Evaluation of StarCap 1500® as an Excipient in Extended Release Hydrophilic Matrix Systems

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Purpose

Hypromellose (hydroxypropyl methylcellulose, HPMC) and polyethylene oxide (PEO) are commonly used as rate-controlling polymers in formulations of hydrophilic matrix systems for oral extended release (ER) drug delivery due to their aqueous solubility, availability and broad regulatory acceptance.[1] Fillers are generally used in hydrophilic matrices to enhance pharmaco-technical properties of the tablets (improving compressibility, flow and/or mechanical strength) or to modify the drug release profile. Fillers in hydrophilic matrices may exert varying effects on controlled release characteristics of the system, depending on the drug, the polymer level and the level of filler itself. Lactose, microcrystalline cellulose, dicalcium phosphate and Starch 1500®, partially pregelatinized starch, are generally used as fillers in formulation of hydrophilic matrices. The objective of the present study was to evaluate the use of StarCap 1500, a unique co-processed mixture of globally accepted excipients, corn starch and pregelatinized starch, as an alternative filler in hydrophilic matrices of HPMC or PEO using different model drugs. For comparative purposes, commonly used fillers were also evaluated.

Methods

Formulations and Preparation of Matrix Tablets

Extended release HPMC matrix formulations of two model drugs, theophylline (TP) and chlorpheniramine maleate (CPM), at 30% w/w, were prepared using StarCap 1500, spray dried lactose or microcrystalline cellulose (MCC) as a filler at 49.25% w/w (**Table 1**). The ER PEO matrix formulations comprised metformin HCl (MFH) at 50% w/w and StarCap 1500 and/or MCC at 29% w/w (**Table 2**). Lactose was not used as a filler in PEO matrix formulations because of its reported impact on release profile during stability studies.[2] The rate controlling polymers, METHOCEL™, premium cellulose ethers, K4M Premium CR and POLYOX™, water soluble resins, WSR Coagulant, were used at 20% w/w, since higher levels of the polymers may mask differences in drug release caused by individual fillers.[3]

All ingredients, with the exception of magnesium stearate, were passed through an ASTM 30 mesh sieve and blended in a twin shell blender (Patterson Kelly, USA) for 10 minutes. Magnesium stearate was then added to the blender and mixed for up to 5 minutes (batch size, 1 kg). Tablets were manufactured on an instrumented rotary tablet press (Piccola, Riva, Argentina). HPMC matrix tablets were compressed using standard, round, concave tooling (9.5 mm) at the target weight of 333 mg and the compression forces of 4 kN-18 kN (compression pressure of 56 MPa-252 MPa). PEO matrix tablets (1000 mg) were compressed using caplet-shaped tooling (19.1 mm × 9.3 mm) at the compression forces of 20 kN-30 kN (compression pressure of 127 MPa-190 MPa).

Methods (cont'd)

Table 1. Composition of HPMC Matrix Tablets of Theophylline (TP) and Chlorpheniramine Maleate (CPM)

Ingredients	Composition (% w/w)					
	F1	F2	F3	F4	F5	F6
Theophylline (TP), Medilom, Belgium	30.00	30.00	30.00	-	-	-
Chlorpheniramine maleate (CPM), Mahrshee, India	-	-	-	30.00	30.00	30.00
METHOCEL K4M Premium CR, The Dow Chemical Co., USA	20.00	20.00	20.00	20.00	20.00	20.00
StarCap 1500, Colorcon, USA	49.25	-	-	49.25	-	-
Spray dried lactose, Fast Flo, Foremost Farms, USA	-	49.25		-	49.25	
Microcrystalline cellulose, Microcel 102, Blanver, Brazil,	-		49.25	-	-	49.25
Fumed silica, Aerosil A-200, Evonik Germany	0.50	0.50	0.50	0.50	0.50	0.50
Magnesium Stearate, Mallinckrodt,USA	0.25	0.25	0.25	0.25	0.25	0.25
Total	100.00	100.00	100.00	100.00	100.00	100.00

