Barrier Membrane Coating of Hydrophilic Matrices of Sparingly Soluble Drug, Acetaminophen: A Strategy to Reduce Possible Food Effect

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Purpose

Hydrophilic matrices (HM) are very popular and a widely used formulation option for oral extended release (ER) drug delivery. In general, low viscosity hypromellose (hydroxypropyl methylcellulose, HPMC) is recommended for formulating matrices of sparingly soluble APIs.[1, 2] However, it is reported in the literature that hydrophilic matrices formulated with low viscosity polymers may result in variable drug release under fed stomach conditions. This is commonly referred to as "food effect".[3]

In this study, hydrophilic matrices of a sparingly soluble model drug, acetaminophen (APAP), were developed using METHOCEL™ K100LV Premium CR as the rate controlling polymer along with fillers of varying solubility: lactose or Starch 1500® partially pregelatinized starch.

For the purpose of simulating the fed stomach conditions, in vitro drug release studies were carried out at different agitation rates and using two-stage media change over. Barrier membrane coating may protect against food effect and help reduce drug release variability, as reported elsewhere.[4]

Hence, the objective of the present study was to investigate the application of a barrier membrane (BM) coating on APAP matrices, consisting of an aqueous ethylcellulose dispersion (Surelease® E-7-19010) and a pore former (Opadry® film coating) as a strategy to reduce drug release variability and possible food effect when dealing with hydrophilic matrices of a sparingly soluble model drug.

Experimental Methods

Formulation and Tablet Preparation

The composition of APAP extended release matrix tablets is shown in **Table 1**. APAP, HPMC (METHOCEL K100LV Premium CR), filler and colloidal silicon dioxide were sieved through a 30 mesh (590 micron) screen and then blended in a twin-shell blender (Patterson-Kelley, USA) for 10 mins. The powder blends were lubricated with magnesium stearate for 3 mins and compressed using an instrumented rotary press (Piccola, Riva, Argentina) with standard concave tooling (9.5 mm) to a target weight of 400 mg. Tablets with sufficient mechanical strength [hardness (tensile strength) > 15 kP (3.4 MPa)] were used for application of coating.

Application of Barrier Membrane Coating

APAP matrix tablets, with lactose and Starch 1500, were coated with a BM coating consisting of a combination of Surelease E-7-19010 and an HPMC-based Opadry system as a pore-former at the weight ratio of 85:15 w/w. Prior to application, the coating systems were dispersed in water at 10% w/w solids content. Tablets were then coated to 2 to 8% weight gain (WG) in a 12" fully perforated coating pan (Labcoat I, O'Hara Technologies, Canada) using a 1 mm spray gun (970/7-1S 75, Schlick, Germany). The recommended coating process parameters for Surelease were used for application of the barrier membrane coating (**Table 2**).

Dissolution Studies

In vitro dissolution studies of the uncoated and coated APAP matrix tablets were conducted using Apparatus II (paddle) with sinkers in 900 mL of specified dissolution media at 37°C ± 0.5°C. The in vivo fed state condition was simulated using a two-stage dissolution study, first using pH 4.5 acetate buffer for 4 hours (50, 100 and 150 rpm), followed by pH 6.8 phosphate buffer (100 rpm) for the remaining 12 hours. The elevated mechanical stress under fed stomach was simulated by varying agitation rates during the first stage of dissolution. APAP release was determined spectrophotometrically at a wavelength of 245 nm. Drug release profiles were compared using similarity factors ($f2$).[5]

Table 1. Composition of Extended Release Acetaminophen Matrix Tablets

Ingredients	Supplier	Composition (%w/w)	
		Starch 1500	Lactose
APAP (Compap, PVP3)	Mallinckrodt, USA	50.0	50.0
PVP (Compap, PVP3)	Mallinckrodt, USA	1.8	1.8
Hypromellose (METHOCEL K100 LV Premium CR)	IFF, USA	30.0	30.0
Partially pregelatinized starch (Starch 1500)	Colorcon, USA	17.2	-
Lactose monohydrate (FastFlo)	Foremost, USA	-	17.2
Colloidal silicon dioxide (Cab-O-Sil M5P)	Cabot Corp., USA	0.5	0.5
Magnesium stearate	Mallinckrodt, USA	0.5	0.5
Total		100.0	100.0

Table 2. Coating Process Parameters for Application of BM Coating of APAP (200mg) ER Matrix Tablets

Parameter	Value
Tablet charge (kg)	1
Inlet temperature (°C)	55-57
Bed temperature (°C)	42-45
Exhaust temperature (°C)	47-49
Air flow (m^3/hr)	290
Spray rate (g/min)	6-8

Results and Discussion

Figure 1. Dissolution Profiles of Uncoated APAP (200 mg) ER Matrix Tablets Containing Lactose as Filler

