Evaluation of Hydroxypropyl Methylcellulose Matrix Systems as Swellable Gastro-Retentive Drug Delivery Systems (GRDDS)

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Received 4 December 2009; revised 21 April 2010; accepted 22 April 2010

Published online 22 June 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22252

ABSTRACT: Utilizing gastro-retentive drug delivery systems (GRDDS) to increase absorption of weakly basic drugs by extending their transit time is a promising approach. Swellable systems were evaluated for this purpose. Such systems demonstrate dual mechanism of release—diffusion and erosion. GRDDS requires maintaining its dimensions, which demands diffusion as a predominant mechanism of release (Fickian). In this work, dypyridamole, a weakly basic drug, together with various grades of hydroxylpropyl methylcellulose and different excipients were evaluated for release and swelling properties. Dissolution data were analyzed by curve fitting to various models to estimate predominant release mechanism. It was found that matrices containing a swellable diluent like microcrystalline cellulose demonstrated predominantly Fickian mechanism of release, whereas soluble diluents (lactose and mannitol) contributed to a mixed mechanism of release. Addition of copovidone increased the swelling and survivability, whereas sodium chloride altered the erosion behavior. A correlation between matrix weight loss and drug release was obtained, which further consolidated the analysis. Correlation for the soluble excipients was linear, whereas that for the swellable excipient was nonlinear, implying predominance of Fickian release mechanism for the latter. Hence, the selection of excipients can influence matrix survivability and release kinetics, which can be used for developing GRDDS. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:150–163, 2011

Keywords: diffusion; oral drug delivery; hydrogels; mathematical model; gastrointestinal transit; solid dispersion; polymers; controlled release; dissolution; formulation

INTRODUCTION

The controlled release (CR) delivery of weakly basic drugs can be challenging due to solubility limitations as dictated by its pK_a and the pH solubility profile.[1,2] Typically, the pH solubility profile of weakly basic drugs show significantly low solubility (or equal to its intrinsic solubility) in the biorelevant pH's (higher than its pK_a). Thus, drug release from CR matrices, of such actives may vary as a function of their movement into various segments of GIT, leading to lower bioavailability.[3] This aspect also is critical when seeking a conventional CR delivery system that has a meaningful extent of exposure.

A simple method to understand the relationship between the saturation solubility and the transit time is the maximum absorbable dose (MAD) model[4]

$$\mathrm{MAD(mg)} = C_s K_a \mathrm{SIWV} \times \mathrm{SITT} \qquad (1)$$

where C_s is the saturation solubility (mg/mL) at pH 6.8, K_a is the absorption rate constant (1/min), SIWV is the small intestinal water volume available for dissolution of the compound generally assumed to be ~250 mL, and SITT is the small intestinal transit time of the drug, generally assumed to be ~4.5 h (270 min).

For drugs where MAD numbers are smaller than the required dose, solubility enhancement is called for. For a typical weakly basic drug having low solubility at pH 6.8 (e.g., 0.5 μg/mL) with no permeability limitations ($k_a = 0.03$/min), the MAD for normal transit time is calculated as 10 mg. Using this computation, a balance between the transit time and solubility enhancement may be obtained. For example, for a higher dose (200 mg), a transit time of 88 h is calculated or alternatively, a 20-fold solubility enhancement is needed. A reasonable transit time of

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Journal of Pharmaceutical Sciences, Vol. 100, 150–163 (2011)

8.8 h is obtained if a 10-fold solubility enhancement is utilized. Therefore, for drugs where a very high solubility enhancement may not possible, complete absorption can be achieved by manipulating the transit time. Foregoing arguments can be the basis for developing GRDDS for weakly basic drugs.

