Investigating the processing characteristics of different plasticisers in cationic polymer based film-coating formulations

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Introduction

In the field of pharmaceutical film-coating applications, a huge variety of different polymers are used as a film-forming agent. Depending on the individual functionality and application, polymers can either be soluble or insoluble in aqueous media whereas other polymers offer pH-dependent solubility:

- Gastric resistance: anionic polymers such as poly(methacrylic acid-co-ethyl acrylate), opening pH-value > 5.5 [1]
- Taste masking: cationic polymers such as poly(methyl methacrylate-co-(2-diethylaminoethyl) methacrylate), opening pH-value < 5.5 [2]

Both polymers are available as aqueous dispersions. Yet, they do not only differ in the opening pH-value and application respectively, they also vary in regard to the pH-value of their aqueous dispersion. This in turn affects the plasticiser which ought to be used to alter minimum film-forming temperature (MFFT) and elasticity of the final coat.
Ester-based plasticisers (e.g. triethyl citrate) are prone to hydrolysis in aqueous environment [3]. The degree of hydrolytic sensitivity thereby strongly correlates not only with the nature and polarity of the plasticiser molecule but also with the pH-value of the surrounding aqueous media. The aim of this study was the evaluation of such plasticisers in a cationic polymer dispersion which holds an alkaline characteristic. The results are intended to deliver important insights vital for galenical development conducted under the roof of Quality by Design (QbD).

Materials and methods

In this investigation, the poly(methyl methacrylate-co-(2-diethylaminoethyl) methacrylate) (Kollicoat® Smartseal 30 D, BASF) was used. The tests were conducted with the plasticisers triethyl citrate (Acros Organics) and dibutyl sebacate (Aldrich Chemistry).

Measuring of pH-value
A Titrando 836 (Metrom) equipped with a Hamilton pH-electrode was used. The change of pH-value was recorded using the Tiamo software (Metrom). To avoid any wrong indications due to either temperature alterations or carbon dioxide absorption, the measuring was conducted within a closed and sealed sample device under controlled conditions of 23 °C. The measurement was started after flooding the sample device with argon as a cover gas.

Measuring of electrophoretic mobility
All samples were diluted with 10 mM KCl directly before measuring, without alteration of the pH-value. A Zetasizer Nano (Malvern) was used as measuring equipment (electrophoretic measuring at 150 V) [4].

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 – 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 (T_{g2}) was determined with a heating rate of 20 K/min (n=2).

Dissolution testing
A standard USP Dissolution Apparatus 2 (Paddle) from ERWEKA, equipped with continuous on-line UV measuring (Agilent 8453) was used. Since taste-masking functionality is to be delivered in the oral cavity, phosphate buffer (pH 6.8) was used as dissolution media (700 ml ±1%, 37 °C ±0.5 K, n=13).

Results and discussion

Research shows that some plasticisers (e.g. citric acid esters) are prone to hydrolysis in aqueous environment [3]. Ester molecules like triethyl citrate (TEC) obey an equilibrium reaction between acid and ester state in aqueous media (Figure 1). As a result, some amounts of citric acid and free ethanol (EtOH) may develop as soon as the TEC is introduced into aqueous polymer dispersions. The degree of free acid and alcohol production is thereby also influenced by the pH-value of the system.

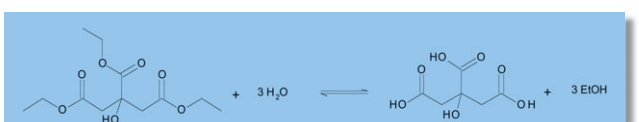

Figure 1. Hydrolysis of TEC in aqueous environment.

Poly(methacrylic acid-co-ethyl acrylate) dispersion (which is used for gastric resistant coating applications) holds an acidic pH-value of about 3 [1]. Hence, some additional amounts of citric acid in the media hardly matter, since the whole system is in an acidic state anyway. The situation is different for poly(methyl methacrylate-co-(2-diethylaminoethyl) methacrylate) dispersion which owns an alkaline pH-value. In this particular case, the resulting citric acid is consumed by a neutralisation reaction and thus drawn out from the equilibrium. The alkaline environment can even be regarded as a catalyst enhancing the reaction speed of the hydrolysis of TEC. As a consequence, more and more citric acid is produced, eventually leading to a declining pH-value of the dispersion (Figure 2).

