# Comparing various plasticisers regarding their effect on the film-coating properties of Kollicoat® MAE 30 DP

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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) [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 compendial 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)

In the field of gastric resistant film-coating, the choice of plasticiser is particularly crucial with respect to processability and properties of the formed film. Furthermore, regulatory aspects regarding maximum daily intake or the use of select plasticisers in specific regions have to be regarded as well [2].

Poly(methacrylic acid-co-ethyl acrylate) can be applied without any further additives but plasticiser as gastric resistant coat [3], making the choice of plasticiser even more important. This is because characteristics such as water up-take of a tablet core during the first 2 hours of the dissolution test as this strongly depends on the hydrophilic-lipophilic character of the coat. This work was intended to compare the impact of 7 hydrophilic and 3 lipophilic plasticisers on the characteristics of a MAE based coating formulations. In this regard, glass transition temperature, elasticity of isolated films, water up-take of films and cores as well as the dissolution characteristics were tested.

## MATERIALS AND METHODS

### Materials

An aqueous dispersion of poly(methacrylic acid-co-ethyl acrylate) (Kollicoat® MAE 30 DP, BASF) was chosen for this study. As hydrophilic plasticisers, triacetin (TAC [Kollisolv® GTA]), propylene glycol (PG [Kollisolv® PG]), poly(ethylene glycol) (PEG [Kollisolv® PEG]) 400 and 6000, poloxamer 124 (P 124 [Kollisolv® P 124]), all BASF, triethyl citrate (TEC), acetyl triethyl citrate (ATEC), both Jungbunzlauer, were used. As lipophilic plasticizers, acetyl tributyl citrate (ATBC) from Jungbunzlauer, tributyl citrate (TBC) from Merck and Dibutyl Sebacate (DBS) from Aldrich Chemistry, were used.

The tablet core consisted of the following excipient: 15.5% Caffeine gran. 0.2 – 0.5 (Siegfried), 74.0% Ludipress® LCE, 5.0% Kollidon® CL-F, 5.0% Kollidon® VA64 (all BASF) and 0.5% magnesium stearate (Baerlocher).

### Equipment

As coating equipment, the XL Lab 01 (Manesty) was used. The coater was assembled with the mid-sized drum (diameter 480 mm) and the OptiCoat gun with a bore diameter of 0.8 mm.

Round-shaped tablets with a diameter of 9.0 mm were coated with three coating levels: 3, 4 and 6 mg/cm² according to schema (Table 1).

**Table 1. Coater settings**

| | |
|---|---|
| Batch size | 3.5 kg |
| Drum speed | 12 – 22 rpm |
| Inlet air temperature | 55°C |
| Inlet air quantity | 450 m³/h |
| Spray rate | 13 g/min |
| Atomising pressure | 1.8 bar |
| Pattern air pressure | 1.8 bar |

### Methods

***Preparation of isolated films***
Isolated films were prepared by spraying the dispersion onto a rotating Teflon roll while continuously drying with warm air (fan heater) – film temperature about 33°C. The process was conducted until a final coat thickness of approximately 100 to 150 µm was achieved.

***Differential scanning calorimetry (DSC)***
A DSC Q2000 V24.4 Build 116 was used with a sample weight of 8 to 9 mg. After fast cooling from 150°C the glass transition temperature (Tg) was determined with a heating rate of 20 K/min (n=2).

***Elongation at break (EaB)***
A texture analyser (TA-XT2i HR, Stable Micro Systems) was used to determine the mechanical properties of the film. The test was performed under controlled climatic conditions of 23°C and 54% r.h. [4].

***Dynamic vapour sorption (DVS)***
A SPS11-1µ (pmt analytical) was used for determining the water up-take of isolated films at conditions of: 25°C/60% r.h, 30°C/70% r.h. and 40°C/75% r.h. At each temperature, the samples were dried at 0% relative humidity before altering the relevant humidity (n=3).

***Dissolution testing***
The dissolution test (n=3) was conducted for the first 2 hours at pH 1.1 (HCl, 0.08 mol/L; volume 880 mL) and 37°C (±1 K). A paddle speed of 50 rpm was set. By adding 20 mL of a concentrated potassium phosphate buffer system, the pH value was adjusted to 6.8 for an additional 60 minutes time. The drug release was determined photometrically via on-line measuring.

***Determining the water up-take of cores***
After being weighed, 10 coated tablets were placed in a 'filter bag'. The samples were put in a beaker containing hydrochloric acid (HCl, 0.08 mol/L). One individual bag of each sample was taken out after 1 and 2 hours. After drying the surface carefully, the weight of the tablets was measured again.

