

Dissolution Testing for POLYOX™ Extended Release Matrices

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 rate-controlling carrier.¹ In addition to HPMC, POLYOX™, water soluble resins, (polyethylene oxide; PEO) has more recently been studied as a matrix-forming polymer. This is mainly attributed to its availability in a range of molecular weight/viscosity grades, wide regulatory acceptance and unique swelling and erosion characteristics, which are utilized for modulating release of drugs with different solubility and doses.^{2,3}

When in contact with water, PEO hydrates rapidly and forms a gelatinous barrier layer around the wetted tablet. Drug release occurs by diffusion of the active through the gel layer and/or by gradual erosion of the gel, exposing fresh surfaces containing drug to the dissolution medium. Diffusion is the dominant mechanism controlling the release of water-soluble actives, and erosion of the matrix is the dominant mechanism controlling the release of water-insoluble actives. Typically, however, drug release occurs by a combination of these two mechanisms.

The rates of wetting, swelling and erosion are controlled by polymer molecular weight. POLYOX™ is the commercially available polyethylene oxide in a range of molecular weights for hydrophilic ER matrix systems.

The *in vitro* drug release from hydrophilic matrix tablets may be affected by various factors¹ and is often dependent on the hydrodynamic conditions used during dissolution testing. Different dissolution apparatus operated at varying agitation intensities create different hydrodynamics.⁴ This causes varying degrees of mechanical stress on the hydrated matrix, which may lead to alterations of polymer erosion rate.

The objective of this study was to investigate the influence of different dissolution methods and hydrodynamic conditions in the dissolution vessel on the release of a high solubility drug, metformin hydrochloride (metformin HCl), from an ER matrix formulation containing PEO as the rate-controlling polymer.

MATERIALS AND METHOD

Formulation & Manufacture of ER Matrices

A formulation containing 50% w/w metformin HCl (AMRI, India) as a freely water soluble model drug, 30% w/w PEO (POLYOX WSR-1105, IFF, USA), 19% w/w microcrystalline cellulose (Microcel 102,

Blanver, Brazil), 0.5% w/w fumed silica (Aerosil 200, Evonik, Germany) and 0.5% w/w magnesium stearate (Peter Greven, UK) was prepared.

Microcrystalline cellulose (MCC) and fumed silica were screened together through a 35 mesh (500 µm) sieve. All ingredients except for the magnesium stearate were then blended in a Turbula mixer (Switzerland) for 5 minutes. Magnesium stearate was finally added, and the formulation was blended for an additional 1 minute.

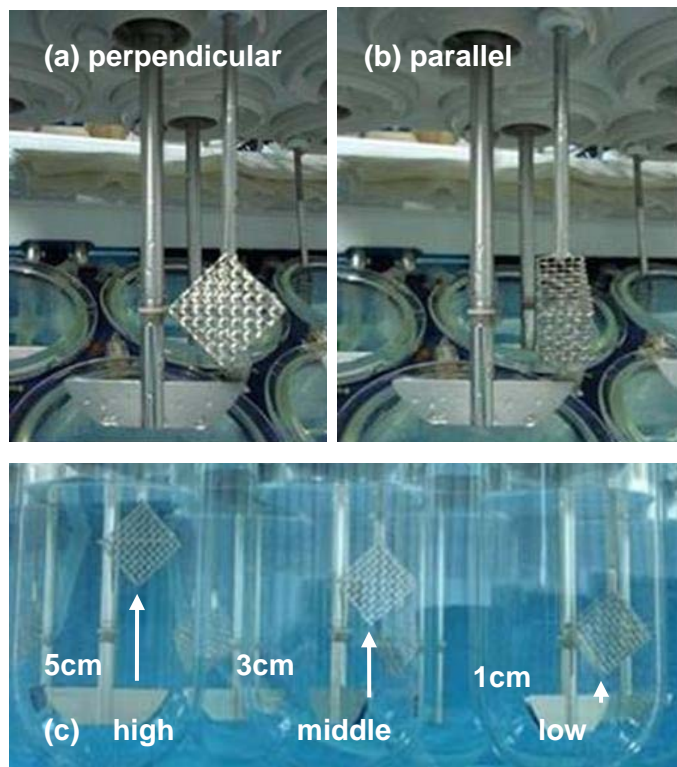
Tablets with a target weight of 1000 mg were manufactured by direct compression using a 10-station rotary Piccola press (Riva, Argentina), fitted with 7 x 18 mm caplet tooling and operated at 20 rpm and 20 kN compression force.