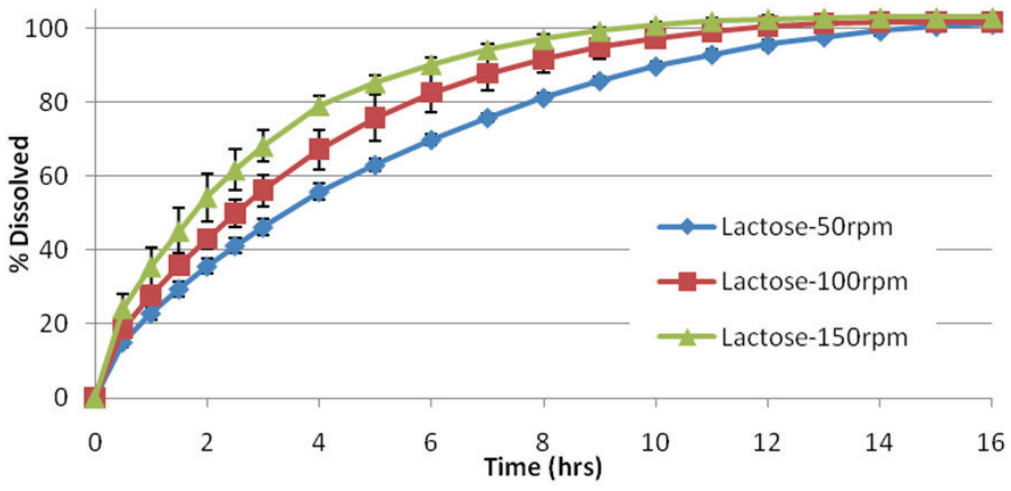


Figure 2. Dissolution Profiles of Uncoated APAP (200 mg) ER Matrix Tablets Containing Starch 1500 as Filler

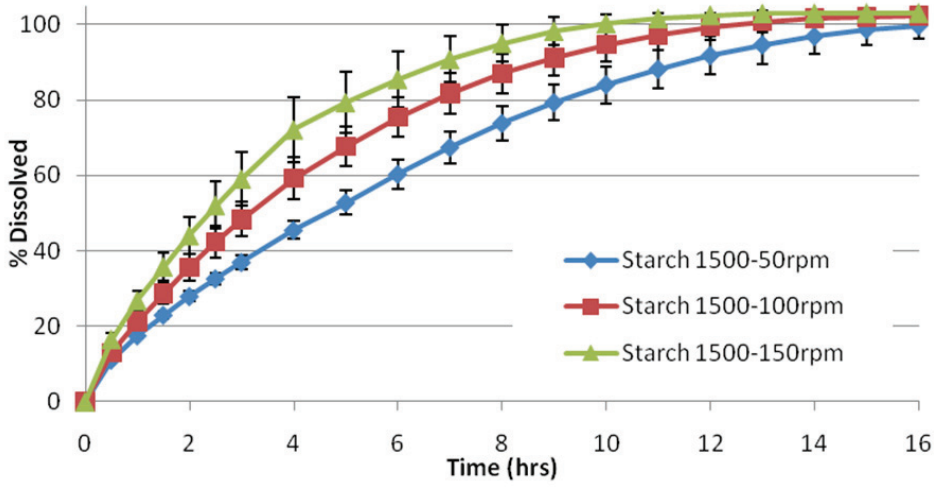


Figure 3. Dissolution Profiles of APAP (200 mg) ER Matrix Tablets Containing Lactose and BM Coating of Surelease and Opadry at 85:15 w/w at 2% WG.