## RESULTS AND DISCUSSION

The plasticiser with the strongest lipophilic character in this investigation was DBS. After incorporating this component into MAE dispersion, phase separation occurred. It turned out that a regular incorporation of this plasticiser into the film-coating dispersion was not possible. Since a regular incorporation procedure was regarded as necessary for this kind of study, this plasticiser was unheeded and focus was set on the remaining ones.

Inherently, MAE forms a very brittle film, which is non-tacky in a dry state due to a $T_g$ of 113°C (± 2 K). Therefore, a plasticiser needs to be introduced to make the polymer accessible for film-coating applications. Due to their better incorporation within the hydrophilic film matrix hydrophilic plasticisers are preferred [5]. Moreover, the physical properties of the final films markedly depend on the character of the plasticiser. For instance, the more hydrophilic the plasticiser is the lower the resulting $T_g$ will be (Figure 1). However, even with a plasticiser content of 15% the $T_g$ remains at a temperature higher than 60°C, making the resulting film non-tacky at ambient temperatures [3].

Especially important for the film-forming process is the hydrophilic character of MAE which allows water to act as a plasticiser as well. Thus, minimum film-forming temperatures (MFFT) of <0°C were determined for formulations holding only 10% TEC or TAC [5].

EaB as a measure for the film elasticity can be used to appraise the risk for cracks in the film's. It was found that both type and concentration of plasticiser distinctively affect this parameter (Figure 2). When comparing the EaB results with those deriving from DVS measuring (Figure 3) a correlation of water up-take and elasticity can be seen which additionally proves the plasticising effect of water. Furthermore, losses in weight indicate certain volatility of PG and at elevated temperatures for TAC [6].

Earlier studies have already revealed that incorporation of PEG 6000 depends on product temperature ($T_p$). In consequence, strongly varying dissolution profiles were observed for tablets coated with Kollicoat® SR 30 D which had been plasticised with PEG 6000 [6]. Something similar seems to happen with Kollicoat® MAE 30 DP as white spots on tablet surfaces are obtained at a $T_p$ of 33°C (Figure 4, Figure 5), indicating precipitated PEG 6000. However, dissolution properties are not affected by the $T_p$, though, even when the tablets were stored for 12 months under climatic conditions (ICH). This means PEG 6000 can be used as a plasticiser. The described effects that high concentrations of PEG (e.g. in laxative applications) interfere with the gastric resistant properties of MAE [7] are not relevant for this application.

Eventually, all hydrophilic plasticisers tested led to the same dissolution profiles (Figure 8). Hardly any drug release is seen in the first two hours of the testing in simulated gastric fluid even at low coating levels such as 3 mg/cm². However, a fast drug release is observed after altering the pH value to 6.8.

Different results were found for the lipophilic plasticisers TBC and ATBC. The incorporation is less homogenous leading to a porous coat (Figure 6, Figure 7) allowing some amounts of active of being released during the first 2 hours of the dissolution testing (Figure 9). Improvement could be achieved by using a high shear mixer (HS) to prepare an aqueous micro emulsion of the plasticiser first (Figure 9) that is then added to the coating dispersion. However, to gain reliable functionality, a higher coating level such as 4 mg/cm² is recommended (Figure 10).

Even though it is difficult to incorporate lipophilic plasticisers, they are advantageous regarding water permeation. The amount of water permeating the coat during the first two hours of the acid test clearly depend on the character of the plasticiser with less water permeating when lipophilic plasticisers were used (Figure 11).