Drug Dissolution Testing

Drug release was measured in an AT7 (Sotax, UK) dissolution bath at 50, 100, 150 & 200 rpm using a range of dissolution techniques:

- USP I (baskets)
- USP II (paddles)
- USP II (paddles) with sinkers (11x31 mm, Sotax)
- 2.38 mm (8-mesh) stationary quadrangular baskets (QBs)⁵ from Quality Lab Accessories (USA) and positioned within the dissolution vessel using the following configurations:
- Perpendicular or parallel to the shaft of the paddle (Figure 1a & 1b)
- In a low, middle or high position (i.e. 1, 3, or 5 cm) above the paddle (Figure 1c)

Figure 1: Position of QBs in the dissolution vessel relative to the paddle



The dissolution medium was 1000 mL of purified water at $37.0 \pm 0.5^\circ\text{C}$. 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 mean and standard deviation (SD) values were calculated. The dissolution results generated were compared using the f_2 factor.^{6,7} An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar.

RESULTS AND DISCUSSION

Reproducible first-order drug release profiles were obtained for all dissolution testing methods used in this study (Figure 2).

Figure 2 shows that metformin HCl release from PEO matrices was slightly, but not significantly, faster when QBs ($f_2 = 57$) or paddles with sinkers ($f_2 = 62$) were used, as compared to paddles without sinkers or USP baskets, all tested at 100 rpm.

The use of QBs resulted in the most reproducible results with SD values of less than 1.3%. The USP II (paddles) method resulted in the highest SD values of up to 7%. This can be explained by the fact that some PEO matrices were found to stick to the bottom of the dissolution chamber or float onto the surface of the dissolution medium, resulting in a variable drug release.

Figure 2: The influence of dissolution method on metformin HCl release from PEO ER matrices (100 rpm)

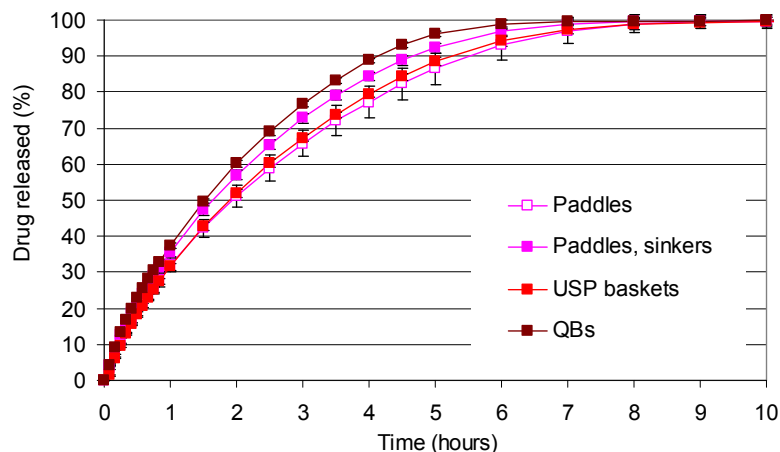


Figure 3 shows that the position of the QBs relative to the shaft of the paddle had no significant effect on drug release from PEO matrices ($f_2 = 80$).

Additionally, positions of the QBs 3 cm or 5 cm above the paddle resulted in a slightly faster metformin HCl release compared to the lower position of 1 cm with f_2 values of 57 and 60 respectively (Figure 4). These results confirm one of the findings of McCarthy et al (2003)⁸, that an area of relatively low fluid velocity exists just above the paddle, resulting in a slightly slower drug release.

