Nutrition & Biosciences

AQUACOAT® ECD: CRITICAL FORMULATION ATTRIBUTES OF PLASTICIZER

Technical Memorandum

TM H073-1

At DuPont, we aim to help our pharma customers with both every day challenges and future solutions. Armed with essential excipients and vital expertise, our broad portfolio is designed to deliver performance and cost advantages in various oral solid dosage forms.

Plasticizer overview

Pseudolatex spheres of Aquacoat® ECD have a glass transition temperature of~89°C/192°F. Various plasticizers have been used to reduce glass transition and minimum film forming (MFFT) temperatures (Figure 1). They are also used to facilitate coalescence and enhance film formation. Plasticizer acts as a lubricant to reduce cohesive intermolecular forces along the polymer chains, thus reducing stiffness and improving the processability of the polymer. Besides these major functions, plasticizer can also be used as an additive to influence drug release rates[1].

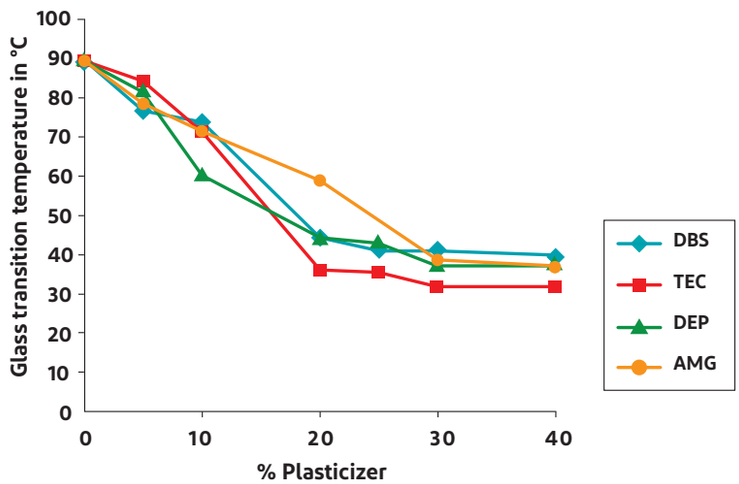
Plasticizer amount

Plasticizer selection is determined mainly by glass transition temperature and solubility parameters. The concentration and type of plasticizer in a coating formulation should be optimized as it plays a critical role in controlling film flexibility, permeability and, in turn, the drug release profile. Insufficient plasticizer can cause film cracking after drying. To avoid this, 20-25% of plasticizer content is recommended based on ethyl cellulose solid content levels.

Type of plasticizers

Plasticizers can be divided into hydrophilic (water-soluble) and hydrophobic (water-insoluble) (Table 1). Water-soluble plasticizers such as TEC (triethyl citrate) produce a hydrophilic film and faster drug dissolution than water-insoluble plasticizers such as DBS (dibutyl sebacate) that retain the film's hydrophobicity (Figure 2).

Figure 1: Plasticizer concentration effect on glass transition temperature of Aquacoat® ECD



DBS = Dibutyl sebacate
TEC = Triethyl citrate
DEP = Diethyl phthalate
AMG = Acetylated monoglyceride

Table 1: Commonly used plasticizers

Water-soluble (Hydrophilic)	Water-insoluble (Hydrophobic)
Triethyl citrate (TEC)	Acetyltriethyl citrate (ATEC)
Polyethylene glycol 200-6000 grade	Diethyl phthalate (DEP)
Propylene glycol	Tributyl citrate (TBC)
Sorbitol sorbitan solution	Dibutyl phthalate (DBP)
	Acetyltributyl citrate (ATBC)
	Dibutyl sebacate (DBS)
	Glycerol triacetate (triacetin)
	Acetylated monoglyceride (AMG)

Plasticizer mixing time

Plasticization, or mixing time, is critical as it determines the amount of plasticizer uptake by polymer particles. Insufficient mixing times may result in non-homogeneous plasticizer distribution in the coating film. The resulting redistribution during aging can cause changes to the drug dissolution profile[2].

Plasticizer uptake is necessary as it softens the polymer, promoting particle deformation and hence coalescence of the film on drying. The rate of plasticizer uptake depends on the type and concentration of plasticizer[3].

Water-soluble plasticizers achieve rapid equilibrium in the aqueous phase of colloidal polymer dispersion, and therefore are not affected by mixing time. However, water-insoluble plasticizers must be emulsified in the polymer dispersion before they can be taken up by colloidal polymer particles.

The rate constant of plasticizer uptake is thus directly related to the water-solubility and solid content of the pseudolatex system. The rate constant order of plasticizers is ATEC > DEP > TBC > DBP > ATBC > DBS: in other words, a plasticizer with comparatively high water-solubility, such as DEP, shows a higher rate constant and faster plasticizer uptake than the water-insoluble DBS. Various studies have also been carried out to predict mass transfer of different plasticizer types based on the dissolution-diffusion model, with minimum mixing times calculated for uptake of approximately 85% of the plasticizer [4].

Minimum mixing time recommendations are summarized in Table 2. This list focuses on plasticizers that have been studied by DuPont. Other plasticizer choices may also be available.

Figure 1: Plasticizer concentration effect on glass transition temperature of Aquacoat® ECD

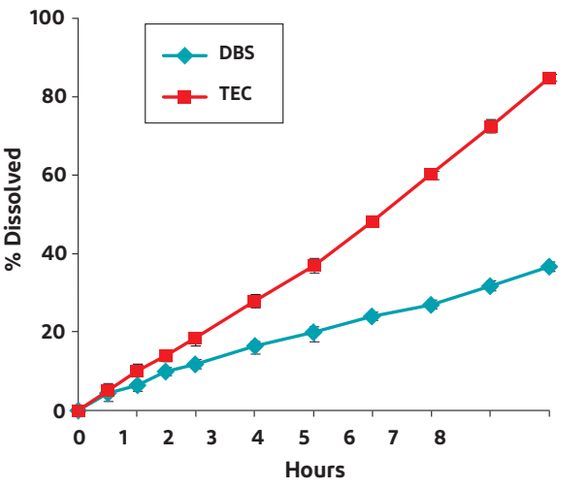


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Table 2: Minimum mixing time recommendations for various plasticizers (based on pilot scale).

Plasticizers	Minimum mixing time (hours)
Triethyl citrate (TEC)	0.5 - 1
Acetyltriethyl citrate (ATEC)	1 - 2
Diethyl phthalate (DEP)	2 - 3
Tributyl citrate (TBC)	2 - 3
Dibutyl phthalate (DBP)	3 -4
Acetyltributyl citrate (ATBC)	4 - 6
Dibutyl sebacate (DBS)	8 - 12

REFERENCES

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2. Siepmann, J., Paeratakul, O., Bodmeier, R.; Modeling Plasticizer in Aqueous Polymer Dispersion; International Journal of Pharmaceutics, 165, 191-200, 1998
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4. Wesseling, M., Bodmeier, R.; Influence of Plasticization Time, Curing Conditions, Storage Time and Core Properties on the Drug Release from Aquacoat®-coated Pellets; Pharmaceutical Development and Technology, 6(3), 325-331, 2001

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