Investigation of a Directly Compressible Metformin HCl 500mg Extended Release Formulation Based on Hypromellose

ABSTRACT SUMMARY

Extended release (ER) formulation of metformin hydrochloride (HCl) presents the formulator with significant challenges due to its poor inherent compressibility, high dose and high water solubility. This study investigates the possibility for development of a direct compression ER matrix tablet using hypromellose.

Keywords: metformin, hypromellose, extended release

INTRODUCTION

There is a continuously growing interest in the pharmaceutical industry for ER oral drug delivery systems. There is also a high interest for design of dosage formulations that allow high drug loading, particularly for actives with high water solubility.

Metformin HCl is an anti-diabetic agent which is prescribed for the treatment of non-insulin dependent diabetes mellitus.[1] The primary benefit of extended release preparations of metformin HCl compared to an immediate release formulation is that a more uniform maintenance of blood plasma active concentration is achieved. Thus, potentially avoiding undesirable peaks and troughs associated with multiple immediate release preparations.

The application of hypromellose (HPMC) in ER tablets is widely studied.[2] When in contact with aqueous solvent, HPMC hydrates rapidly and forms a gel barrier layer around the tablet. The rate of drug release from HPMC matrices is dependent on numerous factors such as type of polymer, drug, polymer/drug ratio, particle size of drug and polymer, and the type and amount of fillers used in the formulation.

Metformin HCl has poor compressibility, and high water solubility (1 in 2). Direct compression of a tablet formulation is preferred in the industry over wet granulation, due to its simplicity, fewer steps, lower cost and faster development time. In this study, the development of direct compression extended release metformin HCL (500mg) tablets using HPMC was investigated.

EXPERIMENTAL METHODS

Table 1 shows that all studied formulations contained 50% w/w metformin HCl (Ferico Labs), 0.5% w/w fumed silica (Aerosil 200) and 0.5% magnesium stearate (Peter Greven). Two grades of hypromellose, METHOCEL™, premium cellulose ethers, K4M CR and METHOCEL™ K100M CR, were used as matrix formers at 30 or 35% w/w. Microcrystalline cellulose (MCC, Avicel PH102) was used as a water-insoluble filler at 14 or 19% w/w.

MCC and fumed silica were passed through a 500ì m sieve. All ingredients with the exception of magnesium stearate were blended in a Turbula mixer for 5 minutes. Then magnesium stearate was added and the formulation was mixed for an additional 2 minutes.

Table 1 – Metformin HCl (500mg) ER Formulations

Materials	Concentration (% w/w)		
	1	2	3
Metformin	50.0	50.0	50.0
METHOCEL™ K4M CR	30.0		
METHOCEL™ K100M CR		30.0	35.0
MCC	19.0	19.0	14.0
Fumed Silica	0.50	0.50	0.50
Magnesium Stearate	0.50	0.50	0.50

Tablets with a target weight of 1000mg and target breaking force of 20 kp were manufactured using an instrumented 10 station rotary Piccola press (Riva, Argentina), fitted with 7x18mm caplet tooling. Tablet ejection forces, weights, breaking force and friability values were determined.

The matrix formulations (Table 1) were compared to a commercially available ER metformin tablets, Glucophage* (500mg) XR (Bristol- Myers Squibb).

Drug release profiles were determined using USP compliant dissolution bath (Vankel), Apparatus II (paddle method) with sinkers. The dissolution media was 1000ml of purified water (37±1°C) with a paddle speed of 100rpm. A dual beam spectrophotometer (Agilent), fitted with 0.1mm cells, was used for detection of metformin HCl at a wavelength of 233nm.

