Formulation of POLYOX™ ER Matrices for a Highly Soluble Active

APPLICATIONS DATA SUMMARY

- POLYOX™, water soluble resins (WSR), can be used as an alternative to HPMC in ER matrix tablets.
- PEO formulations investigated in this study with metformin HCl produced tablets with low weight variation; high breaking force and low friability values at compression forces of 15 and 20 kN.
- To produce a 12-hour release profile for the freely soluble drug metformin HCl, high viscosity grades of PEO should be used at approximately 30% w/w in the formulation. Similar drug release rates were obtained for WSR-301, WSR-303 and METHOCEL™ K100M CR ER tablets.
- In order to guarantee a robust PEO matrix, at least 20% of polymer should be included in the formulation.

INTRODUCTION

Hydrophilic matrices represent a popular and widely used approach for oral extended release (ER) drug delivery. Hypromellose (HPMC) remains the polymer of choice as the release rate-controlling component.[1] In addition to HPMC, polyethylene oxide (PEO) has been extensively studied as a matrix-forming polymer. This is mainly attributed to its availability in a range of molecular weight/viscosity grades, FDA acceptance and unique swelling/erosion characteristics, which can be utilized for modulating drug release.[2, 3] PEO polymers are available commercially under the trade name of POLYOX™.

Metformin hydrochloride is an oral anti-hyperglycemic (anti-diabetic) agent used in the first-line treatment of non-insulin dependent diabetes mellitus.[4] The primary benefit of an extended release (ER) preparation of metformin HCl, compared to an immediate release (IR) formulation, is a uniform blood plasma concentration and, therefore, a uniform clinical effect. This potentially avoids undesirable peaks and troughs associated with multiple immediate release doses. ER preparations also reduce gastric side effects associated with IR formulations of metformin.
Metformin HCl presents formulation challenges due to its poor inherent compressibility, high dose and high water solubility (> 300 mg/mL at 25°C). Previously published by Colorcon, studies investigated the development of ER matrix tablets using HPMC as a matrix former.[5]

The objective of this study was to develop a 12-hour extended release, hydrophilic POLYOX™ matrix formulation of metformin HCl 500 mg and to evaluate the effect of formulation variables such as polymer molecular weight and polymer concentration. The results were compared to the data produced with metformin HCl HPMC ER matrices.

MATERIALS AND METHODS

Formulation & Manufacture of ER Matrices

The effect of polymer molecular weight on PEO performance in the ER matrix was evaluated by using three grades of POLYOX™ (Table 1). Table 2 shows details of the ER matrix formulations used in the study.

Table 1. POLYOX™ Materials Tested in the Study

	Approximate molecular weight	Viscosity range at 25ºC (cP)	
		5% solution in water	1% solution in water
WSR-1105 LEO	900,000	8,800 – 17,600	
WSR-301 LEO	4,000,000		1,650 – 5,500
WSR-303 LEO	7,000,000		7,500 – 10,000

Table 2. ER Matrix Formulations

Material	Supplier	% w/w	mg/tablet
Metformin HCl	AMRI, India	50.0	500
PEO (POLYOX™ WSR-1105 LEO, or WSR-301 LEO, or WSR-303 LEO) or HPMC (METHOCEL™ K100M CR)	Colorcon, USA	30.0	300
Microcrystalline cellulose (Microcel 102)	Blanver, Brazil	19.0	190
Fumed silica (Aerosil 200)	Evonik, Germany	0.5	5
Magnesium stearate	Peter Greven, UK	0.5	1
Total		100.0	1000

A hydrophilic polymer such as PEO rapidly hydrates and produces a gel barrier around the outer part of the matrix. The high water solubility of metformin HCl can result in rapid drug dissolution when small amounts of water in the gel layer are present. Consequently, rapid drug diffusion through the gel into the surrounding medium can occur. For this reason, a water-insoluble filler, microcrystalline cellulose (MCC 90 μm) was used to counter balance the high water solubility of the active.

