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Release of Dextromethorphan Hydrobromide From Matrix Tablets Containing Sodium Carboxymethylcellulose and Hydroxypropylmethylcellulose

Aiman A. Obaidat*, Lama A. Rashdan and Naji M. Najib

Department of Pharmaceutical Technology Faculty of Pharmacy Jordan University of Science and Technology Irbid-Jordan

Abstract

The release of dextromethorphan hydrobromide (DM-HBR) as an example of a water-soluble drug from matrices containing anionic sodium carboxymethylcellulose (Na-CMC) and non-ionic hydroxypropylmethylcellulose (HPMC) was investigated. The release of the drug was studied as a function of the polymers' content either separately or in combination, drug load, and the pH of the release medium. The result obtained indicated that although HPMC had a little retarding effect on drug release from the matrix, Na-CMC significantly reduced the release rate of the drug. An effect which was attributed to the possible charge interaction between the drug and the anionic polymer. This result was confirmed by studying the erosion rates of matrices containing the polymers only and matrices containing the drug in combination with the polymers. When DM-HBR was included in the matrices containing Na-CMC, the erosion was reduced compared to matrices containing the polymer only. This was due to the insolubility of the complex formed between Na-CMC and DM-HBR. The effect of pH on the release of DM-HBR was also studied. The pH affected both the solubility of the drug and the erosion rate of the matrix. This study showed that combining both HPMC and Na-CMC in optimum proportions would result in a near zero-order release from such hydrophilic matrices.

Key Words: HPMC and Na-CMC; Dextromethorphan hydrobromide; Zero-order release; Matrix tablets; pH effect

Introduction

Cellulose derivatives, namely hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (Na-CMC), have attracted considerable attention in recent years and have been used in the development of orally controlled release tablet formulations. Various types of polymers are used to formulate hydrophilic matrices. Their formulation techniques and modeling aspects were extensively reviewed (Buri and Doelker, 1980; Korsmeyer and Peppas, 1983). Among these hydrophilic polymers, cellulose derivatives are still the most commonly used ones for orally controlled release tablet formulations(Baveja *et al.*, 1987; Baveja and Ranga, 1986; Ford *et al.*, 1987).

*Correspondence

The ease of compression, non-toxic nature, and ability to accommodate a large percentage of the drug are some of the attractive reasons behind the popularity of these polymers.

Matrices containing only HPMC generally provide a controlled drug release and it was reported that the release rate decreases as the viscosity of the polymer increases (Daly *et al.*, 1984). However, a major disadvantage of these hydrophilic polymers is that zero-order release has not been obtained. The major reason behind that could be due to the differences between the rate of penetration of the solvent into the core of the tablet and the rate of erosion of the gel. Since these rates are not equal, the diffusional path length for the drug varies with time resulting in a non-linear release. Therefore, matrices containing a combination of HPMC and Na-CMC have been studied where they could provide a close to zero-order release of drugs (Baveja *et al.*, 1987).

In this study we report on a simple technique to achieve a close to zero-order release of a water-soluble drug from hydrophilic matrices using a combination of HPMC and Na-CMC. This was achieved by optimizing the ratios between these polymers and the drug in the matrix. The objective of this study was to prepare orally controlled release dosage form of dextromethorphan hydrobromide (DM-BHR) that would provide a reasonable duration of therapeutic effect with minimum potential for side effects like drowsiness or sedation.

Materials and Methods

Materials

Dextromethorphan hydrobromide (DM-HBR) was a gift from Al-Hikma Pharmaceuticals, Amman-Jordan, Na-CMC (BDH Chemicals, UK), HPMC (Sigma, USA). All other chemicals were of analytical grade and were used without further purification.

Tablet formulae: Different tablets were prepared by mixing 25 mg of DM-HBR with different ratios of either HPMC or Na-CMC. Other tablets were prepared by mixing 25 mg of DM-HBR with combinations of HPMC and Na-CMC in different proportions. To study the effect of drug load, different tablets were prepared by mixing different amounts of DM-HBR with constant ratios of HPMC and Na-CMC. All blends were thoroughly mixed for 15 min using a mixer then compressed into tablets at 5 Ton using a single-punch hand-operated tablet machine fitted with flat-faced punches (13 mm diameter).