Table 2. Composition of PEO Matrix Tablets of Metformin Hydrochloride (MFH)

Ingredients	Composition (% w/w)		
	F7	F8	F9
Metformin hydrochloride (MFH), Wanbury, India	50.00	50.00	50.00
POLYOX WSR Coagulant, The Dow Chemical Co., USA	20.00	20.00	20.00
StarCap 1500, Colorcon, USA	29.00	-	14.50
Microcrystalline cellulose, Microcel 102, Blanver, Brazil,	-	29.00	14.50
Fumed silica, Aerosil A-200, Evonik Germany	0.50	0.50	0.50
Magnesium Stearate, Akros Holland	0.25	0.50	0.50
Total	100.00	100.00	100.00

Characterization of the Blends and Matrix Tablets

Formulations were evaluated for bulk and tapped densities (VanKel Industries, USA), powder flow using a vibratory funnel-type powder flowability tester (Sotax, USA) and loss on drying (LOD) (IR- 200, Denver Instrument Company, USA). All tablets were examined for physical properties including weight variation, thickness, hardness (Multicheck, Erweka, Germany), and friability (VanKel Industries, USA). Drug release was measured in deinoized water (900 mL for TP and CPM matrix tablets and 1000 mL for MFH matrices) using USP apparatus II (paddles) at 100 rpm and 37 ± 0.5°C (n = 6). For each model drug, the similarity factors (f_2) were calculated by comparing release profiles of tablets comprising different fillers prepared at similar compression forces[4] and using the release profiles of tablets comprising StarCap 1500 as references. In addition, the release exponent (n) and release rate constant (k) were calculated by fitting the dissolution data to the Power Law equation: $(M_t / M_{inf} = kt^n)$.[5]

Results

The physical properties of the formulations are shown in **Table 3**. Results indicated that formulations containing StarCap 1500 as filler exhibited comparable or better powder flow properties than lactose or MCC formulations. StarCap 1500 formulations also showed higher LOD values, which could be explained by its relatively high moisture content. The LOD of the neat excipients, StarCap 1500, lactose and MCC, were 8.9, 4.9 and 4.9%, respectively. The compressibility indices of the formulations were in the range of 17%-24%, indicating good to acceptable powder flow.

Table 3. Physical Properties of Formulations

Drug	Polymer	Batch/Fillers	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Sotax Flow (g/sec)	LOD (%w/w)
Theophylline	HPMC	F1- StarCap 1500	0.48	0.62	22	6.7	5.7
		F2- Lactose	0.56	0.71	22	7.2	1.2
		F3- MCC	0.42	0.55	24	6.1	3.1
Chlorpheniramine maleate		F4- StarCap 1500	0.53	0.67	21	5.1	5.9
		F5- Lactose	0.56	0.69	18	6.5	1.3
		F6- MCC	0.45	0.58	23	5.5	2.6
Metformin HCl	PEO	F7- StarCap 1500	0.60	0.72	17	12.2	3.0
		F8- MCC	0.53	0.66	22	9.1	1.3
		F9- StarCap 1500 + MCC	0.57	0.68	18	11.2	2.0

The comparative tablet physical properties are presented in **Table 4**. All tablet formulations showed low weight variation (<1%), also indicating acceptable powder flow. Use of lactose as a filler resulted in the highest ejection forces. For all matrix tablets, the friability values were below 0.5%. Use of MCC as a filler resulted in higher mechanical strength of the tablets. In all instances, mechanical strength of the tablets increased with increasing compression force. Blending of MCC with StarCap 1500 aided in enhancement of mechanical strength of the PEO matrix tablets.

