The Influence of Plasticizer Type and Level on Drug Release from Ethylcellulose Barrier Membrane Multiparticulates

ABSTRACT SUMMARY

The influence of type and level of plasticizers on chlorpheniramine maleate release from ethylcellulose barrier membrane coated beads was investigated. Type and amount of plasticizer influenced drug release rates. Selection of type and amount of plasticizer can be used as an effective tool to tailor drug release.

INTRODUCTION

Plasticizers are added to enhance ethylcellulose film forming properties, render it more pliable and provide films with adequate mechanical properties[1]. Type of plasticizer used determines the intrinsic properties of the polymeric system consequently affecting drug release characteristics, as well as surface and mechanical properties of the applied film coat. The influence of type and level of plasticizers on chlorpheniramine maleate release from ethylcellulose barrier membrane coated beads was investigated.

EXPERIMENTAL METHODS

Drug Layering of Suglets®

Chlorpheniramine maleate (CPM) was coated onto 18/20 mesh (850 - 1000 µm) Suglets, drug layering substrate (Colorcon, USA), to a target drug load of 30 mg/g using a Pam-Glatt fluidized bed coater (FBE-125 equipped with Würster column, 360 mm length) using Hypromellose 2910 (METHOCEL™, premium cellulose ethers, E6, Dow-Wolff Cellulosics, USA) as a binder. Drug layering was carried out at an inlet air temperature of 65- 70^{o}C, fluid delivery rate of 100 g/minute, atomizing air pressure of 22 psi and an air volume of 800 cubic feet per minute (CFM).

Ethylcellulose Coating of Drug Layered Suglets®

The coating formulation comprised ETHOCEL™, premium ethylcellulose polymers, Standard 10 Premium (Dow Wolff Cellulosics, USA) and plasticizer dissolved in the solvent mixture, isopropanol: water (90:10). The nominal viscosity of a 5% solution of ETHOCEL™ Standard 10 Premium ethylcellulose measured at 25oC in an 80:20 solvent mixture of toluene: ethanol is 10 cP. Plasticizers (listed in Table 1) were used at 10, 20 and 30% w/w (with respect to the polymer in the deposited film).

CPM beads were coated to a 10% w/w film weight gain for each of the plasticizer types and levels using a Glatt GPCG 1.1 fluid bed apparatus (Pam-Glatt Pharma Technologies, India).

Dissolution Testing

Drug release was measured from 1 g of coated pellets using a USP compliant automated dissolution bath (Erweka DT 800, Germany), apparatus 1 at 100 rpm. The dissolution medium was 1000 mL of purified water at 37 ± 0.5°C. An online dual beam spectrophotometer (Perkin-Elmer, USA) was used for the detection of CPM at a wavelength of 262 nm over a 24-hour period. Purified water was used as reference.
Following dissolution testing, recovered pellets were examined using an optical microscope, Leica S8 APO Stereomicroscope (Leica Microsystems Inc., USA).

Table 1. Plasticizer Properties

Plasticizer	Supplier	Solubility[2]
Branched esters		
Triethyl citrate (TEC)	Vertellus, USA	soluble
Triacetin	Tessenderlo, USA	soluble
Di-acid esters		
Dibutyl sebacate (DBS)	Vertellus, USA	practically insoluble
Diethyl phthalate (DEP)	Eastman , USA	insoluble in water
Fatty acids		
Fractionated coconut oil (FCO)	Abitec, USA	practically insoluble
Oleic acid (OA)	Croda, USA	practically insoluble

RESULTS AND DISCUSSION

Effect of plasticizer type (Solubility/Structure)

Previous studies have shown that water soluble plasticizers may leach out of polymeric films during dissolution studies or in biological fluids, decreasing film mechanical strength, facilitating pore formation and drug release[3]. Lipophilic plasticizers in contrast have been reported to remain within the film upon exposure to the release media, assuring a mechanically resistant film[4]. Contrary to previous reports, no increased drug release rates were noted where water soluble plasticizers (TEC, triacetin) were used (Figure 1). This was possibly due to the higher mechanical strength of solvent-coated ethylcellulose films, where any probable loss of plasticizer through leaching could only marginally impact the mechanical properties of the film.
Furthermore, leaching of plasticizer from such solvent cast films is also reported to be slower than leaching from pseudo-latex cast films. Bodmeier et al have attributed this to the higher density of solvent cast films[5].

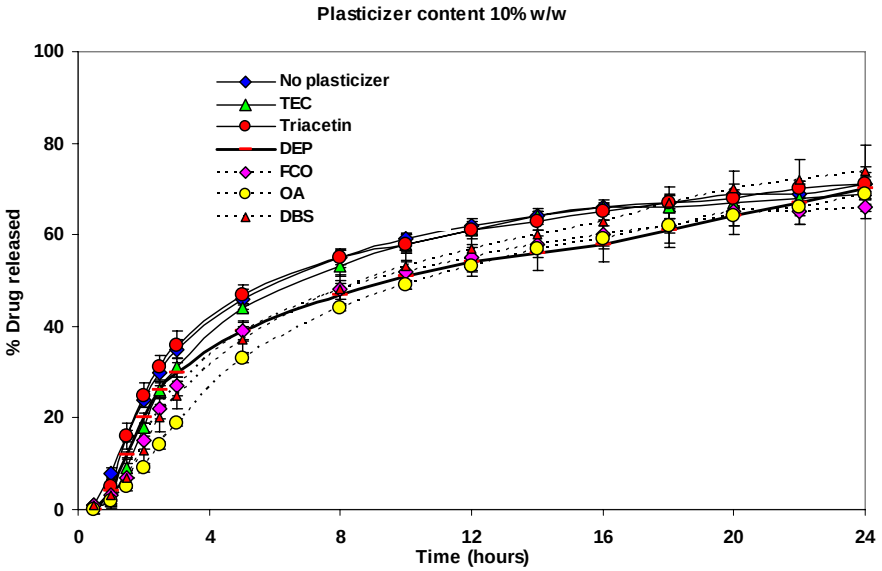
Slowest drug release was observed (Figure 1) from films plasticized by lipophilic plasticizers. A correlation between the mechanical properties of the resulting films and plasticizer molecular structure has been observed. The long chain DBS and fatty acid molecules are thought to penetrate the polymer chains better than the more spherical TEC, DEP and triacetin molecules and their lipophilic nature have resulted in slower drug release[6].