Dissolution studies: The release of the drug was monitored by subjecting the tablets to dissolution using a Vankel dissolution apparatus (Type VK 700, USA) according to USP I method. The basket was rotated at 100 rpm and the temperature of the dissolution medium was maintained at 37 ∓ 1°C. The pH of the dissolution medium was adjusted to the required pH value using a suitable buffer except for low pH values (< 3) where diluted HCl was used as the dissolution medium. Samples, each of 5 ml, were taken at predetermined time intervals and were immediately replaced with a similar volume of the dissolution medium. These samples were filtered through 0.45 μm membrane filters and analyzed spectrophotometrically at 278 nm for the content of DM-HBR using a Shimadzu spectrophotometer (UV-1201, Japan). The dissolution data were expressed as percent

released of DM-HBR against time. To confirm reproducibility of the results, dissolution studies were performed in triplicate for each batch of tablets.

Results and Discussion

The effect of Na-CMC on the release of DM-HBR is shown in Figure 1. The data revealed that the rate of release of DM-HBR decreased with an increase in the ratio of Na-CMC in the matrix. DM-HBR has a high aqueous solubility, therefore, both diffusion and attrition are expected to contribute to its release rate from such matrices. The reduction in the release rate with increasing the proportion of Na-CMC in the matrix is attributed to a reduction in the erosion rate of the matrix. Such a reduction is due to the possible chemical interaction between Na-CMC and DM-HBR. Na-CMC is the sodium salt of carboxymethylcellulose and is expected that it will interact with DM-HBR to produce a complex of low solubility compared to DM-HBR. Therefore, as the amount of the polymer increased the rate of complex formation increases resulting in a slower release rate of DM-HBR. These findings are in consistency with those of Ranga *et al.* (1988) for similar systems.

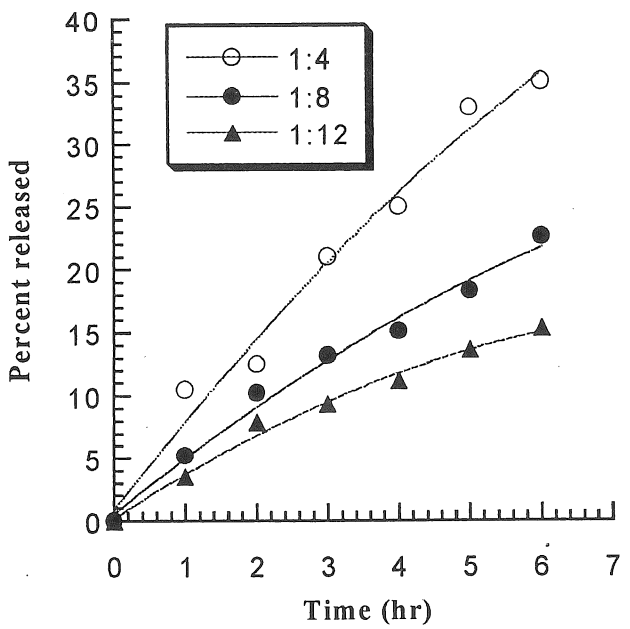

Figure 1. Release of DM-HBR as a function of time from matrix tablets containing drug:Na-CMC in the ratios given in the inset.

The release profiles of DM-HBR from matrices containing different proportions of HPMC are shown in Figure 2. The release rate of DM-HBR was inversely proportional to an increase in the ratio of HPMC in the matrix. A rapid initial release was observed which was attributed to the rapid dissolution of DM-HBR present on the surface and pores of the matrix before the hydration of the polymer and formation of the gel layer takes place. Although there is no chemical interaction between DM-HBR and HPMC, the release rate profile was not linear over release time and it was slightly concave. This behavior is expected and considered logical since a drug of high water solubility was used. This implies that a drug diffusion front would not exist and the increase in the gel layer thickness due to swelling of the polymer (HPMC) would result in a decrease of the drug concentration gradient along the diffusional path length, and hence, decreasing the drug release rate over time. Such an effect is expected to increase with increasing the amount of HPMC in the tablet matrix. As shown in Figure 2, the release rate of DM-HBR decreases with increasing the ratio of HPMC in the matrix.