While various techniques are explored in literature for GRDDS,[5] in the present work swellable GRDDS in the form of CR matrices were explored. It should be noted that since the swellable GRDDS are based on swelling ingredients, the fabrications techniques are similar to that of any CR matrix system. Of the possible matrix materials, hydroxypropyl methylcellulose (HPMC) has been widely used in the formulation of CR matrix tablets because of its hydrophilic gel-forming property, nontoxicity, cost-effectiveness, its wide pharmaceutical applicability, and ability to formulate with various excipients so as to modulate drug release.[6,7] HPMC is available with various substitution types of hydroxypropyl and methyl which influences its swelling and hydration. Each type is also available as various viscosity grades. These properties influence the hydration, swelling, and release kinetics of the matrices. Methocel K100LV is a HPMC grade with low viscosity (around 100 cPs, 2%, w/v, in water at 20°C). Methocel K4M has viscosity around 4000 cPs. Methocel F4M, having a viscosity of 4000 cPs, has a slower swelling and hydration rate because of difference in its substitution type.[6]

The retention of swellable systems is influenced by the size of the delivery device and ingestion of food which constricts the pyloric sphincter.[8] These are designed to expand to produce a drug delivery system that is too large to pass through the pylorus, yet sufficiently small to be swallowed. Among the challenges with this approach, are the risks associated with too slow a release due to a change in pH and, most importantly, the dosage form could potentially pass out of the stomach due to receding matrix size. The other risk is incomplete release because of continuous expansion of the system. Mechanistically, the path length for a drug will gradually increase as matrix swells and as drug diffuses out of the outer layers. This issue is greater if the drug is fairly insoluble. Therefore, to design a swellable conventional CR system for such drugs, typically an erodible tablet is formulated to overcome release issues,[9] which when applied to GRDDS, will lead to expulsion of the matrix from the stomach.

On exposure to water, HPMC hydrates, swells, and forms a gel barrier layer, which retards the diffusion of drug out of the matrix. The size of the matrix increase is due to polymer viscosity, is time dependent, and swelling is higher for higher molecular weight HPMC grades.[10] Soluble drugs are considered to be released by diffusion through the matrix and poorly soluble drugs released by erosion of the matrix.[9,11] For insoluble drugs, the drug release was described as a process that is controlled solely by erosion of the tablet.[12] Therefore, such matrices recede in size when completion of release is demanded in a reasonable time. Mechanistically, it has also been shown that the HPMC has swelling, erosion, and diffusion fronts.[13] It has also been shown that when sparingly soluble drugs are incorporated, there is a disruption of synchronicity of these fronts and possible matrix collapse.[14] Therefore, for utilizing HPMC matrices for designing GRDDS, the completeness of release while maintaining the matrix integrity and size is a technical issue that needs to be resolved. Since swellable matrices like HPMC show a mixed mechanism of release — Fickian and erosion — formulations yielding constant matrix size during the dissolution process will have to be iteratively sought. Such a matrix will suffice a prerequisite for Fickian release as set forth by Huguchi's model, that is, constant size.[15] The contributions to Fickian release and erosion release will have be separated, and the matrices with predominantly Fickian release identified.[16] Fickian release and Higuchi equation are similar and originate from the same physical model of drug depleting from matrix. Former is a mechanistic term, originating from the Fick's law which implies that the release occurs via diffusion. Higuchi equation relates square root of time to release and is a mathematical expression which originates from a pseudo-steady-state analysis of a device having a fixed boundary and a moving drug layer. Higuchi's equation also describes the release as a diffusion process.

Foregoing discussions help extract the performance requirements of a swellable matrix-based GR system: (a) rapid swelling should be achieved and the minimum size of the swollen matrix should be about 10 mm. However, to ease swallowing by a subject, the matrix should be of a nominal size. (b) The release should be complete. (c) The size of the matrix should be maintained throughout the release period. Mechanistically, this means that the release has to be predominantly Fickian as opposed to erosion. (d) The retention is best achieved in fed mode, that is, the matrix should be dosed with food of high calorific value. This also means that the delivery system should have a pH-independent release profile as the pH of the stomach varies from fasted and fed conditions. The fasted gastric pH is 1.3 (1.1–1.6) and fed gastric pH is 4.9 (3.9–5.5).[17]

In the present work, above issues have been addressed to prepare and evaluate CR systems which will serve as a swellable GRDDS based on HPMC matrices, intended for the extended and complete release of the weakly basic dipyridamole (DPD; pK_a: 6.21, solubility: 0.005 mg/mL in pH 6.8 and no