Barrier Membrane Coating of Hydrophilic Matrices: A Strategy to Reduce Drug Release Variability and Possible Food Effect

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Poster Reprint
CRS 2011

Abstract Summary

Extended release, hydrophilic matrix tablets of hydrochlorothiazide (HCTZ) at 200 mg dose were formulated using low viscosity hypromellose (hydroxypropyl methylcellulose, HPMC) as a rate controlling polymer at 30% w/w level. In vitro dissolution studies of this formulation indicated variability in drug release rate at agitation speeds of 50, 100 and 150 rpm (f_2<50). Such an in vitro behavior may indicate a possible food effect. Application of a barrier membrane (BM) coating with Surelease® aqueous ethylcellulose dispersion (E-7-19010) including a pore-former (Opadry® complete film coating system) resulted in consistent and robust drug release profiles at agitation speeds of 50, 100 and 150 rpm (f_2> 60). Near zero order drug release profiles were obtained. Coating weight gain and level of pore former in the BM coating were found to be critical in achieving robust and stable drug release profiles.

Introduction

Hydrophilic matrix systems are most popular among different technologies used in the manufacture of oral controlled release systems because of the simplicity of formulation, ease of manufacturing, low cost, regulatory acceptance, and applicability to drugs with wide range of dose and solubility.

Low viscosity hypromellose (METHOCEL™ K100LV Premium CR) is generally recommended for formulating matrices of low solubility APIs, for example BCS Class II drugs. As the release of such low solubility APIs from the matrix predominantly occurs via an erosion mechanism, control over the matrix erosion is necessary to achieve consistent release, both in fasting and fed states.[1-2] The presence of elevated mechanical forces with increased GI motility under fed state conditions may result in a higher erosion rate of the hydrophilic polymer, which may contribute to the variability of release in the fed state, leading to the so called food effect. [3]

The objective of the present study was to investigate the application of BM coating consisting of an aqueous ethylcellulose dispersion (Surelease® E-7-19010) and a pore former (Opadry®) as a strategy to reduce drug release variability from hydrophilic matrices as a function of hydrodynamics. The effect of coating weight gain and level of pore-former in the BM coating were also evaluated.

Hydrochlorothiazide (HCTZ), a very slightly water soluble drug (solubility of ~ 0.7 mg/mL), at a dose level of 200 mg was used as a model BCS class II drug, where food effect has been reported. The hydrophilic matrix was formulated using HPMC (METHOCEL™ K100LV Premium CR) as a rate controlling polymer at 30% w/w level.

Experimental Methods

Formulation and Tablet Preparation

The composition of hydrochlorothiazide extended release tablets is shown in **Table 1**. Formulations were prepared by blending sieved ingredients including API, HPMC (METHOCEL™ K100LV Premium CR), lactose and colloidal silicon dioxide in a twin-shell blender (Patterson-Kelley, USA) for 10 minutes. The powder blends were lubricated with magnesium stearate for 3 minutes and compressed using an instrumented rotary press (Piccola, Riva, Argentina) at a target weight of 400 mg. Tablets with sufficient mechanical strength [hardness > 15kP (3.4 MPa)] were used for application of a BM coating.

Table 1. Composition of Extended Release Hydrochlorothiazide Matrix Tablets

Ingredients	% Composition (w/w)
Hydrochorothiazide (Hubei Maxpharm, China)	50.0
Hypromellose (METHOCEL™ K100LV Premium CR, Dow Chemical Company, USA)	30.0
Lactose (FastFlo**,** Foremost**,** USA)	19.0
Colloidal silicon dioxide (CAB-O-Sil M5P, Cabot Corp., USA)	0.5
Magnesium Stearate (Mallinckrodt, USA)	0.5
Total	100.0

Application of Barrier Membrane Coating

HCTZ matrix tablets were coated with a BM coating consisting of combination of Surelease® E-7-19010 and HPMC-based Opadry®, as a pore-former, at ratios of 85:15 and 60:40. Prior to application, the coatings were dispersed at a 10% w/w solids level in water. Tablets were then coated to 2-8% weight gain. Standard coating processing parameters were used for application of barrier membrane coating.