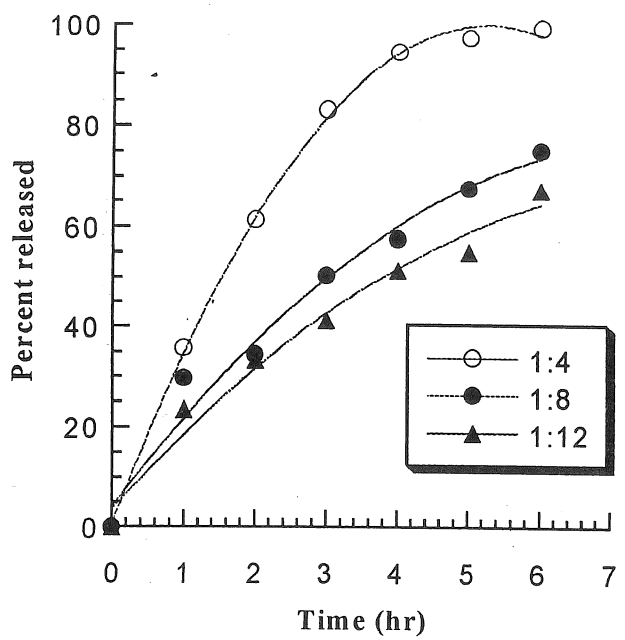

Figure 2. Release of DM-HBR as a function of time from matrix tablets containing drug:HPMC in the ratios given in the inset.

The effect of combining HPMC and Na-CMC in the matrix on the release of DM-HBR was studied. By studying different ratios of the polymers in the matrix we were able to characterize the optimum ratios to obtain a near zero-order release of the drug from the matrix. Figure 3 shows the release of DM-HBR from a matrix containing a mixture of

HPMC and Na-CMC. To analyze the mechanism of release, the dissolution data from such matrix tablets were fitted to the equation of Korsmeyer and Peppas (1983) given below:

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ is the fractional release of the drug, t is the release time, K is the kinetic constant incorporating the structural and geometric characteristics of the release device, and n is the diffusional release constant indicative of the release mechanism. A value of 0.5 for n indicates Fickian release and > 0.5 and ≤ 1.0 for non-Fickian transport and 1 for zero-order or case II transport. When the value of n approaches 1, apparently we can conclude that the release is approaching a zero-order mechanism.

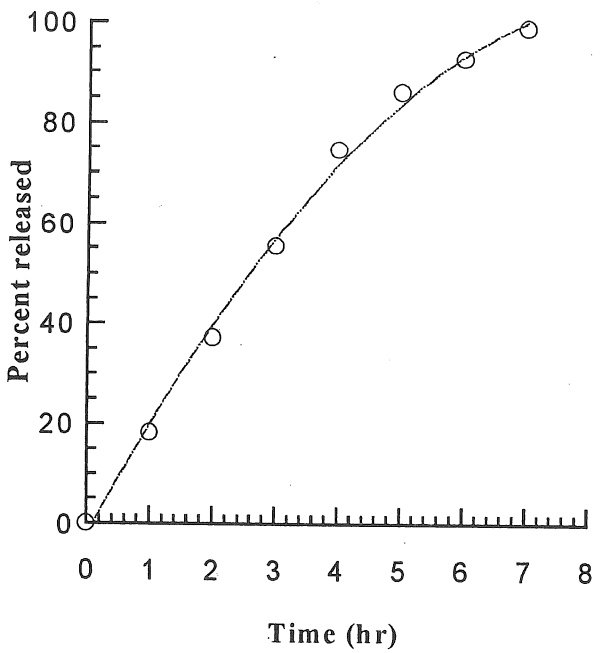

Figure 3. Release of DM-HBR from matrix tablets containing DM-HBR, HPMC and Na-CMC in ratios of 1:3.2:4.8, respectively.

Analysis of the release of the drug in the presence of HPMC and Na-CMC according to the previous equation is shown in Table 1. For values of $M_t/M_\infty \geq 0.6$, the values of n were closer to 1 indicating that the release mechanism is a zero-order release. As shown in Table 1, when the values of M_t/M_∞ increased, the value of n changed to a negligible extent. Therefore, we can conclude that for M_t/M_∞ between ≥ 0.6 and ≤ 1.0 the values of n were

practically constant and the deviation from zero-order release is practically negligible. Another factor that should be considered here is decrease resulting in a slow diffusion of the drug. The gel layer at the tablet periphery which is depleted of the drug will undergo attrition due to the advancement of the swelling front into the glassy polymer. When there is a balance between these two rates (rates of swelling and attrition), the diffusional path length for the drug remains constant and a near-zero order release will be observed. Similar conclusions for a water-soluble drug with similar systems were obtained by other investigators (Guerrero *et al.*, 1999).the high degree of cross-linking between the anionic Na-CMC and non-ionic HPMC leading to an increase in the gel viscosity (synergistic effect) at the periphery of the matrix. Therefore, the rate of swelling will

Table 1. Values of kinetic constant (K), release exponent (n) and correlation coefficient (r^2) following linear regression of dissolution data for values of $M_t/M_\infty \geq 0.6$ from matrix tablets containing HPMC and Na-CMC.

