The Influence of In Vitro Dissolution Method on the Release of a Highly Water Soluble Drug from Polyethylene Oxide and Hypromellose Hydrophilic Extended Release Matrices

PURPOSE

Hydrophilic matrices (HM) 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, 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]

The in vitro drug release from hydrophilic matrix tablets may be affected by various factors[1] 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 on the release of a high solubility drug - metformin hydrochloride (HCl)) from an ER matrix formulation containing either HPMC or PEO as the rate-controlling polymer.

METHODS

Formulation & Manufacture of ER Matrices

Two formulations containing 50% w/w metformin HCl (AMRI, India) as a freely water soluble model drug, 30% w/w PEO (POLYOXTM water soluble resin -1105, IFF, USA) or HPMC (METHOCELTM premium cellulose ether K100M CR,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) were 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 (Switzerland) mixer for 5 minutes. Magnesium stearate was finally added and the formulation was blended for an additional minute.

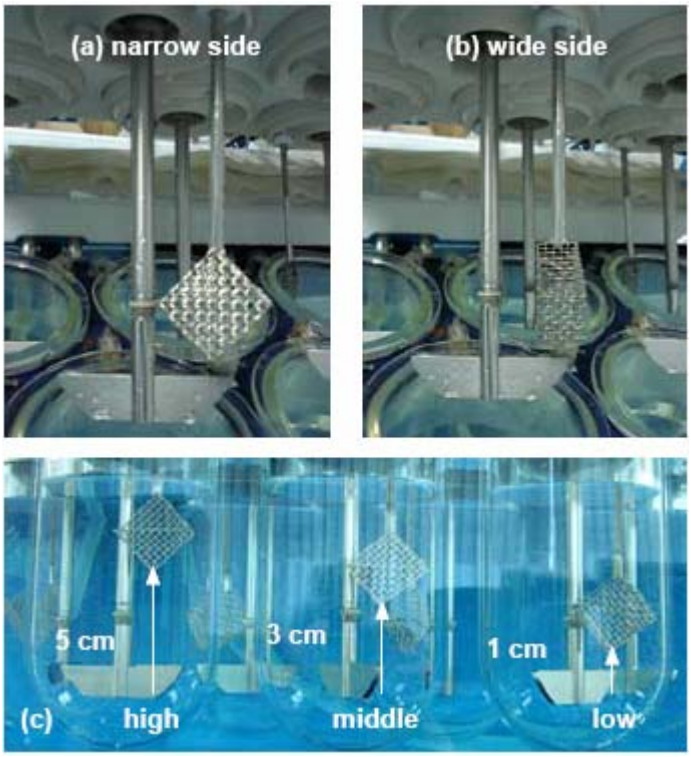
Tablets with a target weight of 1000 mg were manufactured by direct compression using a 10-station rotary Piccola press (Riva, Argentina), fitted with 7 x 18 mm caplet tooling; at 20 rpm and 20 kN compression force.

Drug Dissolution Testing

Drug release was measured in a Sotax AT7 (SOTAX, Switzerland) 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:
    - with their narrow or wide side towards 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 ± 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 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

Both formulations produced reproducible first-order drug release profiles for all dissolution testing methods used in this study (Figures 2 & 3).

Figure 2 shows that metformin HCl release from HPMC matrices was not significantly affected by the dissolution method used. For the PEO tablets, slightly faster drug release was observed when QBs or paddles with sinkers were used, as compared to USP baskets or paddles without sinkers (Figure 3).

Figure 2. The Influence of Dissolution Method on Metformin HCl Release from HPMC ER Matrices

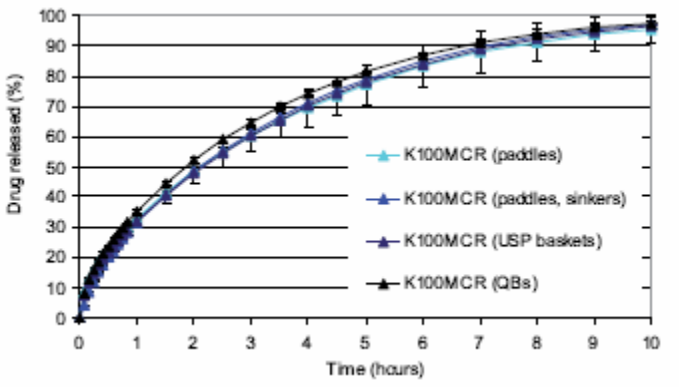
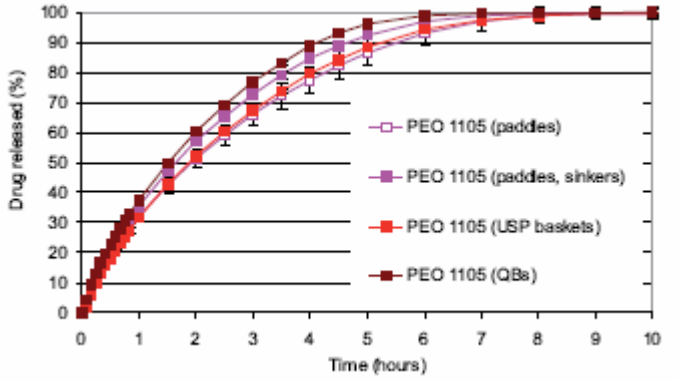