Drug Dissolution Studies

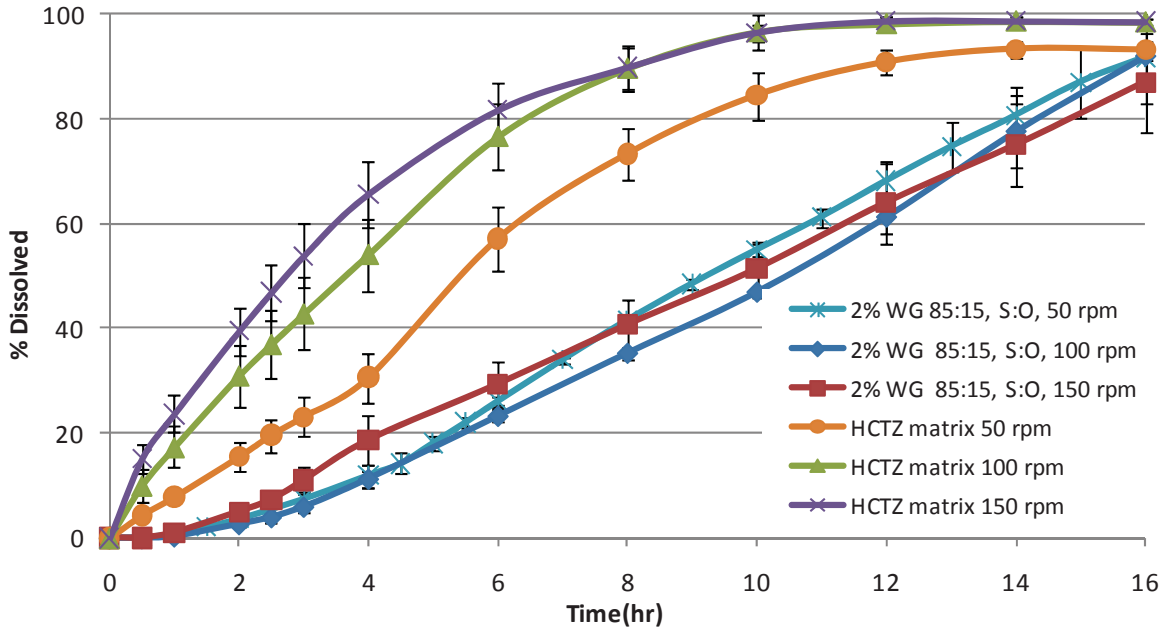
In vitro dissolution studies of the formulated HCTZ ER tablets were conducted using Apparatus II with sinkers and 900 mL of specified dissolution media at 37°C ± 0.5°C. The in vivo, fed state condition was simulated using a two stage dissolution study, first using pH-4.5 acetate buffer for 4 hrs (50, 100 and 150 rpm), followed by pH-6.8 phosphate buffer (100 rpm) for the remaining 12 hrs. Released HCTZ was spectrophotometrically analyzed at a wavelength of 272 nm.

Results and Discussion

As shown in **Figure 1**, HCTZ release from uncoated hydrophilic matrices indicated variability at agitation speeds of 50, 100 and 150 rpm as evident by similarity factor, f_2 values (100 vs. 150 rpm = 54; and 50 vs. 100 rpm = 38.74). Such in vitro behavior may indicate a variable in vivo release rate and, possibly, food effect.

Application of a barrier membrane coating consisting of Surelease® and HPMC based Opadry®, as pore-former, with 85:15 ratio and 2% weight gain (WG) resulted in significant reduction in variability of release and provided near zero order release rate as shown in **Figure 1**. The similarity factor f_2 was > 60 for all the agitation speeds studied. It was hypothesized that the consistent and uniform breakage of the film at the belly band area of the tablet was responsible for the robust drug release rates at various agitation speeds.

Figure 1. Dissolution Profile of HCTZ 200mg ER Tablets Coated with BM Coating Consisting of Surelease® and Opadry® at 85:15 Ratio and 2% WG.



Increasing the pore-former concentration in the BM coating to 40% (**Figure 2**) or increasing the coating weight gain to 4 % (**Figure 3**) or higher led to either variable release rates at different agitation speeds or incomplete release. The observation of film rupture pattern during dissolution study indicated that increasing the concentration of pore-former allowed more infiltration of the media within the film thereby reducing the strength of the film and subsequent variability in drug release rates at the different agitation speeds.

Figure 2. Dissolution Profile of HCTZ 200 mg ER Tablets Coated with BM Coating Consisting of Surelease® and Opadry® at 60:40 Ratio and 2% WG.

