The Influence of Coating System Type on Acetaminophen Release from Ethylcellulose Barrier Membrane Coated Multiparticulates

ABSTRACT SUMMARY:

The process by which drug-layered beads are coated with ethylcellulose (EC) barrier membranes – either in aqueous dispersion form or in organic solvent solution form – can influence the drug release profile. This study was designed to assess the effect of ethylcellulose coating process on drug dissolution from multiparticulates using Surelease®, aqueous ethylcellulose dispersions, or unmodified organic solvent-based ethylcellulose (ETHOCEL™, premium ethylcellulose polymers) solutions. Prior published work has examined similar process effects on coated bead drug delivery, but use modifiers (added plasticizers or surfactants) in the solvent coating process.[1-3] In addition, the effect of core contributions to drug dissolution rates was examined by the use of EC-coated and uncoated microcrystalline cellulose (MCC) beads.

INTRODUCTION:

Ethylcellulose polymer is widely used in pharmaceutical coating, especially when producing modified release dosage forms. Drug release through barrier membrane systems is influenced by several process and formulation variables; however, our understanding of the influence of these variables is hindered by a lack of comprehensive models to guide our coating efforts. The purpose of this work was to study the influence of an aqueous or an organic coating process on drug release profile characteristics from an ethylcellulose barrier membrane coated multiparticulate system.

Either ETHOCEL ethylcellulose (Standard 20 Premium, The Dow Chemical Company) or aqueous ethylcellulose dispersion (Surelease E-7-19040, Colorcon, USA) was used as the barrier membrane polymer. Hypromellose (HPMC, METHOCEL™, premium cellulose ethers E3) was used as the binder for acetaminophen (APAP, Rhodapap, Rhodia, US) layering on MCC beads (Celphere CP-708, 700-850 µm; Asahi Kasei). Ethyl alcohol (200 proof, EMD) and glyceryl monostearate (Spectrum) as a detackifier were used to prepare organic solvent-based ethylcellulose.

EXPERIMENTAL METHODS

Seal Coating of MCC Cores

In some cases, the MCC pellets were seal-coated with Surelease to study the influence of core on drug release. The dispersions were prepared by mixing a weighed amount of Surelease with purified water to produce a final solids content of 15% w/w and mixed for 45 minutes. The compositions for all coating

preparations are shown in Table 1. Known weights of MCC beads were transferred into a fluid bed coating apparatus (VFC-3, Vector Corporation, USA), equipped with a bottom-spray nozzle and Würster insert. The Surelease dispersions were then sprayed onto 3.0 kg of MCC beads. The coating process parameters are shown in Table 2.

Drug Layering onto Seal-Coated MCC Cores

Drug dispersions were prepared by mixing a weighed amount of drug and binder with a suitable solvent system to produce a final solid concentration of 11% w/w. (Table 1). The drug dispersion was then sprayed onto 2.0 kg of seal-coated beads in a Vector VFC-3 fluid bed apparatus. The coating process parameters are shown in Table 2.

Coating of Drug-layered Beads with Aqueous EC Dispersions

The drug-layered beads were coated with Surelease, which comprises EC, ammonium oleate as stabilizer and fractionated coconut oil as plasticizer. The dispersions were prepared according to the composition shown in Table 1 and sprayed to known weights of drug-layered beads in a Vector VFC-3 fluid bed coater. The coating process parameters are shown in Table 2. Coated beads were stored at ambient lab conditions before dissolution testing.

Table 1. Composition of all coating solutions

Layer	Ingredients	Kg
Seal-Coat	Surelease E-7-19040	1.80
	Deionized water	1.20
	Celphere CP-708 MCC beads	3.00
Drug-Coat	Active (Acetaminophen)	0.08
	METHOCEL E3	0.10
	Ethanol/Deionized water	1.60
	Seal-coated MCC beads	2.00
Dispersion Barrier Coat	Surelease E-7-19040	1.60
	Deionized water	1.07
	Drug-coated beads	2.00
Organic Solvent Barrier Coat	ETHOCEL Std 20 Premium	0.05
	95% Ethanol/Deionized Water	0.95
	Glycerol monostearate	0.001

Coating of Drug-layered Beads with Solvent-Based EC Solutions

The drug-layered pellets were coated with ethanolic EC containing no additives (Table 1). Known weights of drug-layered pellets were transferred into a nitrogen-inerted Vector MFL.01 micro fluid bed coater. The coating process parameters are shown in Table 2. Coated beads were stored at refrigerated conditions before dissolution testing.