Microcrystalline cellulose and fumed silica were screened together through a 35-mesh (500 μm) sieve. All ingredients except magnesium stearate were then blended in a Turbula (Type T2 C, Willy A. Bachofen, Switzerland) shaker mixer at 30 rpm for 5 minutes. Magnesium stearate was finally added, and the formulation was blended for an additional 1 minute.

The effect of polymer concentration on drug release from PEO matrices was evaluated using PEO WSR-1105 at 5%, 10%, 20%, 30%, 40% and 49% w/w in the formulation with 50% w/w metformin HCl (50% w/w), 0-44% w/w MCC qs, 0.5% fumed silica and 0.5% w/w magnesium stearate.

Tablets with a target weight of 1000 mg were manufactured by direct compression using a 10-station rotary Piccola (Riva, Argentina) press, fitted with 7 x 18 mm caplet tooling; and operated at 20 rpm and 5 kN, 10 kN, 15 kN and 20 kN compression force.

Testing of Tablet Physical Properties

Tablet breaking force values were determined using a tablet hardness tester (Schleuniger, Germany). Tablet friability was determined using a friability tester (Copley, UK) rotating at 25 rpm for 4 minutes.

Drug Dissolution Testing

Drug release was measured in an AT7 (Sotax, UK) dissolution bath at 100 rpm using USP Apparatus II (paddles) and 2.38 mm (8-mesh) stationary quadrangular baskets (QBs)[6] from Quality Lab Accessories (USA), which were positioned within the dissolution vessel perpendicular to, and 3 cm above, the shaft of the paddle.

The dissolution medium was 1000 mL of purified water at 37.0 ± 0.5ºC. Samples were analyzed with a dual beam spectrophotometer (Perkin Elmer, USA) using 0.1 mm quartz cells at a wavelength of 233 nm. Measurements at each time point were performed in triplicate, and the mean and standard deviation (SD) values were calculated. Purified water was used as a reference.

Drug release was determined for PEO and HPMC matrices manufactured at 20 kN compression force.

RESULTS AND DISCUSSION

Tablet Physical Properties

Weight variation for all manufactured matrices was found to be less than 2% indicating acceptable formulation powder flow (Figure 1).

Figure 1. Tablet Weight Variation for the Formulations Described in Table 2 (n = 20)

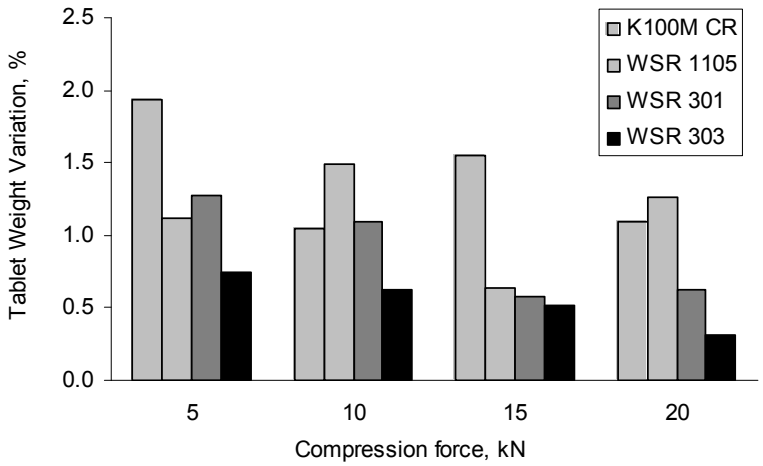


Figure 2 shows the tablet breaking forces for the formulations described in Table 2. Similar values were produced for all three grades of PEO. Tablet mechanical strength increased from approximately 3 kp to 9 kp, 15 kp and 20 kp with an increase in compression force from 5 kN to 10 kN, 15 kN and 20 kN respectively. The HPMC formulation produced the strongest tablets with breaking force values of up to 32 kp.

