The Influence of Drug Solubility on Release from Ethylcellulose Barrier Membrane Coated Multiparticulates

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Abstract Summary

The influence of drug solubility on release from ETHOCEL™ Premium Ethylcellulose (EC) coated beads was investigated. Drug release was retarded with decreasing drug solubility. Apart from drug solubility, other factors such as affinity of the drug for the barrier membrane or the degree of ionization of the drug may also influence drug release rates. Similar trends in drug release were observed for solvent and aqueous coated EC. The addition of a pore-former yielded a faster drug release. Poorly soluble drugs exhibit significantly slower release when coated with EC using an organic solvent.

Introduction

A previous study investigated the relationship between drug solubility and release in aqueous ethylcellulose coating (Surelease®, Colorcon, USA).[1] The objective of this work was to carry out a comparative evaluation of drug release from solvent coated ethylcellulose multiparticulates using the same model drugs.

Experimental Methods

Drug Layering of Sugar Spheres

Four model drugs; chlorpheniramine maleate (CPM), guaifenesin (GUA), acetaminophen (APAP) and amlodipine besylate (AMD) of varying solubility were used in this study. The model drugs were coated in an aqueous dispersion onto 18/20 mesh (850 - 1000 µm) sugar spheres (SUGLETS™ Colorcon, USA) in a Pam-Glatt GPCG-1 fluidized bed coater (Pam-Glatt Pharma Technologies, India) equipped with a Würster column (200mm length) using Hypromellose 2910 (METHOCEL™ E6 Premium LV, The Dow Chemical Company, USA) as a binder. The four model drugs used in this study are listed in **Table 1**. Process parameters employed in the drug layering are shown in **Table 2**.

Table 1. Drug Characteristics

Drug	Drug Assay (mg g^{-1})		Drug solubility[2, 3, 4] (in water)
	Previous Study *	Current Study	
CPM	37.4	29.5	250 mg/mL (Freely soluble)
GUA	37.5	32.7	14.3-16.7 mg/mL (Soluble)
APAP	30.0	30.7	14 mg/mL (Soluble in hot water)
AMD	26.9	33.0	3.5 mg/mL (Slightly soluble)

*Data from reference 1

Experimental Methods (cont'd)

Ethylcellulose Coating of Drug-Layered Sugar Spheres

Coating solutions were prepared by dissolving ETHOCEL™ 10 Std Premium (EC) (The Dow Chemical Company, USA) with and without HPMC 2910 (METHOCEL™ 6 cP) as pore-former, at a 75:25 ratio in the solvent mixture comprising, isopropanol and water (90:10). Dibutyl sebacate [DBS, Vertellus, USA] (10% w/w with respect to the polymer) was added as a plasticizer. Drug layered beads were coated to a 10% weight gain using a GPCG 1.1 fluid-bed apparatus. Ethylcellulose barrier membrane coating process parameters are shown in **Tables 3 and 4**.

Table 2. Drug Layering Process Parameters

Parameter	Model drugs			
	CPM	GUA	APAP	AMD
Inlet temperature (°C)	65- 70	52 - 58	43 - 48	42 - 45
Product temperature (°C)	45 48	43 - 48	38 - 40	38 - 40
Fluid delivery rate (g/min)	100	8-10	2-3	2- 3
Atomization pressure (bar)	1.5	1.2-1.5	0.5	0.4

Table 3. Coating Parameters used for EC Coating (without pore-former)

Parameter	Model Drugs			
	CPM	GUA	APAP	AMD
Charge (g)	600	600	600	600
Air velocity (m/s)	11.0 - 12.5	8.5 - 8.7	9.0 - 9.3	9.5 – 10.0
Inlet air temperature (°C)	34 - 35	40 - 43	40 - 42	38 - 39
Product temperature (°C)	32 - 33	33 - 35	35 - 37	35 - 36
Fluid delivery rate (g/min)	5 - 6	6 - 8	6.5 - 8	6 - 7
Atomization pressure (bar)	0.8 – 1.0	1.0	0.8	0.9
Solids concentration (%)	7	7	7	7

Table 4. Coating Parameters used for EC Coating (with pore-former)

Parameter	Model Drugs			
	CPM	GUA	APAP	AMD
Charge (g)	600	600	600	600
Air velocity (m/s)	9.0 – 9.8	8.0 – 8.5	9.2 – 9.7	9.0 – 10.0
Inlet air temperature (°C)	39 – 41	40 – 42	42 - 43	38 - 39
Product temperature (°C)	35 – 37	32 – 35	35 – 37	34 - 36
Fluid delivery rate (g/min)	6 - 8	6 - 8	7- 8	6 - 8
Atomization pressure (bar)	0.9	1.0	0.9	0.9 - 1.0
Solids concentration (%)	7	7	7	7

Dissolution Testing

Drug release was measured from 1.0 g of coated pellets (n=6) 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 drug (CPM at a wavelength of 262 nm; GUA at a wavelength of 273 nm; APAP at a wavelength of 243 nm and AMD at a wavelength of 240 nm) over a 24 hour period. Purified water was used as the reference.