Table 2. Coating process parameters

Parameter	Seal-coat	Drug-coat	Aqueous Dispersion Barrier coat	Solvent Barrier coat
Inlet temp, (Cº)	58 - 65	50 - 55	50 - 55	63 - 72
Product temp, (Cº)	43 - 46	41 - 44	38 - 42	41 - 43
Air Volume, (CFM)	80 - 90	70 - 90	70 - 90	
Spray rate, (gmin-1)	10 - 13	6 - 10	7 - 10	0.24 – 0.32
Atomizing air pressure, (psi)	30	30	30	9.2

Dissolution Studies

Drug release from EC coated beads was measured using USP XXII, method 1 with either Vankel VK7010 (Varian, US) or Distek 2100C (with H-P 8452A diode array spectrophotometer), in 900 mL of deionized water at 37 ± 1 °C and 100 rpm of basket rotational speed. APAP detection was performed at 243 nm (UV). Assay replicates were three-fold for the aqueous dispersion-coated beads or six-fold for the solvent EC-coated beads; averages over all replicates are plotted with respective standard deviation error bars.

RESULTS AND DISCUSSION

Core Effects on Drug Dissolution

To examine any potential effects of core beads on drug release, control experiments were conducted employing both seal-coated and uncoated beads. Literature suggests that MCC cores should not develop osmotic pressure or swelling that might influence drug release.[4,5] However, our results indicated that Surelease seal-coated, drug-layered beads exhibited slower APAP dissolution than drug-layered, uncoated beads (Figure 1). Further work is underway to develop an explanation for the mechanisms involved.

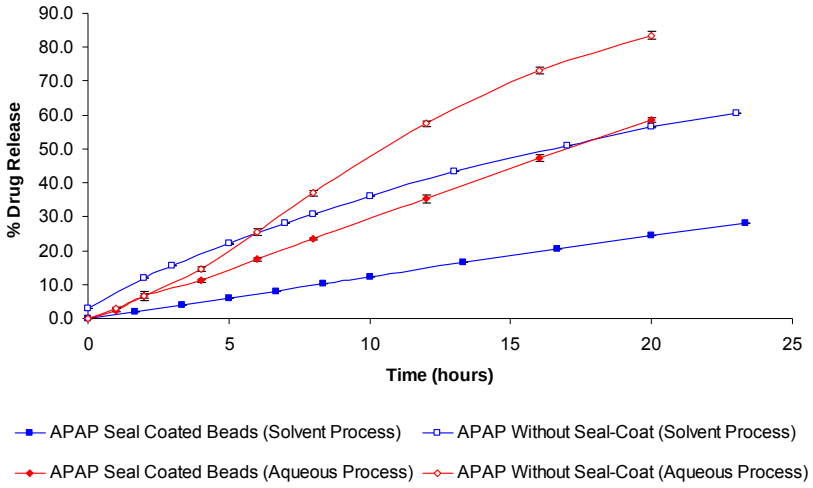

Figure 1. Effects of core and coating process on drug release from 5% w/w EC-coated APAP beads.

Effect of EC Coating Process

APAP dissolution rates also were sensitive to the EC coating process used. The rate of drug release from solvent-coated beads was slower than that from beads coated with Surelease (Figure 1). Film coats from an aqueous dispersion (e.g. Surelease) generally have higher permeability relative to organically applied EC coating.

CONCLUSIONS

Both aqueous and organic applications of ethylcellulose on APAP layered beads resulted in an extended drug release. Keeping the formulation variables such as; dose, coating level, core size, binder type and concentration constant, the dissolution rate depended on the type of the coating applied and presence of a seal-coat on the MCC starter beads. Unmodified solvent-based EC coatings released APAP at a slower rate than water-based Surelease coatings applied at equivalent levels. Additionally, the dissolution rate of beads without a seal-coat was significantly faster than those with a seal-coat, regardless of which process was used.

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