Maintaining Similar Drug Release from Hypromellose Matrices with Identical Dimensions, but Different Dose Strengths

INTRODUCTION

During early phase of clinical trials it is often required to use blinded formulations with a range of drug doses. In order to eliminate any placebo effects associated with the visual and organoleptic properties of the solid dosage form, it is important that the tablets have identical appearance.[1&2]

The design of blinded extended release (ER) formulations with increasing dose of the active and similar drug dissolution is more challenging than for immediate release tablets, especially if the active concentration is greater than 10% w/w.

Hypromellose (hydroxypropyl methylcellulose, HPMC) is extensively used in the formulation of ER matrix systems, where the rate of drug dissolution is mediated by a hydrated gel layer on the surface of the tablet.[3] Factors such as polymer type and concentration, solubility of the active, polymer/drug ratio, choice of fillers and matrix size are critical factors affecting drug release rate.

The objective of this work was to develop ER formulations suitable for blinded early phase clinical trial studies using two model drugs.

MATERIALS AND METHODS

Six ER matrix formulations (Table 1) containing 30% w/w of HPMC as a drug release controlling polymer were developed using Colorcon HyperStart®, oral solid dose formulations service.[4] Chlorpheniramine maleate (CPM), a freely water soluble drug (1 in 4) and theophylline (TP), a slightly water soluble drug (1 in 120), were used as model actives. Formulations also contained combinations of lactose (soluble filler) and microcrystalline cellulose (insoluble filler); fumed silica as a flow aid and magnesium stearate as a lubricant.

When drug concentration was increased from 10% to 20% and 30% w/w, the amount of either soluble or insoluble filler was reduced accordingly in order to balance the ratio of soluble and insoluble components of each formulation.

Table 1. Formulations Used in this Study

Materials	Supplier	Concentration					
Chlorpheniramine maleate	Avocado Research Chemicals Ltd	10.0	20.0	30.0			
Theophylline	Knoll AG				10.0	20.0	30.0
Hypromellose 2208 (Methocel™ K4M CR)	Colorcon	30.0	30.0	30.0	30.0	30.0	30.0
Spray dried lactose (FastFlo)	Foremost	30.0	20.0	10.0	24.5	24.5	24.5
Microcrystalline Cellulose (Avicel PH102)	FMC	29.0	29.0	29.0	34.5	24.5	14.5
Fumed silica (Aerosil 200)	Degussa	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	Peter Greven	0.5	0.5	0.5	0.5	0.5	0.5
Total:		100.0	100.0	100.0	100.0	100.0	100.0

Lactose, microcrystalline cellulose (MCC) and fumed silica were screened together with one of the drugs through a 500 micron sieve and placed into a high-shear mixer (Model P1/6, Diosna); HPMC was added and blended for 3 minutes at 400 rpm impeller and 1000 rpm chopper speed. Magnesium stearate was then added and mixed for an additional 1 minute at 400 rpm impeller speed.

Tablets were manufactured using direct compression on an instrumented 10 station rotary tablet press (Piccola, Riva) fitted with 9 mm standard concave tooling, to a tablet weight of 333 mg and a breaking force of 10 kp.

Drug release testing was conducted using an automated dissolution bath (Sotax), Apparatus II (paddle method) at 100 rpm in 1000 mL of 37±1°C water with sinkers. A double beam spectrophotometer was utilized for online UV detection. CPM and TP concentrations were measured at wavelengths of 261 nm and 271 nm respectively.

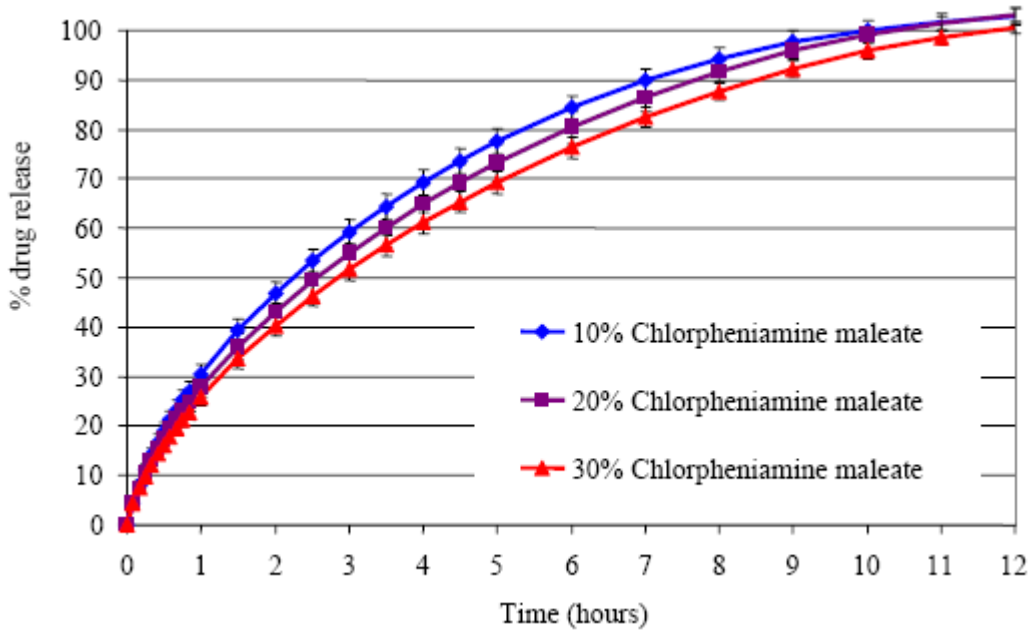
Dissolution profiles from the matrix formulations manufactured in this study were compared using f2 analysis.[5&6] A value of f2 between 50 and 100 indicates similarity between two dissolution profiles.