M_t/M_∞	Time (hr)	K (hr^{-n})	n	r^2
0.746	4	0.1125	0.8556	0.9964
0.860	5	0.1123	0.8602	0.9967
0.926	6	0.1119	0.8608	0.9975
0.988	7	0.1117	0.8613	0.9986

The effect of pH on the release of DM-HBR was also studied. A change in the pH of the dissolution medium did not have a significant effect on the release rate of DM-HBR from matrices containing only HPMC. This is due to the fact that HPMC is a non-ionic polymer, therefore, its swelling is not expected to be affected by changes in the pH. However, in the case of matrices containing Na-CMC, the change in pH had a significant effect on the release of DM-HBR. Two main factors are expected to contribute in this case and these are: the solubility of DM-HBR decreases with an increase in pH, and the erosion of Na-CMC decreases with increase in pH. DM-HBR is a drug with high solubility and a pKa of 8.3. Based on our results, a pH of 7.4 was suitable to study the release of DM-HBR and it was the pH of interest for our study. Although the erosion of matrices containing only Na-CMC was significant but it was reduced when DM-HBR was included in the matrix. As explained earlier this was due to the possible charge interaction between Na-CMC and DM-HBR which will result in the formation of a complex of lower solubility. Figure 4 shows the erosion of matrices containing HPMC, Na-CMC, or a combination of both at different pH values. Combining Na-CMC and HPMC in the matrix resulted in a significant reduction in the erosion as shown in Figure 4.

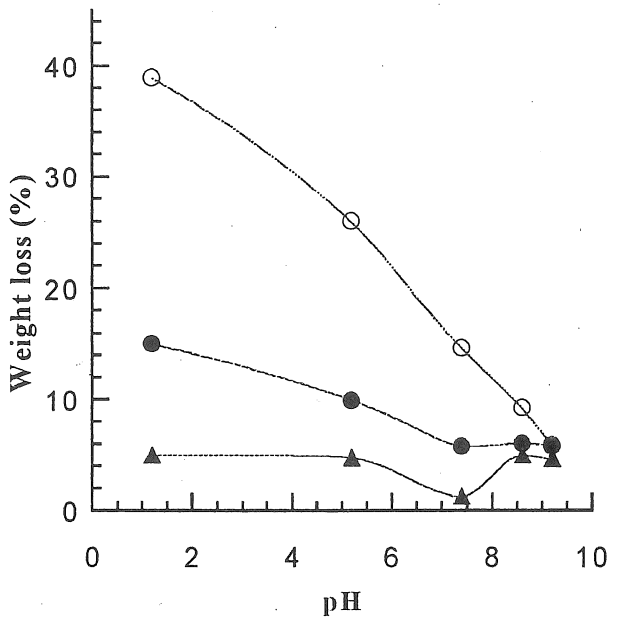

Figure 4. Effect of pH on the erosion of matrices composed of polymers only. (○) 200 mg Na-CMC, (●) 100 mg HPMC + 100 mg Na-CMC, (▲) 200 mg HPMC.

We examined the effect of drug load on its release from the matrices. Increasing the proportion of DM-HBR in the matrix resulted in an increase in its release rate. This is expected since more of the drug will be available for dissolution and release from the matrix.

In conclusion our results indicated that diffusion through the gel layer and attrition were the major controlling parameters for the release of the highly water-soluble model drug (DM-HBR) from matrices composed of HPMC and Na-CMC. Optimizing the ratios of the drug, HPMC, and Na-CMC in the matrix tablet would result in maintaining the diffusional path length of the drug so that a zero-order release can be achieved. It is important to point out that there was no excipients included in our formulations. The presence of other components could affect the overall hydrophilicity of the system due to changes in polymer plastification. Our future work will be focused on the interaction between DM-HBR and Na-CMC and the methods to confirm this interaction in such matrix tablets.

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