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Investigation of the Relationship between Formulation Variables and Drug Release in Aqueous Ethylcellulose Coating

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Introduction

Drug release through barrier membrane systems is influenced by several process and formulation variables, which can be manipulated to obtain desired release characteristics. For example, the addition of hydrophilic polymers is a popular means of modifying drug release through polymeric films. However, most of the critical variables do not act independently from one another and consequently final release characteristics are often unpredictable. The purpose of this work was to study the critical factors and their degree of influence on drug release characteristics from an aqueous ethylcellulose (Surelease®) barrier membrane coated system.

Materials and Methods

Hypromellose (HPMC, Methocel™ E5) and polyvinyl alcohol (PVA) were used as pore-formers (PF) for an ethylcellulose dispersion (Surelease E-7-19040, Colorcon, USA). SureSpheres™ (850-1000 µm; Colorcon, USA) were used as substrates for layering chlorpheniramine maleate (CPM) acetaminophen (ACE, Rhodapap, US), amlodipine besylate (AML, Cadila Pharmaceutical Ltd., India) and guaifenesin (GUA, Delta Synthetic Co., Taiwan). The binder used for drug layering was Opadry® YS-1-7006 (Colorcon, USA). CPM beads (37.4 mg/g), as well as beads layered with ACE (30.0 mg/g), AML (26.9 mg/g) and GUA (37.5 mg/g) were coated with Surelease containing varying amounts of pore-formers.

Drug Layering Onto Nonpareil Cores

Aqueous drug dispersions were prepared by mixing a weighed amount of drug with a 7% Opadry YS-1-7006 solution to produce a final drug concentration of 25%. The drug dispersions were then sprayed onto 2.5 kg of nonpareils in a Glatt GPCG-3 fluid bed apparatus. The drug layering was done at a spray rate of 5-8 $gmin^{-1}$, product temperature ranging from 41-44°C, fluidizing air volume of 88-180 m3h-1 and atomizing air pressure of 1.5 bar.

Coating of Drug-loaded Beads with Surelease and PF

The drug-loaded pellets were coated with Surelease dispersion containing 0-25%w/w PF. The dispersions were prepared according to the composition shown in Table 1. Weighed amount of PF's were first dissolved in water for 1 hour before 25%w/w Surelease was added and mixed for another hour. Known weights of drug-loaded pellets were transferred into a fluid bed coating apparatus (Fluid Bed 0002, Fluid Air Inc, USA), equipped with a bottom-spray nozzle and Wurster insert. The coating process parameters were: product temperature: 38-43°C; fluidizing air volume: 20-32 m^3h^{-1}, spray rate: 4-10 $gmin^{-1}$ and atomizing air pressure: 15 psi. The beads were coated to levels ranging from 4-20% and stored at ambient lab condition before dissolution testing.

Dissolution Studies

Drug release from coated pellets was investigated by dissolution (USP XXII, method I, Vankel VK 7010, Varian, US) using 1000 ml of deionised water as the dissolution medium which was maintained at 37 ± 1 °C. The basket speed was set at 100 rpm. At predetermined time intervals, samples were collected and assayed spectrophotometrically at 265, 273, 243 and 240 nm for CPM, GUA, ACE and AML respectively. The percent drug released was obtained from the average of at least three determinations.

Table 1. Composition of Coating Dispersions (Total Solid Content = 12.5%w/w)

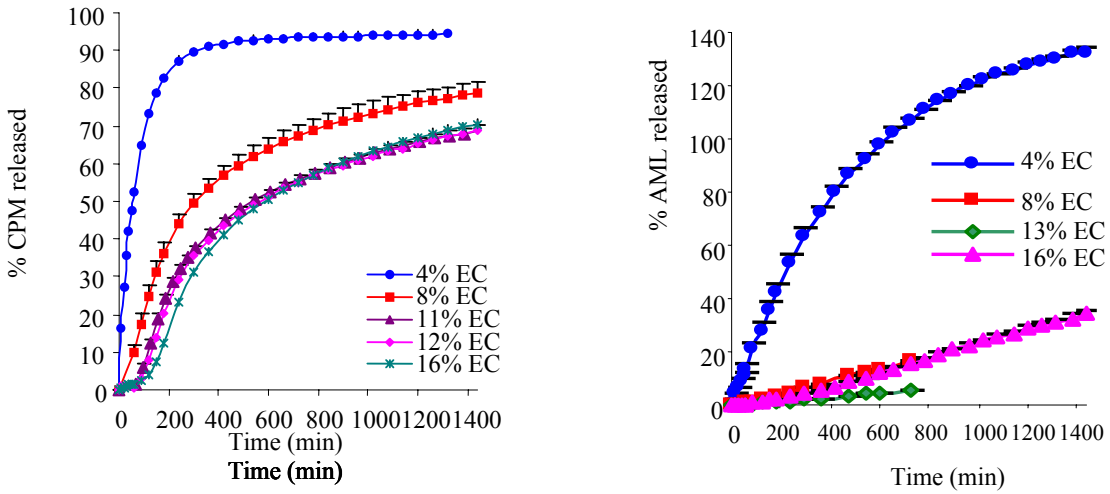
PF (%w/w total solid content)	Weight of PF (g)	Surelease (25%w/w)	Weight of water
0	0.00	500	500.00
5	6.25	475	518.75
10	12.50	450	537.50
15	18.75	425	556.25
20	25.00	400	575.00
25	31.25	375	593.75

Results & Discussion

Effect of Coating Level

Ethylcellulose is a widely used polymer of choice for controlling drug release through a barrier membrane. The desirable release rate is generally attained by controlling the diffusion rate of the drug through the ethylcellulose barrier film. Based on Ficks first law of diffusion, assuming that other variables such as surface area of the substrate and the concentration gradient across the film remaining constant, the release rate is primarily governed by the thickness and permeability of the film. However, the dissolution profiles of coated beads (Figure 1) demonstrated that the theory only holds up to a certain coating level. With the exception of ACE beads, no further reduction in release rate was observed after 8%, 11% and 13% of Surelease applied on AML, CPM, and GUA beads respectively (Figure 1).