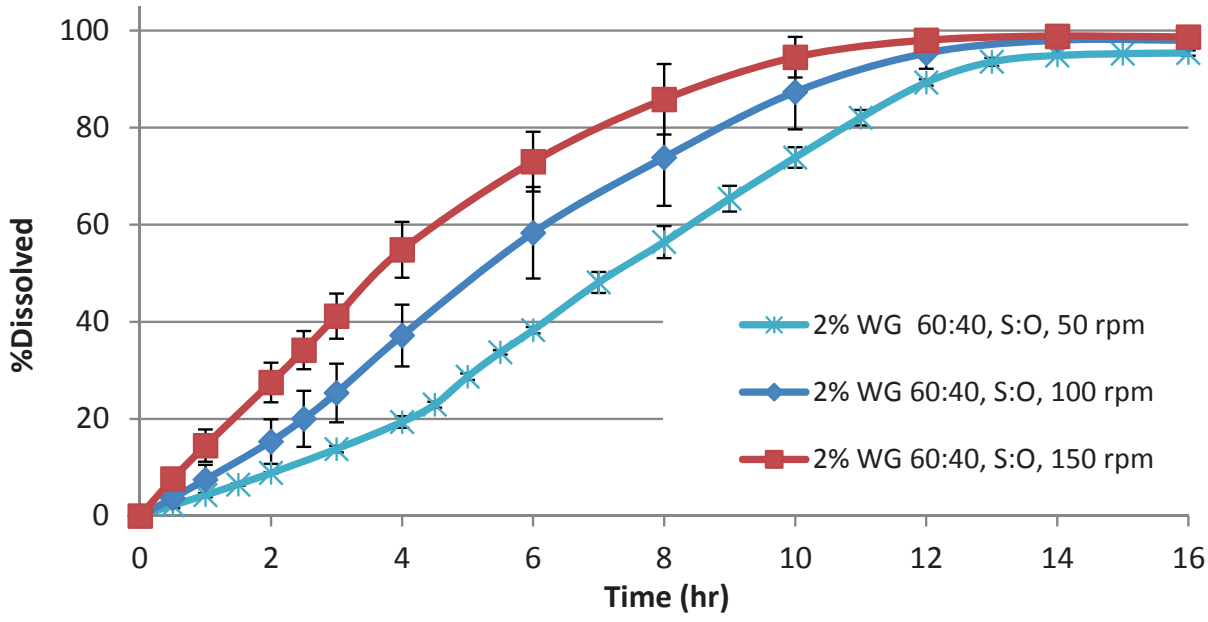
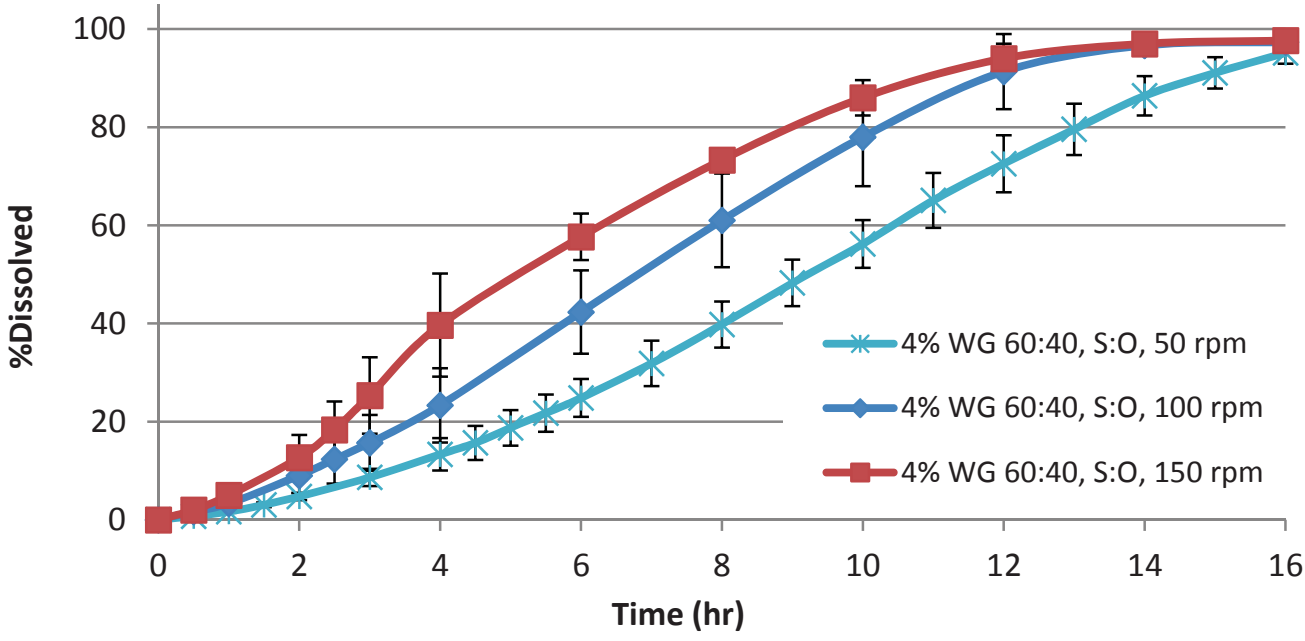


Figure 3. Dissolution Profile of HCTZ 200 mg ER Tablets Coated with BM Coating Consisting of Surelease® and Opadry® at 60:40 Ratio and 4% WG.



Conclusions

The application of a barrier membrane coating consisting of Surelease® and HPMC based Opadry® as a pore-former was found to be a useful approach for obtaining robust and consistent drug release profiles from hydrophilic matrices, which showed minimal sensitivity to agitation speed (hydrodynamic conditions) and possible food effect. Coating weight gain and level of pore-former in the BM coating were found to be critical in achieving consistent drug release profiles which may resist highly variable mechanical forces acting on matrix formulations in fed and fasted state.

References

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