A Drug Release Study From Hydroxypropylmethylcellulose (HPMC) Matrices Using QSPR Modeling

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ABSTRACT: This investigation is aimed at characterization of the mode of release from two different substitution types of HPMC and the effect of chemical structure of drugs using the QSPR (Quantitative - Structure–Property Relationship) technique. To this end, release profiles of HPMC matrices of several drugs containing the same formulation and compressed at a constant pressure were studied. QSPR method was used to establish statistically significant relationships between release parameters and the structural descriptors. Structural descriptors consisted of molecular mechanical, quantum mechanical and graph-theoretical parameters, as well as the partition coefficient and the aqueous solubility of the drugs. The results showed that the most important factors determining the release profile from both HPMC K4M and HPMC E4M matrices were the aqueous solubility of drugs (which could be substituted efficiently by dipole moment) and the size of the drug molecules. Comparison of drug release from matrices prepared using the two grades of HPMC showed very distinct differences for some drugs, as evaluated by the similarity factor. The results indicated that the source of the difference could be sought in the drug properties (as exemplified by the aqueous solubility and surface area) as well as the rate of erosion (that depends mainly on the polymer type). © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:3334–3351, 2007

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INTRODUCTION

A method of obtaining a sustained-release product is to embed or disperse the solid medicinal compound in an insoluble matrix by compression of a physical mixture of the compound and a polymeric material.[1] This has attracted considerable attention and has been described by several researchers.[2–5] Matrix tablets have long been used to obtain sustained drug delivery and it was Higuchi who first presented a detailed mathematical analysis of this release.[6]

Hyroxypropylmethylcellulose (HPMC) is one of the most widely used polymers in the preparation of oral controlled drug delivery systems. To achieve controlled release through the use of a water-soluble polymer such as HPMC, the polymer must quickly hydrate on the outer tablet skin to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent wetting of the interior and disintegration of the tablet core. Once the protective gel layer is formed, it controls

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the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. Hydroxypropyl methylcellulose (HPMC) products vary chemically and physically. The major chemical differences are in degree of methoxyl substitution, moles of hydroxypropoxyl substitution (MS), and degree of polymerization. Varying ratios of hydroxypropyl and methyl substitution in different products influence properties such as organic solubility and the thermal gelation temperature of aqueous solutions and swelling behavior.[7]

It has been shown that mechanism of release and the release profiles from matrices depend not only on the type of the polymer but also on the properties of the drug.[8–10] For example the release mechanisms of propranolol HCl and indomethacin from HPMC matrices are significantly different.[8,9] In a study on the release of drugs from polyvinylalcohol matrices, it was observed that the release rates of potassium chloride, phenylpropanolamine hydrochloride and bovine serum albumin decrease as the molecular size of the drug increases.[2] Although the phenomenon was attributed to decreased diffusivity and molecular weight was taken as the criterion of molecular size, the study was not aimed at establishing any explicit relationship. In another investigation where molecular weights of the drugs classified in groups of roughly similar solubilities were compared, molecular weight and solubility were indicated as the possible factors affecting drug release from matrices.[11] Baveja et al. investigated release characteristics of six water-soluble bronchodilators from HPMC K4M matrices in order to find correlation between release rate and molecular geometry of the drugs.[12] They showed that despite almost identical aqueous solubilities different drug molecules showed different release rates from HPMC matrices, which was related to the accessible surface area of the drugs. However, it must be stressed that as the drugs used in the study consisted of only structurally related beta-blockers, the findings cannot be extrapolated to other drugs.

Quantitative Structure–Property Relationship (QSPR) is a valuable tool that employs specialized statistical techniques to relate the property under investigation to the molecular structure of the chemicals represented by physico - chemical properties or structural descriptors. The resulting QSPR models facilitate understanding of the property in terms of chemical structure, ultimately enabling the investigators to estimate the property for other similar compounds. The aim of the present investigation was to rationalize the release characteristics of different drugs from HPMC matrices in terms of the chemical structure of the drugs and the properties of the polymer. To achieve this goal, separate QSPR models were established for drug release from HPMC K4M or HPMC E4M matrices and the resulting models were compared. The models were obtained using the release data of 15 drugs (belonging to different chemical classes) from matrices prepared using HPMC K4M and E4M. Chemical structure of the drugs were represented by a wide range of molecular descriptors such as partition coefficient ($\log P$), pK_a, atomic charges, orbital energies, dipole moment, length, surface area and electrostatic potentials on the surface, molecular connectivity indexes and shape indices, solubility and solubility parameter.

MATERIALS AND METHODS

Materials

Acetaminophen (Acros Organic, UK), diclofenac sodium (Sobhan Co., Iran), fluoxetine HCl (Pars-Daru, Iran), naproxen (Pars-Daru, Iran), piroxicam (Sigma, USA), propranolol HCl (Acros Organic, UK), sulfamethoxazole (Logman, Iran), diltiazem HCl (Acros Organic, UK), ibuprofen (Acros Organic, UK), atenolol (Daru-Pakhsh, Iran), diphenhydramine HCl (Acros Organic, UK), imipramine HCl (Logman, Iran), theophylline monohydrate (Acros Organic, UK), trifluoperazineHCl (Sobhan Co., Iran) and trimethoprim (Logman, Iran) were obtained. Two HPMC (Hypromellose) grades, HPMC (Methocel) K4M Premium CR and HPMC (Methocel) E4M Premium CR were gifts from Colorcon, UK.

Preparation of Tablets

The matrices were prepared by mixing 20 g of the drug (with particle size in the range of 45–125 μm) with 20 g of HPMC K4M or HPMC E4M for 10 min using a small double cone mixer. Magnesium stearate was then added to the mixture and mixed for a further 1 min. The final mixtures were compressed on an 8-mm punch and die using single punch machine (Erweka, Germany) at a constant pressure of 10 kN. The weight of each tablet was 202 mg which included 100 mg drug (49.5%), 100 mg HPMC K4M (49.5%) and 1% magnesium stearate.