Effect of plasticizer level

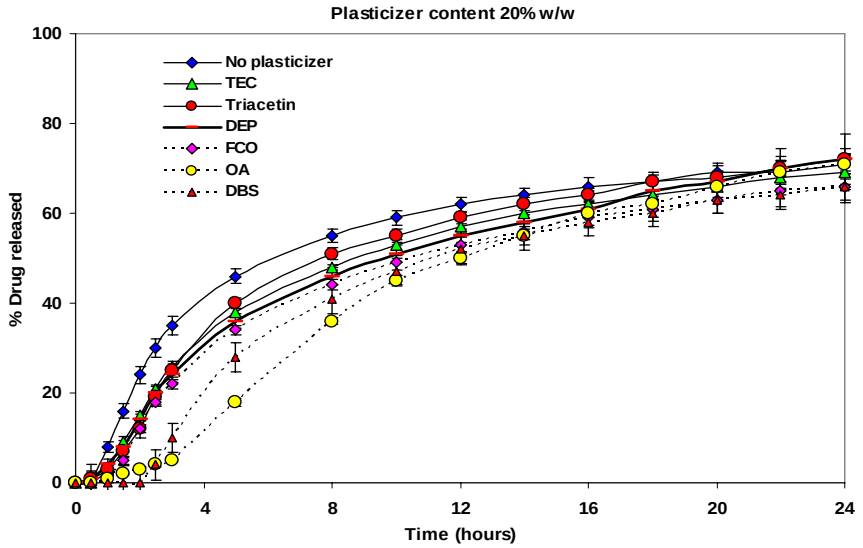
Drug release from coated beads decreased with increasing plasticizer content (Figure 1 (a/b/c)). This may be attributed to a more coherent EC film produced as a result of reduced residual internal stress within the coating[7]. Drug release was significantly reduced where lipophilic plasticizers (DBS, FCO, OA) were used at 30% w/w. Microscopic images of pellets following the dissolution test are shown in Figure 2. Decreased drug release rates may be attributed to the hydrophobic nature of such plasticizers. These lipophilic plasticizers reduce wettability and permeability to water, decreasing the exposure of the pellets to the dissolution medium, resulting in slower onset and rate of drug release[4, 8].

Figure 1. CPM Release Profiles from EC Coated Beads: (a) Plasticizer Content 10% w/w (b) Plasticizer Content 20% w/w (c) Plasticizer Content 30% w/w

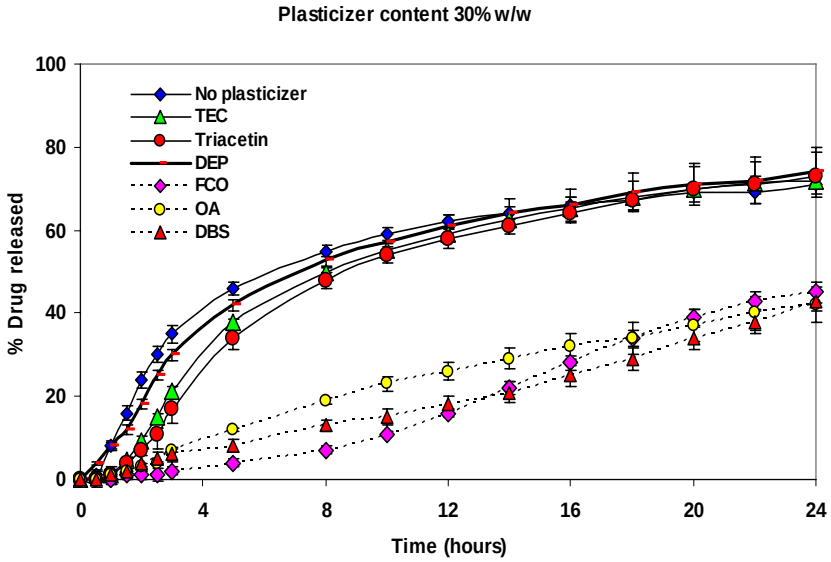
(a)



(b)



(c)



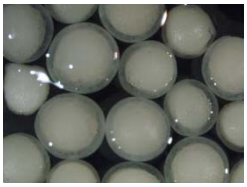
CONCLUSIONS

Type and amount of plasticizer can significantly influence drug release rates. Selection of type and amount of plasticizer requires careful consideration and can be used as an effective tool to tailor drug release. Future work will investigate incorporation of pore-formers to improve % terminal drug release.

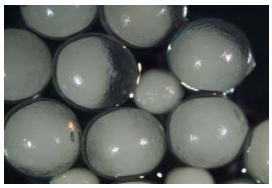
Figure 2. Optical Microscopic Images of Pellets Following the Dissolution Test (Plasticizer level: 30% w/w)

DBS

FCO



OA



DEP

TEC

Triacetin

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