Figure 2. Tablet Breaking Force Values for the Formulations Described in Table 2 (n = 20)

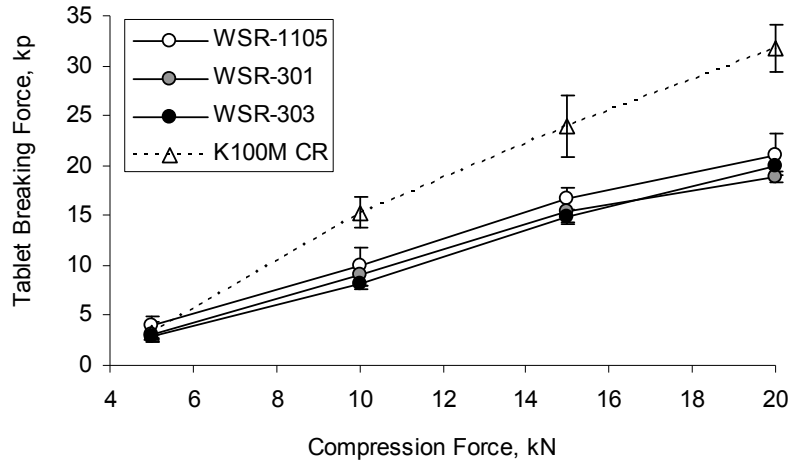
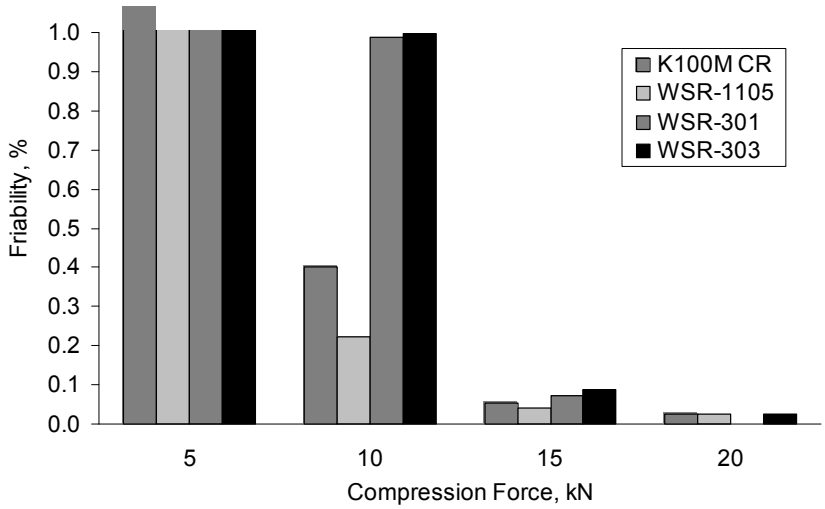


Figure 3 shows tablet friability for all four formulations (Table 2). Acceptably low values of less than 0.1% were obtained at compression forces of 15 kN and 20 kN.

Figure 3. Tablet Friability Values for the Formulations Described in Table 2



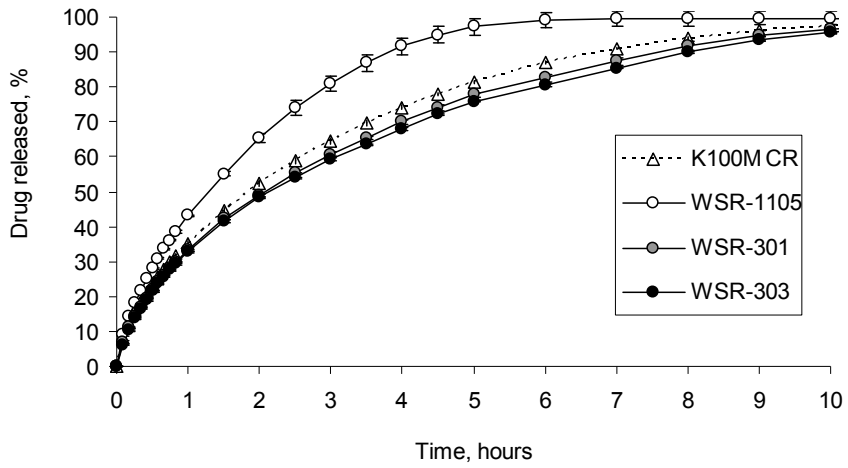
Effect of Polymer Molecular Weight on Drug Release

All three formulations generated reproducible first-order drug release profiles (Figure 4). The graph shows that with an increase in molecular weight of POLYOX™ from 900,000 to 4,000,000, metformin HCl release rate was significantly reduced. An increased molecular weight leads to a greater degree of polymer chain

entanglement and an increase in gel strength, which tends to decrease the rate of diffusion of the drug. There is however, a maximum molecular weight beyond which no further change in release rate occurs. As can be seen from the graph, an increase in PEO molecular weight from 4,000,000 to 7,000,000 did not significantly alter the release rate of the water soluble active.

