The Influence of Dissolution Media pH on Drug Release from Ethylcellulose Coated Multiparticulates

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Abstract Summary

The influence of dissolution media pH on drug release from ETHOCEL™ Premium Ethylcellulose coated beads was investigated. Drug release was found to be independent of dissolution media pH.

Introduction

In order to achieve a consistent extended drug release, it may be necessary to maintain similar drug release while dosage form travels across the physiological pH range. The objective of this work was to carry out a comparative evaluation of drug release from ethylcellulose coated multiparticulates in both gastric and intestinal pH media for ionic or non-ionic drugs.

Experimental Methods

Drug Layering of Sugar Spheres

Four model drugs; chlorpheniramine maleate (CPM), guaifenesin (GUA), acetaminophen (APAP) and amlodipine besylate (AMD) were used in this study. The four model drugs are characterized below (**Table 1**).

Table 1. Model Drug Characteristics

Drug	Drug Assay mg g^{-1}	Drug solubility[1, 2, 3] (in water)	pK_a
CPM	29.5	Freely soluble	9.2
GUA	32.7	Soluble	-
APAP	30.7	Sparingly soluble	9.5
AMD	33.0	Slightly soluble	8.6

The model drugs were coated 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, International Flavors and Fragrances Inc., USA) as a binder. Process parameters employed in the drug layering are listed in **Table 2**. Poorly soluble drugs (APAP and AMD) required a higher proportion of binder to assist with adherence of the suspended drug particles onto the coating substrate. The poorly soluble drugs do not contribute to the viscosity of the drug layering dispersion thus allowing for higher % drug solids for the coating dispersion. Lower fluid delivery rates were used for a more uniform application of the poorly soluble drug.

Soluble drugs (CPM and GUA) contribute to the coating solution viscosity. The higher viscosity of the coating solutions therefore, required the use of a lower % of the drug as well as a lower content of the binder in the drug layering solution. The drug layering solution was applied at higher atomization pressure and a higher bed temperature than insoluble drugs.

Experimental Methods (cont'd)

Table 2. Drug Layering Process Parameters

Parameter	Model Drug			
	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)	8 - 10	8 - 10	2 - 3	2 - 3
Atomization pressure (bar)	1.5	1.2-1.5	0.5	0.4
Drug layering dispersion/ solution				
API concentration (%)	7	7	25	25
Binder concentration (%)	3	3	5	5

Ethylcellulose Coating of Drug Layered Sugar Spheres

Coating solutions (7% solids concentration) were prepared by dissolving ETHOCEL™ 10 Std Premium (EC) (International Flavors and Fragrances Inc., USA) in a 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. Coating process parameters for the EC coating are listed in **Table 3**.

Table 3. Coating Parameters used for EC Coating

Parameter	Model Drug			
	CPM	GUA	APAP	AMD
Charge (g)	600	600	600	600
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

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 in 1000 mL of dissolution medium. The dissolution media evaluated were purified water; 0.1 N HCl and USP pH 7.4 phosphate buffer at 37 ± 0.5°C. An online dual beam spectrophotometer (Perkin-Elmer, USA) was used for the detection (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. The respective dissolution media were used as the reference.

Results and Discussion

Drug release across a barrier membrane is expected to occur via diffusion through the polymer network, channels or pores formed in the coating. A partitioning of drug in a polymeric film coat is generally expected to be dependent on the state of ionization of the drug molecule, molecular affinity (determined by solubility parameter) and its aqueous solubility. The degree of ionization of a drug depends on its pKa and the pH of the aqueous solution in which it is dissolved. Acetaminophen, a very weak organic acid (pKa =9.5) is expected to be essentially non-ionized at physiological pH (both at 0.1 M HCl and pH 7.4 buffer). Acetaminophen solubility does not vary from pH 1.2-8.0 corresponding to the in vivo range in the GIT.[4] As expected, a pH independent behavior was observed in the case of acetaminophen (**Figure 1**).

Guaifenesin, a neutral molecule, with absence of any ionizable groups in the molecule also showed pH independent drug release (**Figure 2**). Guaifenesin is less soluble in a more acidic environment, while in a higher pH environment, guaifenesin is readily soluble.[5] Chlorpheniramine maleate (pKa=9.20), salt of the weak base chlorpheniramine and maleic acid, has been reported[6] to have similar solubility, in both 0.1 M HCl and in pH 7.4 phosphate buffer at 37°C also showed pH independent release behavior (**Figure 3**).

Amlodipine besylate, salt of a weak base amlodipine, has mixed ionization within the physiological pH range. Drug release from coated pellets, however, was found to be independent of pH (**Figure 4**). Amlodipine has a maximum solubility in acidic pH.[7]

Such pH independent release from EC coated pellets has also been reported previously by other researchers.[8,9]

Figure 1. ETHOCEL™ coated acetaminophen beads

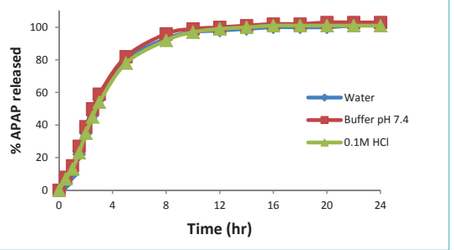


Figure 2. ETHOCEL™ coated guaifenesin beads

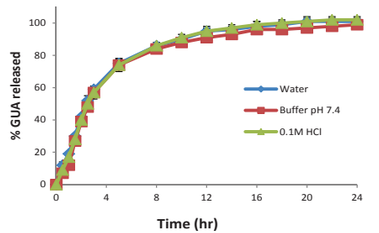


Figure 3. ETHOCEL™ coated chlorpheniramine maleate beads

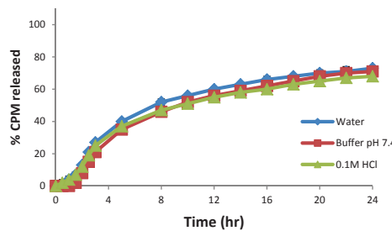
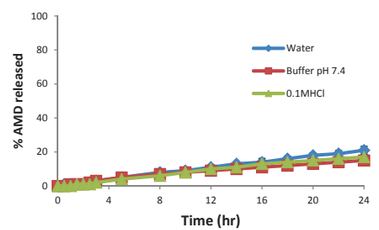


Figure 4. ETHOCEL™ coated amlodipine besylate beads



Drug release rate independent of pH of the dissolution medium may indicate that drug diffusion was the dominant mechanism of drug release[8]. It has been reported that, pH independent drug release at higher barrier membrane weight gains attributed to a more complete film formation and a controlled rate of drug diffusion through the film.[10]

Although formulations containing CPM (possibly a result of an interaction between CPM and ethylcellulose) and AMD (possibly a result of AMD's very low water solubility) demonstrated very slow and incomplete release, drug release may be accelerated via reduction in the barrier membrane film thickness, or increased permeability of the film by inclusion of a pore former such as hypromellose.

Conclusion

Drug release from ETHOCEL™ coated pellets was found to be independent of the pH of the dissolution medium for a range of actives with varying solubility.

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