Figure 3: The influence of QBs position relative to the shaft of the paddle on metformin HCl release from PEO ER matrices (100 rpm)

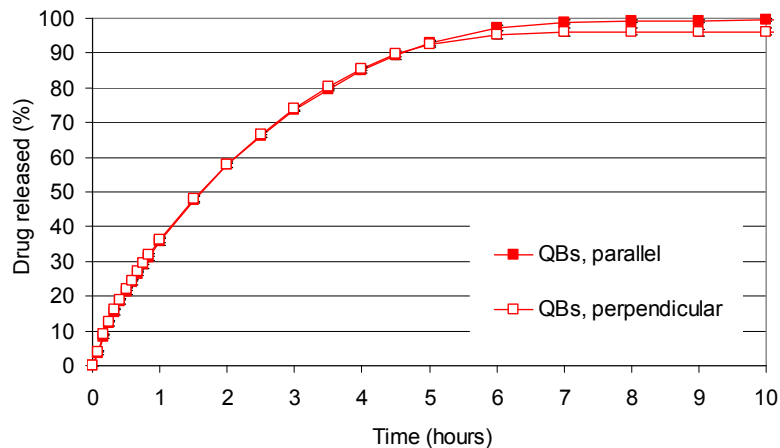
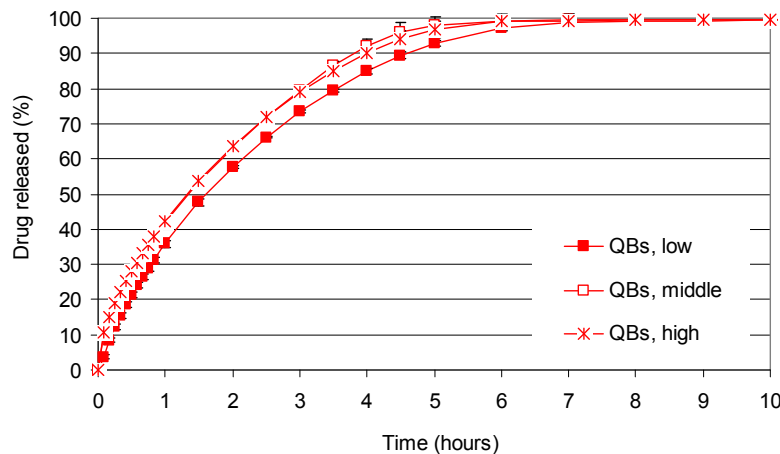
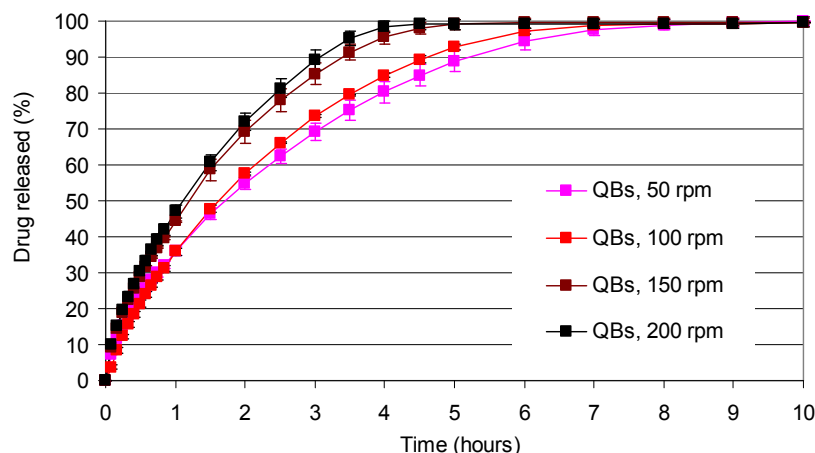


