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SUSTAINED RELEASE TABLET FORMULATION FOR A NEW IRON CHELATOR

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ABSTRACT

Sustained release tablet formulations for a new orally active iron chelator (1,2,dimethyl-3-hydroxy-pyrid-4-one, DMHP or L1) have been developed. Coprecipitates containing DMHP and polymer were prepared and compressed into matrix-type tablets. The dissolution profiles as a function of (1) the type of polymer, and (2) polymer content, were determined. Both Eudragit types (RLPM and RSPM) and all hydroxypropylmethylcellulose (HPMC) grades (E4M, E10M, and K4M) exhibited significant sustained release activity. Above a certain ratio, increase in the polymer concentration did not provide any further decrease in the release rates. All grades of HPMC and both Eudragit RSPM and RLPM showed non-Fickian release kinetics. The role of HPMC and Eudragits in the formulation of a sustained release tablet of a water soluble drug is demonstrated.

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INTRODUCTION

The transfusion-dependent anaemias such as thalassaemia major that cause iron overload can be fatal in most cases. The only chelating drug that has been approved and currently in use is Desferrioxamine mesylate (DF; Desferal®) (1-2). Although DF is now well established (3) and its use reduces or prevents the complication of iron overload (4), it has the disadvantages of no oral absorption, rapid metabolism, a very short $t_{1/2}$ of only 5 to 10 minutes (after i.v. administration) and ototoxicity (5). Therefore, in clinical practice it is administered as a slow infusion for 6-8 hours (6-7) for at least 5 days a week, year in and year out, making the dosage regimen very taxing and expensive.

Many new iron chelators including rhodotorulic acid, cholylhydroxamic acid, 2,3-dihydroxybenzoic acid, and isonicotinyl hydrazone (PIH) have been tried in man, but have been rejected either because of their toxicity or inactivity following oral administration (8-9).

Recently a new class of orally effective iron chelators, α-ketohydroxypyridones have been synthesized and tested in human and various animal models (10-13). The most prominent amongst α-ketohydroxypyridones is 1,2-dimethyl-3-hydroxypyrid-4-one (DMHP or L1). It has been shown to promote urinary iron excretion in animals and humans. It is currently being administered to thalassemia patients under the direct supervision of physicians in several clinics around the world.

DMHP, although polar in nature, has an aqueous solubility of only 15 mg/mL. To induce adequate iron excretion, the drug should be given in high doses (usually 2 to 3 g per day for a 70 kg patient). A solution formulation at this high dose would require a large volume. A tablet dosage form therefore, is essential for convenient administration of large doses of DMHP. Because of the short elimination half-life ($t_{1/2}$) of DMHP (approximately 1 hour in dogs and rabbits as seen in our preliminary pharmacokinetic studies), it is an ideal candidate for the development of a sustained release dosage form.

The present work deals with the development of a matrix type of sustained delivery system using various grades and ratios of hydroxypropylmethylcellulose (HPMC) and Eudragit acrylic resins. DMHP was either physically mixed with the polymer or dispersed in the polymer matrix by coprecipitation. Tablets were prepared from these physical mixtures and coprecipitates, and their dissolution profiles tested in pH 2.0 buffer. The kinetics of release are also reported.

MATERIALS

The Chemicals: 3-Hydroxy-2-methyl-4-pyrone (Maltol, Sigma Chemical Co., St. Louis, MO and Aldrich Chemical Co., Inc., Milwaukee, WI), Avicel (Microcrystalline Cellulose PH101 (MCC), FMC Corporation, Philadelphia, PA), Eudragit RLPM and RSPM (Röhm Pharma, GMBH, Darmstadt, West Germany), Methocel E4M, E10M and K4M (all Premium CR grades, gifts from The Dow Chemical Co., Midland, Michigan), Methylamine (40%) (Fisher Scientific, Fair Lawn, N.J.).