RESULTS AND DISCUSSION

All formulations produced robust tablets with a low tablet weight variation of less than 2% and breaking force in excess of 8 p.

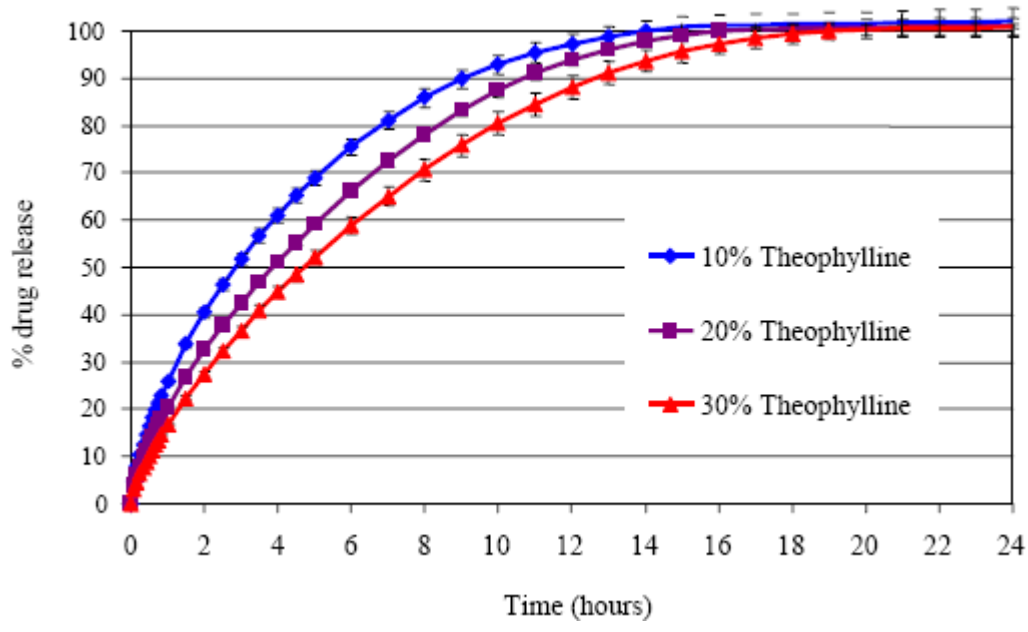
For the tablets containing chlorpheniramine maleate, where dissolution of the active occurs primarily through diffusion, altering the ratio of lactose to drug and maintaining a constant level of insoluble filler (MCC) produced almost identical release profiles (Figure 1). In these matrices the soluble filler acted essentially as a drug surrogate. Formulations containing 10 or 30% w/w CPM produced release profiles with f2 values of 74 compared to the profile for 20% w/w drug formulation indicating similarity.

Figure 1. Drug Dissolution from Chlorpheniramine Maleate ER HPMC Matrices



The theophylline matrices where drug release mechanism is more complicated and is mediated by both diffusion and erosion were more challenging to formulate. Combinations of soluble and insoluble fillers (Table 1) were employed in trying to achieve similar drug dissolution for the different dosage strengths. The drug release profiles from the HPMC matrices containing 10 and 30% w/w TP (Figure 2) produced f2 values of 52 to 55, respectively as compared to the 20% w/w TP formulation. These f2 values indicate borderline similarity.

Figure 2. Drug Dissolution from Theophylline ER HPMC Matrices



CONCLUSIONS

Extended release HPMC matrix formulations for CPM and TP (as model drugs) of identical size, shape and weight were developed based on the Colorcon HyperStart service. These matrices are suitable for blinded clinical studies where similar release profiles of different drug doses are required.

For the tablets containing 10, 20 and 30% w/w of a freely water soluble drug, where dissolution of the active occurs primarily through diffusion, altering the ratio of lactose to drug and maintaining a constant level of insoluble filler produced almost identical release profiles. In these matrices the soluble filler acted essentially as a drug surrogate.

ER matrices with 10, 20 and 30% w/w of a slightly water soluble drug, where release mechanism of the active is more complicated and is mediated by both diffusion and erosion, were more challenging to develop. Increasing amount of the active by simply reducing concentration of an insoluble filler in the formulation did not produce identical release profiles. For poorly soluble drugs therefore, additional work is needed that would take into account drug solubility and possibly matrix density, porosity and swelling parameters.

REFERENCES

1. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, Mcquay HJ. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Control. Clin. Trials. 17(1) (1996) 1-12.
2. Heejung B, Liyun N and Davis CE. Assessment of Blinding in Clinical Trials. Control. Clin. Trials. 25(2) (2004) 143-156.
3. Rajabi-Siahboomi AR and Jordan MP. Slow Release HPMC Matrix Systems. Eur. Pharm. Rev. 5 (2000) 21-23.
4. Colorcon technical literature, 2004.
5. Federal Register, Food and Drug Administration, Volume 60, No.230, 1995, p.61642.
6. Moore JW and Flanner HH, Mathematical Comparison of Dissolution Profile. Pharm. Tech., 20(6) (1996) 64-74.

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