Figure 4: The influence of QBs position above the paddle on metformin HCl release from PEO ER matrices (100 rpm)



Drug release from hydrophilic matrices is controlled by diffusion through the gel layer and erosion of the gel at the tablet surface. For metformin HCl, a water soluble compound, the rate of release from the matrix is determined predominantly by diffusion. Drug release from such formulations is often independent of the hydrodynamic conditions within the dissolution vessel. For the manufactured PEO ER tablets however, drug release was faster from matrices placed in QBs when higher paddle rotational speeds of 100 rpm ($f_2 = 72$), 150 rpm ($f_2 = 50$) and 200 rpm ($f_2 = 46$) were employed, compared to 50 rpm (Figure 5). This may be explained by the fact that a polymer with relatively low molecular weight and viscosity was used in this study, and therefore, faster erosion may be expected under increased agitation intensity.

Figure 5: The influence of paddle speed on metformin HCl release from PEO ER matrices using quadrangular baskets



CONCLUSIONS

Reproducible first-order metformin HCl release profiles were obtained using POLYOX™ as a matrix former, for all dissolution testing methods used in this study.

Metformin HCl release from PEO matrices was slightly, but not significantly, faster when QBs ($f_2 = 57$) or paddles with sinkers ($f_2 = 62$) were used, as compared to paddles without sinkers or USP baskets.

The position of the QBs relative to the shaft of the paddle had no significant effect on drug release from PEO matrices ($f_2 = 80$). Additionally, positions of the QBs 3 cm or 5 cm above the paddle resulted in a slightly faster metformin HCl release compared to the lower position of 1 cm with f_2 values of 57 and 60 respectively. Drug release was found to be faster from matrices placed in QBs when higher paddle rotational speeds of 100 rpm ($f_2 = 72$), 150 rpm ($f_2 = 50$) and 200 rpm ($f_2 = 46$) were used compared to 50 rpm.

The use of QBs resulted in the most reproducible dissolution results with SD values of less than 1.3%. Therefore, it is recommended to use quadrangular baskets, wherever possible instead of USP I (basket) and USP II (paddles), or alternatively using USP II with sinkers, for *in vitro* drug dissolution testing from hydrophilic matrix tablets based on POLYOX™.

REFERENCES

1. Levina M., Rajabi-Siahboomi A.R., 2006. Application of a modeling system in the formulation of extended release hydrophilic matrices. Pharm. Tech. Eur., 18(7), 20-26.
2. Choi S.U., Lee J., Choi Y.W., 2003. Development of a directly compressible poly(ethylene oxide) matrix for the sustained-release of dihydrocodeine bitartrate. Drug Dev. Ind. Pharm., 29, 1045-1052.
3. Li H., Hardy R.J., Gu X., 2008. Effect of drug solubility on polymer hydration and drug dissolution from polyethylene oxide (PEO) matrix tablets. AAPS PharmSciTech, 9(2), 437-443.
4. Costa P., Sousa Lobo J.M., 2001. Influence of dissolution medium agitation on release profiles of sustained-release tablets. Drug Dev. Ind. Pharm., 27(8), 811-817.
5. USP 27/NF 22, 2004, p. 779.
6. Moore J.W. and Flanner H.H., 1996. Mathematical comparison of curves with an emphasis on in-vitro dissolution profiles. Pharm. Tech., 20(6), 64-74.
7. FDA, Federal Register, Volume 60, No.230, 1995, p.61642.
8. McCarthy L.G., Kosiol C., Healy A. M., Bradley G., Sexton J.C., Corrigan O.I., 2003. Simulating the hydrodynamic conditions in the United States Pharmacopoeia paddle dissolution apparatus. AAPS PharmSciTech, 4 (2), 1-16.

For more information, contact your Colorcon representative or call:

North America	Europe/Middle East/Africa	Asia Pacific	Latin America
+1-215-699-7733	+44-(0)-1322-293000	+65-6438-0318	+54-11-4552-1565

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