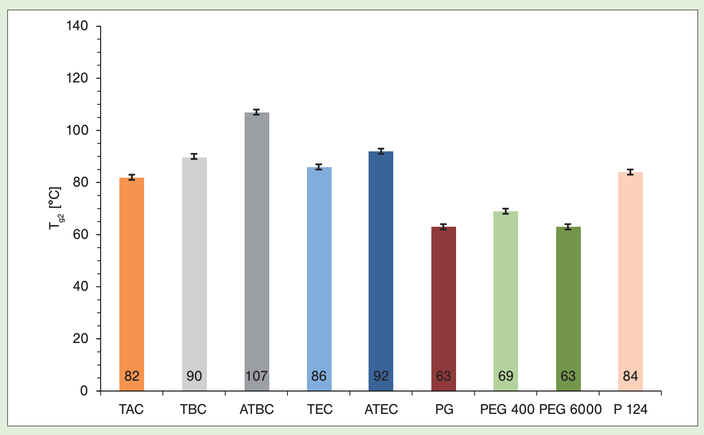


**Figure 1. $T_g$ of isolated MAE films bearing 15 % of different plasticisers (mean ±s, n=2).**

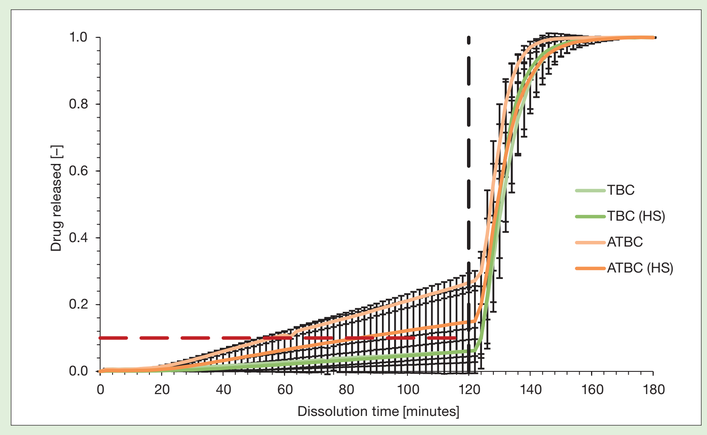


**Figure 9. Dissolution profiles of MAE coated caffeine tablets (coating level: 3 mg/cm²) holding 15% of different lipophilic plasticisers (mean ±s, n=3).**

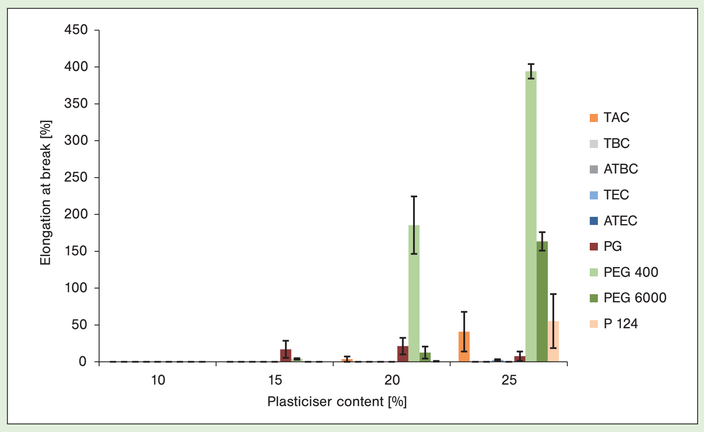


**Figure 2. Elongation at break of isolated MAE films bearing various plasticisers in different concentrations (mean ±s, n=5).**

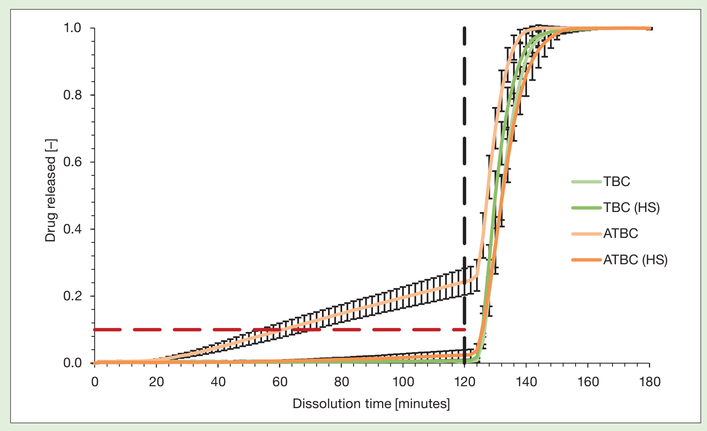


**Figure 10. Dissolution profiles of MAE coated caffeine tablets (coating level: 4 mg/cm²) holding 15% of different lipophilic plasticisers (mean ±s, n=3).**