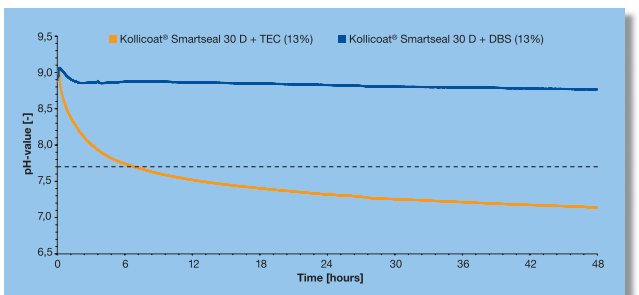

Figure 2. Change in pH-value over time for plasticised Kollicoat® Smartseal 30 D.

Generally, latex dispersions are sensitive systems stabilised by tailored surfactant solutions. They create a dedicated surface charge, separating the particles from each other, thus overcoming the risk of coagulation. Whether a system is thermodynamically stable can be described by zeta-potential which in turn can be determined by means of mobility measuring. Henry's equation describes the relationship between mobility and zeta-potential and how to convert one quantity into the other (Figure 3).

$$\mu_e = \frac{\varepsilon \cdot f(\kappa\alpha) \cdot \zeta}{6 \cdot \pi \cdot \eta}$$

Figure 3. Henry's equation – electrophoretic mobility (μ_e), dielectric constant of the dispersion medium (ε), Henry's function (f($\kappa\alpha$)), zeta potential (ζ), dynamic viscosity (η) [4].

If a plasticised poly(methyl methacrylate-co-(2-diethylaminoethyl) methacrylate) dispersion is tested, a constant change in electrophoretic mobility will be seen for TEC based formulations. Reason being is the continual formation of citric acid and a resulting neutralisation of the dispersion. No such change was found for a dispersion plasticised with dibutyl sebacate (DBS) (Figure 4). Most likely there are two main reasons for the more inert character of DBS: firstly, poorer water solubility and secondly, a more distinctive hydrophobic character next to the ester-bond, reducing the likelihood of a hydrolysis reaction.

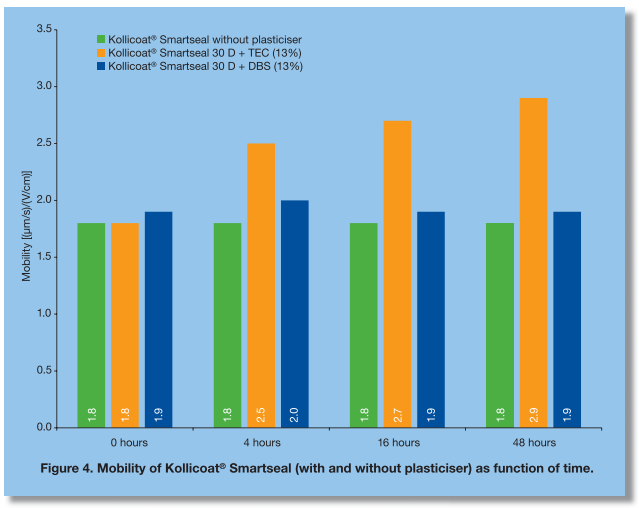

Figure 4. Mobility of Kollicoat® Smartseal (with and without plasticiser) as function of time.

The change in pH-value and the resulting change in zeta-potential over time (Figure 4) are crucial for the thermodynamical stability of the dispersion plasticised with TEC. At a pH-value of about 7.7 zeta-potential of the dispersion is zero (Figure 5), indicating that the dispersion is destabilised and prone to coagulation. With regard to dispersions of high solid matter content (e.g. 32.6%) this leads to a solidification of the whole liquid formulation (Figure 6) after about 48 hours. Dispersions of lower solid matter contents (e.g. 20.0%) merely contain some smaller coagulates. These particles however can cause severe trouble during the coating process, for instance by clogging the nozzle's orifice. Sieving the dispersion (generally recommended as a standard procedure) does not help in this case, since there is a continuous formation of new coagulates.
Furthermore, it can be assumed that citric acid interacts with the functional groups of the cationic polymer resulting in a partly neutralisation. This interaction however changes the coating characteristics of the polymer. Experiments showed that the formed film becomes tackier and therefore requires some anti-tacking agent to remain easily processible.