RESULTS AND DISCUSSIONS

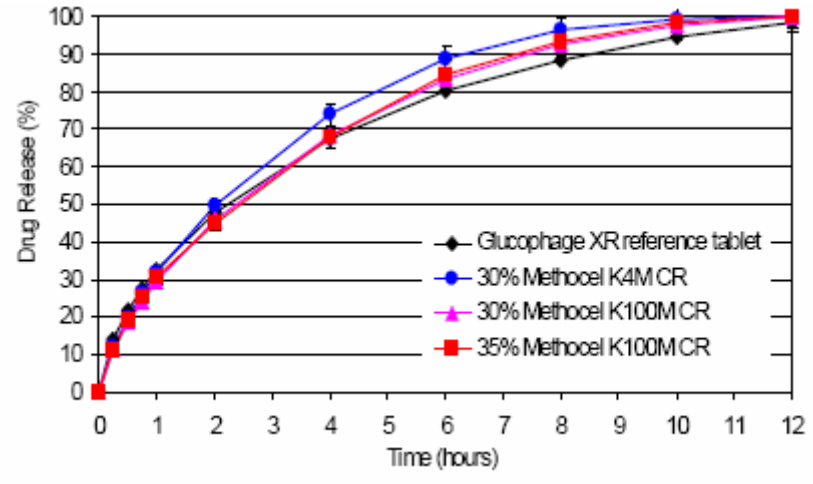
All formulations under investigation here had good powder flow indicated by low value of Carr's index and resulting in low tablet weight variation (Table 2). Ejection forces for all tablets were relatively low indicating sufficient lubrication of powder blends. Tablet breaking force values of approximately 20-21 kp and low friability (0.15% or less) were produced.

Figure 1 shows drug release from the three test formulations and the reference product Glucophage (500mg) XR. All four dissolution profiles appear to be similar.

Table 2. Manufacturing and Tablet Parameters

Formulation	Glucophage Tablets	1	2	3
Carr's Index (%)	N/A	18	18	22
Pre-compr. Force (kN)	N/A	2.0 0.1	1.9 0.1	2.8 0.1
Main compr. Force (kN)	N/A	27.7 1.9	19.6 1.3	20.4 0.8
Ejection Force (N)	N/A	312 45	277 33	270 12
Tablet Weight (mg)	1021 5	998 16	1014 8	1014 8
Tablet Weight Variation (%)	0.50	1.56	0.74	0.82
Tablet Break. Force (kp)	18.7 1.2	21.3 1.5	20.8 1.5	20.1 1.6
Tablet Friability (%)	0.01	0.15	< 0.01	0.15

Figure 1. Metformin HCl Dissolution Profiles



The molecular weight of the HPMC polymer in a matrix tablet, and therefore apparent viscosity of the hydrated polymer, is important in determining the drug-release properties. It is generally accepted that drug dissolution from tablets is slower for higher viscosity grades of HPMC polymers. However, in this study similar metformin release rates were observed for tablets containing 30% of METHOCEL™ K4M CR or 30% of METHOCEL™ K100M CR despite differences in polymer molecular weight. The same was reported in literature [3, 4, 5] where it was claimed that drug release from formulations containing METHOCEL™ K4M, K15M or K100M may not significantly differ for a highly water soluble drug. The mechanism of drug release in these formulations is mainly governed by diffusion and as the drug is so highly soluble, polymer viscosity grade did not significantly affect the diffusion rate. However, when considering *in vivo* behavior of these systems, the erosion rate will also become important (in comparison to the dissolution testing conditions) and thus a higher viscosity grade may produce a more robust formulation.

In general, slower release may be achieved with higher polymer levels or higher viscosity grade of HPMC in the formulation. This is mainly due to the longer period of time required to reach the disentanglement concentration at the tablet surface, which in turn equates to greater resistance to surface erosion. Such phenomenon is more significant in the gastro-intestinal tract where the attrition on the hydrated surface of the matrix is greater. This is because drug release does not result solely from diffusion of the active through the hydrated polymer, but also from polymer erosion leading to a thinner hydrated gel layer i.e. shorter diffusional path for drug release.

In summary, formulation 2 with 30% METHOCEL™ K100M CR produced the desired release profile (similar to Glucophage XR) with: good powder flow, lowest compression force (19.6 kN), 0.74% of tablet weight variation and friability below 0.01%.

CONCLUSIONS

Consistent and robust extended release metformin HCl (500mg) matrix tablets, using hypromellose (METHOCEL™ K100M CR) were produced by direct compression. 30%w/w inclusion of the controlled release polymer in the formula resulted in drug release profile similar to the Glucophage XR (500mg) tablet.

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