Results and Discussion

The rank order for aqueous solubility is CPM > GUA > APAP > AMD. Drug release rate followed the rank order: GUA >APAP > CPM > AMD (**Figures 1, 2 and 3**), regardless of coating solvent.[1] Ragnarsson et al. attributed faster drug release rates of soluble drugs to a steeper concentration gradient and an increased osmotic pressure difference over the membrane.[5] This has also been reported by Hjartstam's, where they suggested that an increased osmotic pressure difference may induce tensile stresses in the film leading to greater permeability.[6]

Figure 1. Coated with ETHOCEL™ 10 cP (10% w/w)

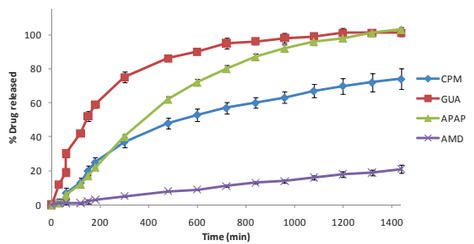


Figure 2. Coated with Surelease® (16% w/w)

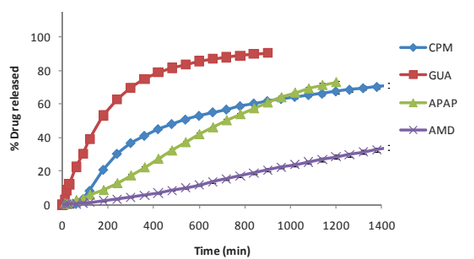
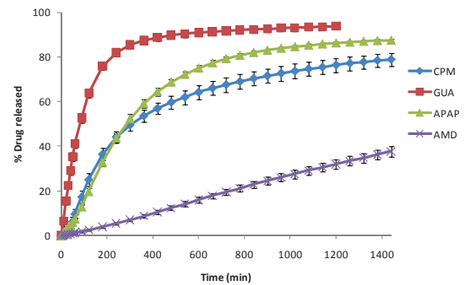


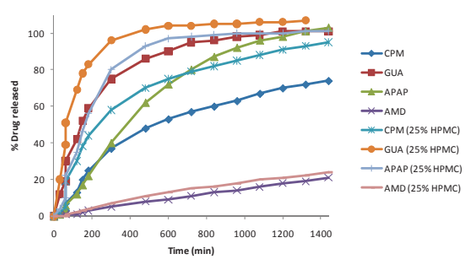
Figure 3. : Coated with Surelease® (8% w/w)



A deviation from the trend was observed for CPM, a freely water soluble drug with a low affinity for EC.[7] Slower release was observed for CPM as compared to APAP (sparingly water soluble) for solvent as well as aqueous coated EC.

Guaifenesin, a neutral molecule and water soluble drug, showed faster release than CPM. For a slightly soluble drug (amlodipine), a very slow drug release was obtained where EC was applied using an organic solvent. The addition of a pore-former did not result in any increase in the drug release rate for amlodipine. (**Figure 4**).

Figure 4 Coated at 10%w/w with ETHOCEL™ 10 cP with/without pore-former: METHOCEL™ E6 (75:25)



Formulation containing CPM and AMD demonstrated very slow and incomplete drug release, which reflects AMD's very low water solubility, and potential interactions between CPM and ethylcellulose. Drug release may be modulated via changes in the barrier membrane film thickness, increased permeability of the film by inclusion of a pore former such as hypromellose or use of an aqueous EC system, such as Surelease®.

Conclusion

Multiparticulates solvent coated with ethylcellulose barrier membrane lead to slower drug release than when coated with aqueous dispersion. Drug release rate increased with addition of hypromellose as a pore-former. Unexpectedly, the rank order of release rate did not follow that of drug solubility. This may be related to different partition coefficient of drugs into the ethylcellulose membrane. Similar trends in drug release were observed for solvent as well as aqueous coated EC.

References

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