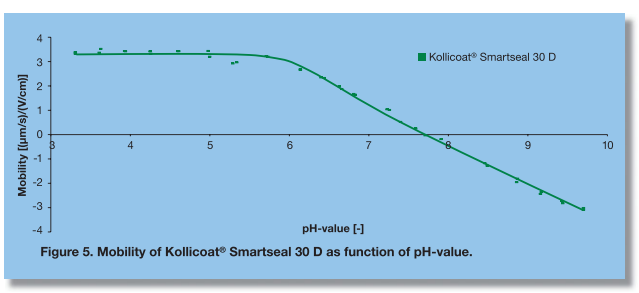

Figure 5. Mobility of Kollicoat® Smartseal 30 D as function of pH-value.

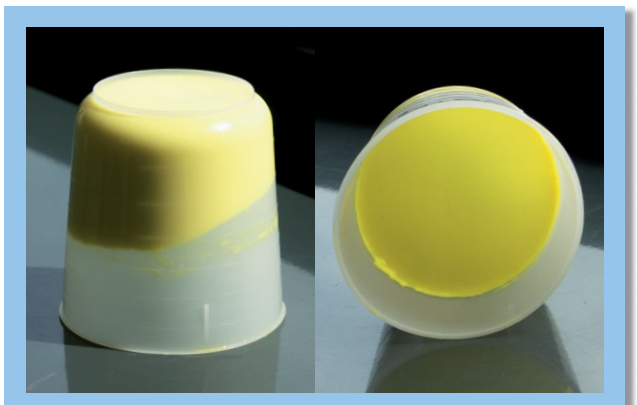

Figure 6. Dispersion of Kollicoat® Smartseal 30 D plasticised with TEC (13%) and a solid matter content of 32.6% after 48 hours incorporation time of the plasticiser.

Another aspect needs to be considered as well. Due to the constant neutralisation and the resulting continuous degradation of TEC, the amount of plasticiser is time-dependently reduced. As a result, less plasticiser is available to alter the physical chemical properties of the polymer. Consequently, T_g of the dispersion plasticised with TEC is higher after 48 hours compared to the initial value [5].

It can be assumed that an increased T_g also indicates an elevated MFFT. While keeping all the process parameters and in particular product temperature during the coating process constant, an increased MFFT leads to a poorer coalescence of the latex dispersion during film-formation. The resulting coat is less homogeneously formed leading to a change in functionality. Employing dissolution testing as a measure for functionality, the results for the freshly prepared dispersion were perfect, with no drug release at all within the two hours testing time. When the same dispersion was applied after 48 hours, the dissolution characteristics changed distinctively. With no drug release within 20 minutes of the dissolution testing, taste masking functionality was still sufficiently provided. However, dispersions plasticised with DBS did not show this time-dependent change in dissolution characteristics and never presented any drug release [5].

Conclusion

Degradation of plasticisers (hydrolysis) and the formation of acids have not been problematic for established dispersions holding an acidic pH-value. Things are different for the alkaline poly(methyl methacrylate-co-(2-diethylaminoethyl) methacrylate) dispersion. The stability and pH-value of this dispersion is distinctively affected by the choice of plasticiser and the lifetime of the plasticised dispersion respectively.

Generally, both plasticisers investigated in this study (TEC and DBS) led to an easy and reliable film-coating process resulting in coated substrates with perfect taste-masking functionality. But depending on the lifetime of the dispersion, effects such as changing zeta-potential or MFFT can be observed. This does not present a problem, if the film-coating formulation is handled properly and being processed within one day. However, the issue must be addressed, particularly in situations where QbD aspects are applied during formulation development.

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