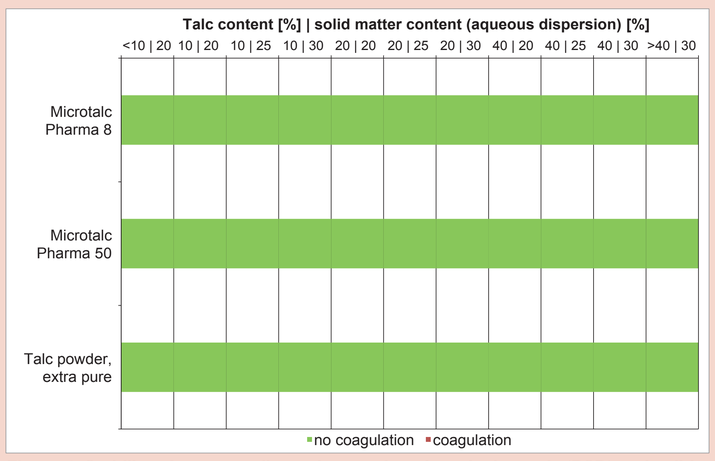

Figure 4. Stability of aqueous dispersions as function of talc grade (PSD) and solid matter content (15% TEC contained).

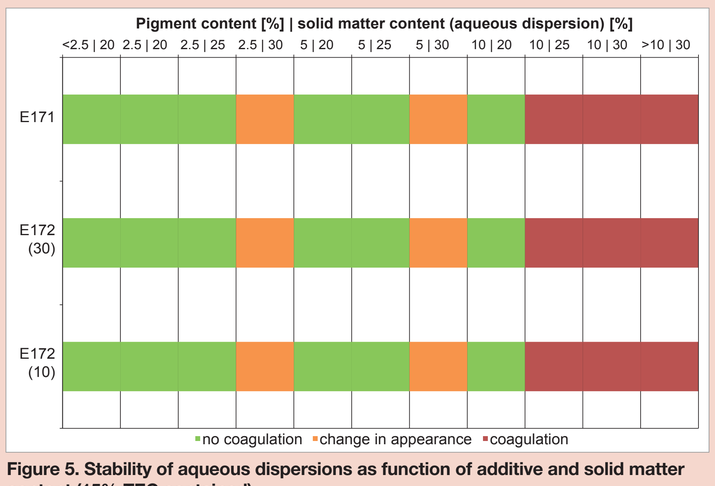

Figure 5. Stability of aqueous dispersions as function of additive and solid matter content (15% TEC contained).

Colourants

The chemical nature of lakes and dyes serving as colourants in film-coating is very diverse. Thus, various effects can be observed when adding colourants to the formulation. Aluminium lakes (Figure 6) decompose in acidic media, eventually exposing the aluminium core which interacts with the latex droplets. Azo-colourants (Figure 7) directly interact with the dispersion, also resulting in coagulation. In any case, the interaction probability increases with an increasing solid matter content, or higher quantities of colourant added (Figure 8). Consequently, a colourant should be dosed in the lowest quantity required. Additionally, the solid matter content of the formulated dispersion must be kept low as well (e.g. 20%).

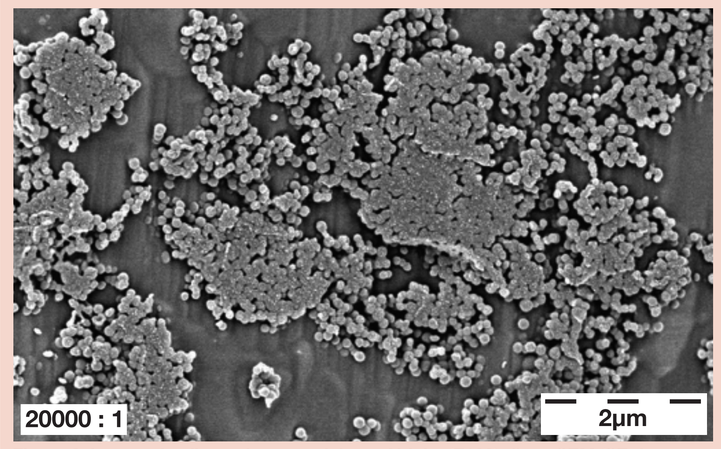

Figure 6. Image of a dispersion containing a Al-lake (E133), Cryo-SEM (SE detector, 2 kV, 5 µA), Pt sputtered 10 nm.