Drug release from the K100M CR formulation was comparable to the dissolution data produced with the WSR-301 and WSR-303 formulations.

Figure 4. Metformin HCl Release Profiles from PEO ER Matrices (n = 6)



Effect of Polymer Concentration on Drug Release

A sufficient polymer concentration in the hydrophilic matrix system is required to form a uniform gel barrier around the tablet upon hydration. This barrier is expected to prevent the drug from immediate release into the dissolution medium. If the polymer concentration is too low, a complete gel layer may not form resulting in a significant amount of drug being released too quickly or in the worst case, tablet disintegration.[7] Figure 5 shows that an increased PEO level in the formulation resulted in a decreased drug release rate. It can be seen that polymer concentrations of less than 20% are insufficient to produce adequate extended release of metformin HCl.Similar results were reported by IFF for HPMC ER matrices.

A further increase in PEO concentration from 20% to 40% resulted in a slower drug release profile. This effect of slower metformin HCl release for higher polymer level is due to the longer period of time required to reach the polymer chain disentanglement concentration at the tablet surface, which in turn equates to greater resistance of the matrix to surface erosion.[9-12]

There appears to be a threshold level of drug release rate retardation that was achievable, beyond which, an increase in PEO level (from 40% to 49%) did not result in further decrease in metformin HCl dissolution rate. This is because drug release does not occur only by PEO gel layer erosion, but also from drug diffusion through the hydrated polymer layer.

Figure 5. Effect of Polymer (Polyox WSR-1105) Concentration on Metformin HCl release (n = 3)

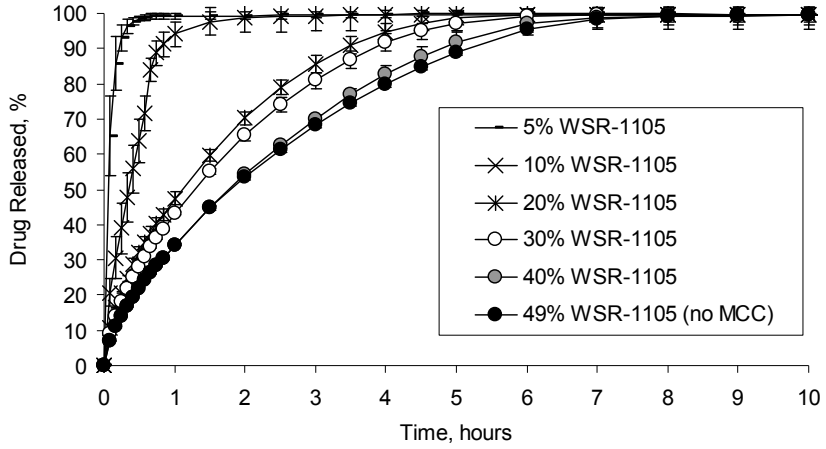


Figure 4 also shows that an increase in PEO concentration resulted in lower standard deviation values, potentially leading to a more robust matrix formulation. More polymers in the formulation means more polymers on the tablet surface and, thereby, more reliable barrier gel layer formation.

CONCLUSIONS AND RECOMENDATIONS

POLYOX polymers can be used as an alternative to HPMC in ER matrix tablets.

PEO formulations investigated in this study with metformin HCl produced tablets with low weight variation; high breaking force and low friability values at compression forces of 15 kN and 20 kN.

To produce a 12-hour release profile for the freely soluble drug metformin HCl, high viscosity grades of PEO should be used at approximately 30% w/w in the formulation. Similar drug release rates were obtained for WSR-301, WSR-303 and METHOCEL™ K100M CR ER tablets.

In order to guarantee a robust PEO matrix, at least 20% of polymer should be included in the formulation.

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