Figure 3. The Influence of Dissolution Method on Metformin HCl Release from PEO ER Matrices



For both formulations, 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 and HPMC 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.

The position of the QBs relative to the shaft of the paddle had no significant effect on drug release from HPMC or PEO matrices. Additionally, for the PEO tablets, position of the QBs 1 cm above the paddle resulted in a slightly slower metformin HCl release compared to the higher positions of 3 cm or 5 cm. 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.

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 as a water soluble compound, the rate of release from a hydrophilic matrix is determined predominantly by diffusion. The in vitro release from such formulation is most often independent of the hydrodynamic conditions in the dissolution vessel. Figure 4 shows that the rate of drug dissolution from the HPMC matrices was not affected by the paddle rotational speed used.

For PEO tablets, however, drug release was significantly faster from matrices placed in QBs when higher paddle rotational speeds were used (Figure 5). The difference between results in Figure 4 and Figure 5 could be explained by differences in polymer viscosity. The lower viscosity of PEO compared to HPMC leads to a lower gel strength and greater effect of erosion on drug release. Therefore, with an increase in agitation intensity, the degree of mechanical stress on the hydrated matrices increased resulting in a faster metformin HCl release.

Figure 4. The Influence of Paddle Speed on Metformin HCl Release from HPMC ER Matrices Using Quadrangular Baskets

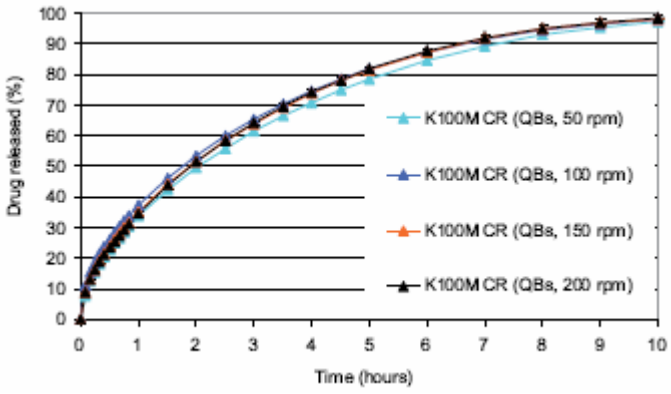
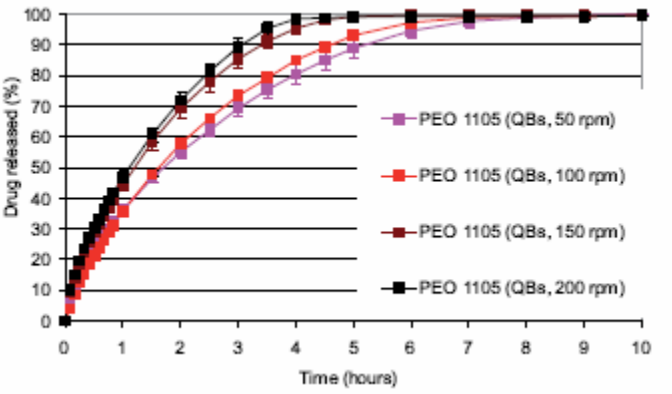


Figure 5. The Influence of Paddle Speed on Metformin HCl Release from HPMC ER Matrices Using Quadrangular Baskets



CONCLUSIONS

Metformin HCl release from the HPMC matrices was not significantly affected by the choice of dissolution method, position of the QBs in the vessel, or paddle rotational speed.

For the PEO matrices, there was a significant change in metformin HCl release when different configurations and agitations were utilized.

The difference in HPMC and PEO performance was entirely due to differences in polymer viscosities.

For both formulations, 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 instead of USP I (basket) and USP II (paddles) for in vitro drug dissolution testing from hydrophilic matrix tablets based on HPMC or PEO.

This ADS was adapted from the 2008 AAPS poster.

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.

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