Figure 1. Effect of Coating Level on (a) CPM (b) AML Released from Surelease Coated Beads.

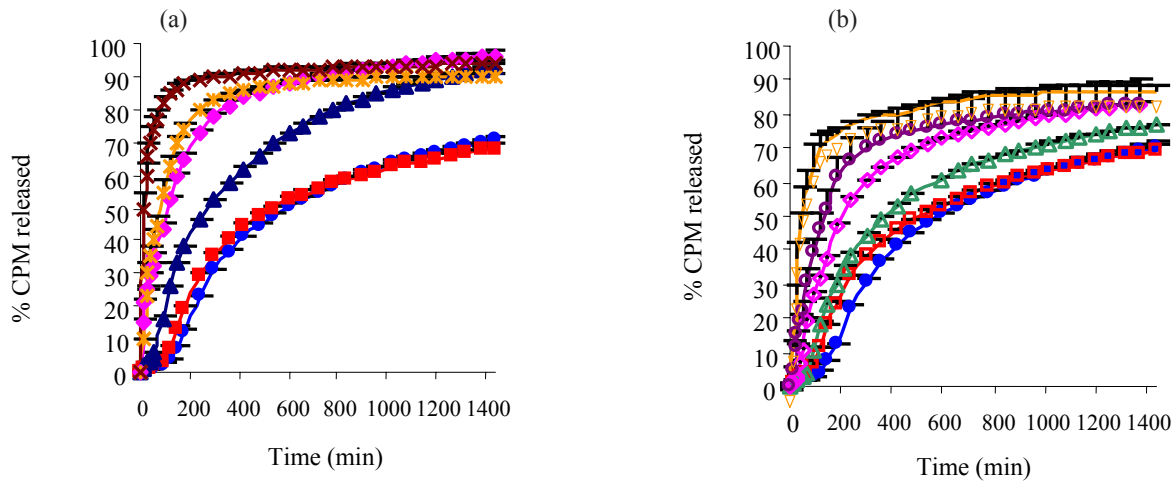


Effect of Pore-Former Levels

A wide range of CPM release profiles were obtained through incorporation of hydrophilic polymers, such as HPMC or PVA to Surelease films (Figure 2). When present in small quantities, HPMC and PVA have been shown to be compatible with Surelease dispersions[1] and do not significantly affect the physical film properties. The increase in the release rate for CPM beads corresponded with the level of HPMC and PVA, and was dependent on the coating level of Surelease. Both the pore-former and coating levels must therefore be considered in order to obtain the desired release profile. Analysis of the release data for CPM coated beads indicated that the pore-former level had a much greater influence on release rate than coating level.

Figure 2. Influence of (a) HPMC and (b) PVA Concentration on CPM Release from Surelease Coated Beads at 16% Coating level.

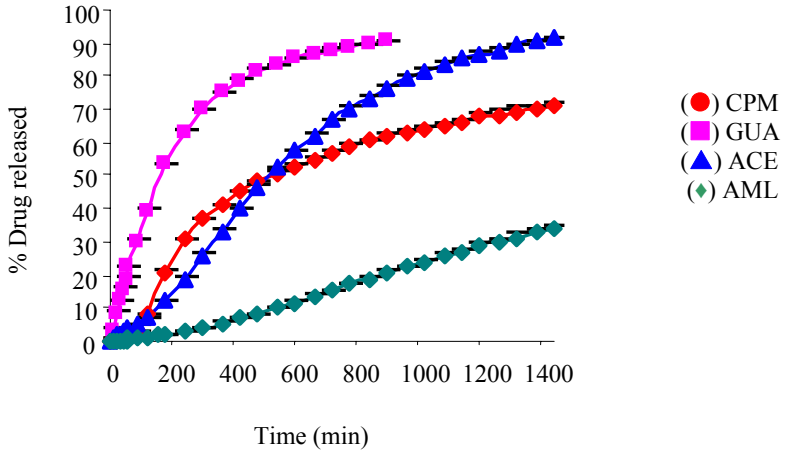
(●) EC, (■) EC:HPMC (95:5), (▲) EC:HPMC (90:10), (♦) EC:HPMC (85:15); (*) EC:HPMC (80:20); (×) EC:HPMC (75:25) (□) EC:PVA (95:5), (△) EC:PVA (90:10), (◊) EC:PVA (85:15); (O) EC:PVA (80:20); (▽) EC:PVA (75:25)



Effect of Aqueous Drug Solubility

In addition to the properties of the barrier membrane, aqueous solubility of the drug has been reported to affect the release characteristic (2). Generally, the release rate increased as aqueous solubility of the drug increased, as shown in Figure 3. However, drug release profiles did not follow the rank order of their aqueous solubility, indicating that there are other important factors to be considered.

Figure 3. Drug Release Profiles of Beads Coated with 16% Surelease



Conclusions

The incorporation of HPMC or PVA has shown to be effective in modifying drug release characteristics through a Surelease barrier membrane system. By controlling the critical variables, such as pore-former concentration, coating level and drug solubility, the desired release characteristic can be achieved. Further work is underway to study the influence of drug properties on release through barrier membrane films.

References

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2. Akbuga, J. *International Journal of Pharmaceutics* 100 (1993) 257-261

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