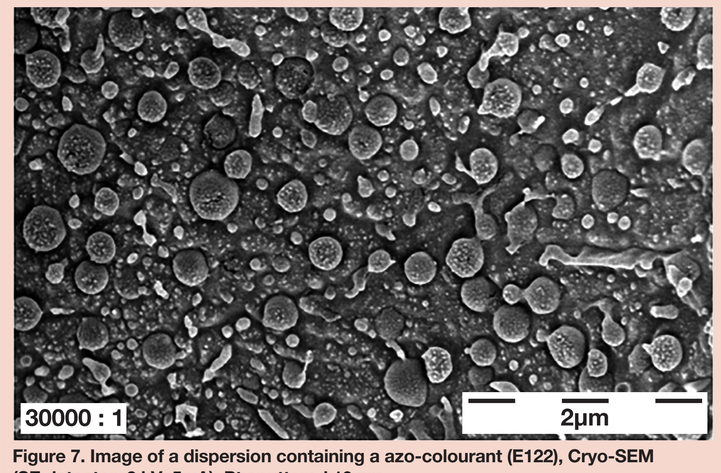

Figure 7. Image of a dispersion containing a azo-colourant (E122), Cryo-SEM (SE detector, 2 kV, 5 µA), Pt sputtered 10 nm.

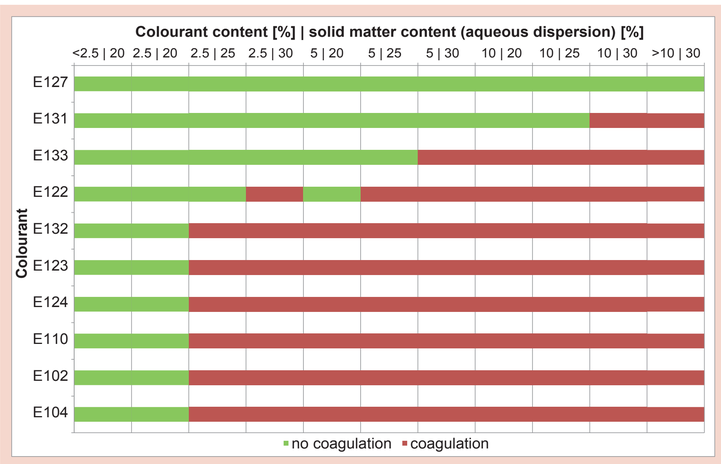

Figure 8. Stability of aqueous dispersions as function of additive and solid matter content (15% TEC contained).

CONCLUSION

An aqueous dispersion of poly(methacrylic acid-co-ethyl acrylate) is easy to work with, but requires some attention when being handled and formulated. Freezing of the dispersion must be avoided, and a plasticiser is essential for a proper film formation. Further additives such as pigments or colourants can interact with the latex dispersion and should be used in the lowest concentration required. Additionally, the solid matter content of the formulations containing additives should be reduced.

At least for tablet coating, which does not necessarily require an anti-tacking agent, a formulation merely consisting of polymer and plasticiser should be considered. In this case a colourless top-coat provides the enteric release functionality whereas an instant release sub-coat can be employed to serve as carrier for the colour impression [3]. In various formulations, a sub-coat is required anyway, due to incompatibilities between polymer and drug [4].

REFERENCES

[1] Nollenberger, K.; Albers, J.; Poly(meth)acrylate-based coatings, Intern. J. Pharm, 457 (2), 461-469 (2013).

[2] Agnese, Th.; Cech, Th.; Comparing various plasticisers regarding their effect on methacrylic acid/ethyl acrylate copolymer; 9th CESPT 2012; Dubrovnik, Croatia.

[3] Agnese, Th.; et. al; Investigating the benefit of delivering gastric resistant functionality to a tablet via applying a colourless top-coat; 8th PBP W.M.; Istanbul, Turkey.

[4] Bang, F; et. al.; Poly(methacrylic acid-co-ethyl acrylate): comparing three different grades in regard to preparation and functionality features in enteric release film-coating applications; 2nd ECP; Krakow, Poland

Presented at:
11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology;
March 19 – 22, 2018; Granada, Spain
Pharma Solutions Sales Europe | E-ENE/PT532