Table 4. Physical Properties of Matrix Tablets*

Drug	Polymer	Batch/Fillers	Weight Variation (%)	Hardness (kp)	Hardness (MPa)	Friability (%)
Theophylline	HPMC	F1- StarCap 1500	0.5	9.9 ± 0.5	2.33	0.0
		F2- Lactose	0.7	14.8 ± 0.5	3.59	0.0
		F3- MCC	0.9	16.0 ± 0.8	3.88	0.0
Chlorpheniramine maleate		F4- StarCap 1500	0.3	8.3 ± 0.3	2.02	0.0
		F5- Lactose	0.2	18.4 ± 0.8	4.77	ND
		F6- MCC	0.5	18.4 ± 0.4	4.67	0.0
Metformin HCl	PEO	F7- StarCap 1500	0.4	10.4 ± 0.8	0.86	0.5
		F8- MCC	0.4	15.7 ± 0.6	1.34	0.3
		F9- StarCap 1500 + MCC	0.5	13.0 ± 0.6	1.11	0.2

*n = 20 except for batch F5, where n = 5, as tablets were compressed manually due to high ejection force. Theophylline and chlorpheniramine maleate tablets were compressed at 14 kN, whereas metformin HCl tablets were compressed at 30 kN.
ND = not determined

Dissolution profiles for theophylline and chlorpheniramine maleate HPMC matrix tablets are shown in **Figure 1**, and release profiles for metformin HCl PEO matrix tablets are shown in **Figure 2**. Regardless of the filler type, all tablet formulations exhibited extended drug release properties. In the case of HPMC matrices, use of lactose as a filler resulted in faster release rate, which could be attributed to its solubility, although the drug release profiles were similar to StarCap 1500 formulations by f_2 criterion (f_2 = 52 for TP and 78 for CPM). Use of MCC, an insoluble filler, also resulted in a drug release profile similar to that of StarCap 1500 formulations (f_2 = 77 for TP and 64 for CPM). For PEO formulations, use of MCC or a blend of MCC with StarCap 1500 resulted in drug release profiles similar to that of the StarCap 1500 formulation with f_2 values of 93 and 94, respectively. In addition, drug release data for all formulations presented a suitable fit ($R^2 \geq 0.99$) to the Power Law Equation with release exponent, n values, ranging from 0.59-0.69, indicating a combination of diffusion and erosion mechanisms for drug release.

Figure 1. Drug Release Profiles for Theophylline and Chlorpheniramine Maleate HPMC Matrix Tablets (Dissolution Study was Conducted using USP Apparatus II, 100 rpm and 900 mL of Deionized Water)

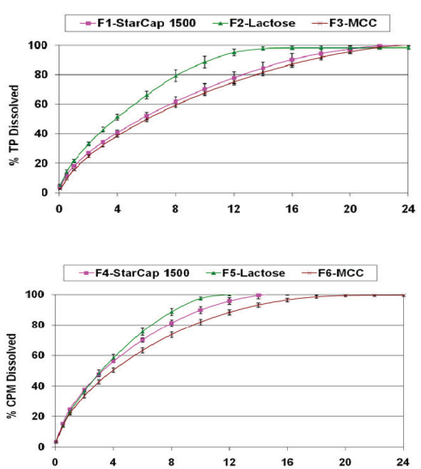
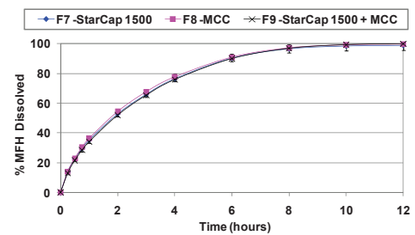


Figure 2. Drug Release Profiles for Metformin HCl PEO Matrix Tablets (Dissolution Study was Conducted Using USP Apparatus II, 100 rpm with Sinkers and 1000 mL of Deionized Water)



Conclusions

The results demonstrated that StarCap 1500 was successfully used as alternative filler in formulation of ER HPMC and PEO matrix tablets. This was true regardless of drug type and dose level. Inclusion of StarCap 1500 in the matrix formulations resulted in comparable or superior powder flow properties when compared to formulas comprising traditionally used fillers such as lactose or MCC. Drug release profiles of all ER formulations with StarCap 1500 as filler were similar to those containing traditionally used fillers such as lactose or microcrystalline cellulose.

References

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