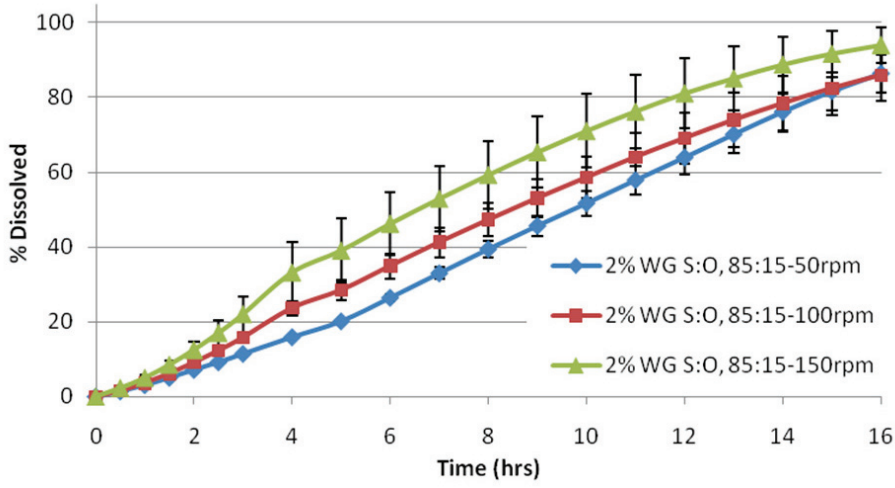
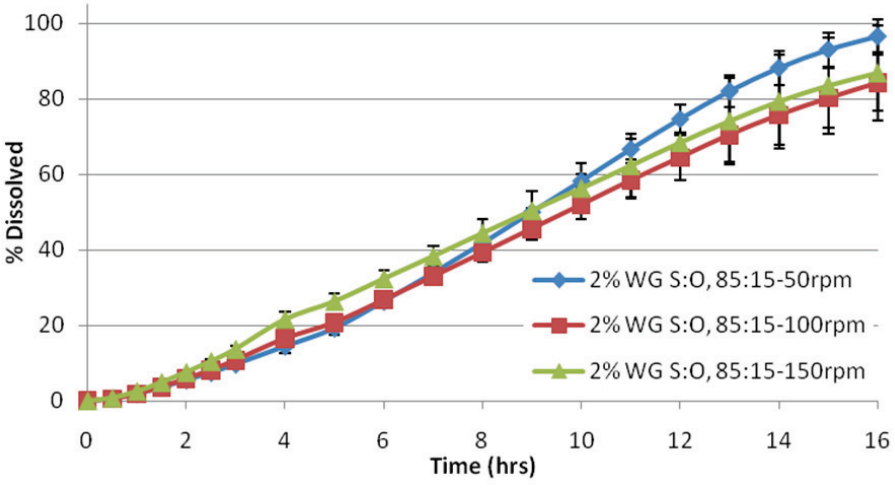


Figure 4. Dissolution Profiles of APAP (200 mg) ER Matrix Tablets Containing Starch 1500 and BM Coating of Surelease and Opadry at 85:15 w/w at 2% WG.



Figures 1 and 2 show the drug release from uncoated hydrophilic matrix tablets of APAP (200 mg) using a soluble filler: lactose, and a partially soluble filler: Starch 1500, respectively. The drug release is highly variable at agitation rates of 50, 100 and 150 rpm, as evident by comparing $f2$ values for lactose and Starch 1500, **Table 3**. Such in vitro behavior may indicate variable in vivo drug release rates and, possible "food effect".

Application of BM coating at 2% WG was an approach used to potentially reduce the observed drug release variability. As a result, reduction in variability and near zero order drug release was achieved. This effect was more significant when Starch 1500 was used as the filler (**Figure 4**) compared to lactose (**Figure 3**). The $f2$ value was >50 for Starch 1500 systems; whereas, matrices formulated with lactose resulted in $f2$ value <50. The potential synergistic effect of Starch 1500 and METHOCEL, coupled with uniform rupture of BM coating around the belly band area of the tablets, is hypothesized to provide robust drug release at various agitation rates.[6, 7]

Table 3. Similarity Factor (f_2) Comparisons for Uncoated and BM coated APAP 200mg ER Matrix Tablets

Formulation	Type of filler	50 rpm vs 100 rpm	150 rpm vs 100 rpm	50 rpm vs 150 rpm
BM coated matrices	Starch 1500	59	67	61
	Lactose	57	47	37
Uncoated matrices	Starch 1500	47	53	37
	Lactose	50	52	38

Conclusions

The application of barrier membrane coating consisting of Surelease and HPMC-based Opadry system, as a pore former, was found to be a useful tool to obtain robust and consistent drug release profiles from hydrophilic matrices of the sparingly soluble drug, APAP. BM coated matrices showed minimal sensitivity to varying agitation rates and possible food effect. Inclusion of Starch 1500, in particular, as an excipient in the matrices resulted in uniform drug release from BM coated matrices.

References

1. Tiwari SB and Rajabi-Siahboomi AR. Extended-Release Oral Drug Delivery Technologies: Monolithic Matrix Systems. In: Jain KK, ed. *Drug Delivery Systems, Methods Mol Biol.* Vol. 437, Humana Press: Totowa, NJ; 2008:217-243.
2. Using METHOCEL™ Cellulose Ethers for Controlled Release of Drugs in Hydrophilic Matrix Systems, http://www.colorcon.com Accessed January 26, 2011.
3. Abrahamsson B et al. Drug absorption from nifedipine hydrophilic matrix extended-release (ER) tablet-comparison with an osmotic pump tablet and effect of food. *J Control Release*, 1998; 52(3):301-10
4. Ayrus JW, Coated Platform-Generating Tablets, US Patent 6733784B1
5. Moore JW, Flanner HH. *Pharm. Tech.* 1996; 20(6): 64-74.
6. Mehta RY et al, CRS annual meeting and exposition, National Harbor, MD, 2011.
7. Levina M, Rajabi-Siahboomi AR. The Influence of Excipients on Drug Release from Hydroxypropyl Methylcellulose Matrices. *Journal of Pharm. Sci.*, (2004); Vol. 93, 2746–2754