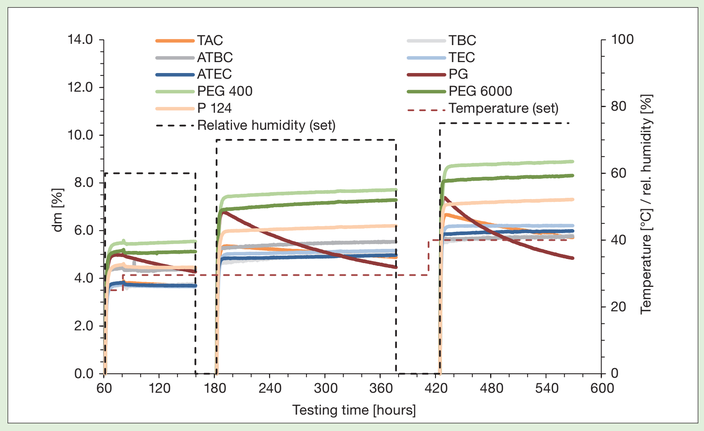


**Figure 3. Humidity up-take of isolated films holding 15% of different plasticisers at different climatic conditions.**

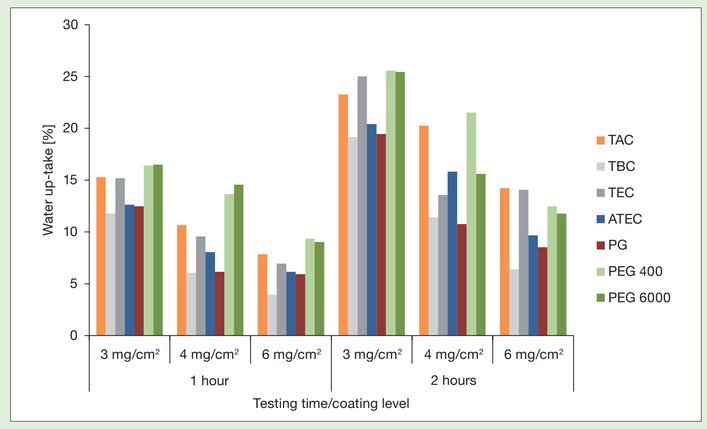


**Figure 11. Water up-take of MAE coated caffeine tablets (different coating levels) holding 15% of different plasticisers (mean, n=10).**

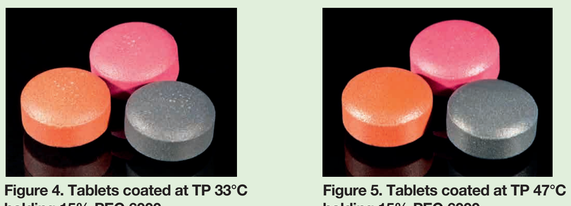

**Figure 4. Tablets coated at TP 33°C holding 15% PEG 6000.**



**Figure 5. Tablets coated at TP 47°C holding 15% PEG 6000.**

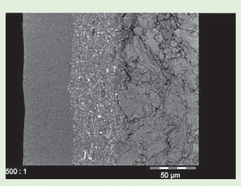


**Figure 6. SEM (EsB) image of a MAE coat holding 15% TEC.**

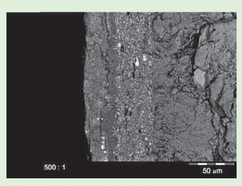


**Figure 7. SEM (EsB) image of a MAE coat holding 15% ATBC.**

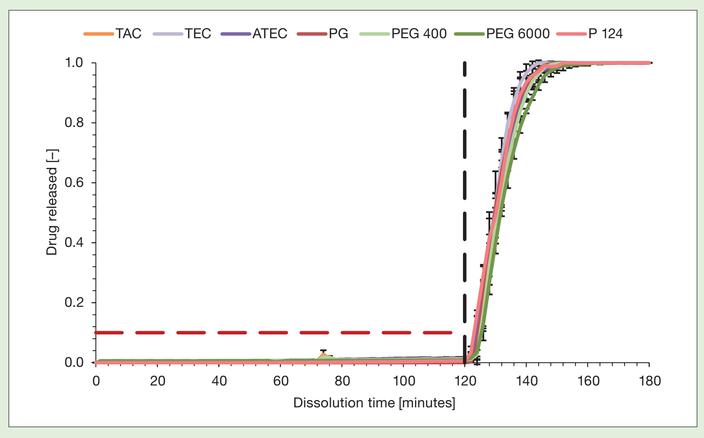


**Figure 8. Dissolution profiles of MAE coated caffeine tablets (coating level: 3 mg/cm²) holding 15% of different hydrophilic plasticisers (mean ±s, n=3).**

## CONCLUSION

MAE inherently forms films, which are non-tacky in a dry state due to a $T_g$ of 113°C, but rather brittle. Thus, plasticisers should be introduced to make the polymer accessible for film-coating applications. Hereby, the tested hydrophilic and lipophilic plasticisers reduced the $T_g$ merely to a level of about 65 to 85°C. As MAE based polymer films of perfect functionality can be obtained, at product temperatures of less than 30°C, it can be assumed, that water is acting as additional plasticiser during the coating process.

A similar conclusion is gained when correlating the results of dynamic vapour sorption and elongation at break measuring: plasticisers which lead to a higher humidity up-take yield more elastic films.

However, hydrophilic plasticisers lead to a higher water up-take during the first 2 hours of the dissolution testing. If water up-take is crucial to the tablet and thus needs to be minimised, lipophilic plasticisers should be selected. For instance, using tributyl citrate instead of polyethylene glycol 400 halves the amount of water permeating during the gastric resistance testing.

By choosing the right plasticiser, the coat can be tailor-made for a particular dosage form.

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