EXPERIMENTAL

(i) Preparation of Coprecipitates:

DMHP was synthesized according to the method published by Kontoghiorghes and Sheppard (13). The required amount of DMHP and Polymer (Eudragit or HPMC) were weighed out and dissolved in ethanol (95% v/v). The solvent was evaporated to dryness to obtain a granular solid. Each batch of the prepared coprecipitates was tested for DMHP content. Coprecipitates were directly compressed into tablets and were used for dissolution studies.

(ii) Preparation of tablets:

100 mg of coprecipitate or physical mixture was compressed on a Manesty single punch compression machine at constant pressure, using 7/32" dia flat punch set. The setting of the tablet machine was kept constant throughout the study.

(iii) Tablet Properties:

All properties of tablets were evaluated within 24 hrs after compaction. The mean crushing strength (n=5) was determined using a hardness tester (Erweka hardness tester, Erweka Apparatebau, GMBH, Frankfurt, Germany). For the determination of friability, 5 tablets were dedusted with a soft brush to remove all adhering particles and accurately weighed. The tablets were placed in a friabilator (Erweka Friabilator, Erweka Apparatebau, GMBH, Frankfurt, Germany), rotated for 4 minutes or 100 revolutions, dedusted to remove adhering particles and reweighed. From the difference of the two weights, the friability of the tablets was calculated.

(iv) Dissolution testing:

The U.S.P. Apparatus #2 (Vander Kamp 600, Van-Kel Ind., NJ), was utilized with the paddles rotating at 50 rpm. A tablet was placed in 900 mL of KCl-HCl buffer previously degassed and equilibrated to 37.0 ± 0.3°C. Three milliliter samples were withdrawn at 5, 10, 15, 30, 60, 90, 120 minutes and then every hour up to 5 hours. Each sample was immediately centrifuged to remove any undissolved particles and 1 mL of clear supernatant was withdrawn and diluted up to 10 mL with buffer solution. The absorbance of the solution was determined at 276 nm. Drug concentration of each sample was calculated from a standard curve. Each dissolution study was done in triplicate.

RESULTS AND DISCUSSION

Initially, we compared the release of DMHP from tablets made from physical mixtures of DMHP and polymer with those made from coprecipitates of DMHP and polymer. The results showed no apparent differences between the two methods of polymer incorporation. However, the granular solid material obtained by coprecipitation was more suitable for tablet compression than just the physical mixtures. Hence coprecipitation was preferred and the results from tablets made from coprecipitates only are presented. The Hardness test showed that all tablets were within a predetermined range of 6 to 8 kg. All batches of tablets passed the friability test, typically the values were less than 1% loss in weight.

The dissolution profiles of DMHP from various tablets in pH 2.0 buffer are shown in Figures 1a through 1f. In all diagrams,

the dissolution profile of DMHP from tablets containing no excipient is shown as the control. Identical experiments in pH 7.4 buffer were carried out. The dissolution profiles were similar to those in acid buffer for all excipients at all ratios. Hence these results are not presented.

In Figure 1a the results of the dissolution profiles of DMHP from tablets containing only DMHP and those containing various ratios of MCC are compared. The concentration of MCC in the tablets was of no significance in DMHP release. All tablets disintegrated and dissolved within a short period of time releasing nearly 100% of the drug. Tablets made from Drug:Eudragit RSPM coprecipitates showed decreased release rates as compared to the release from pure DMHP tablets. Incorporation of a relatively small amount of RSPM (as in DMHP:RSPM 1:0.5) drastically decreased the dissolution of DMHP from tablets. Further increase in RSPM concentration decreased the initial DMHP dissolution only slightly as shown in Figure 1b. However as time progressed, for example, by the end of the study (300 min) Drug:RSPM 1:0.5 tablets had released nearly 100% of DMHP whereas those containing higher amounts of RSPM had only released 60 to 70% of DMHP. Although the same trend was true for tablets made from DMHP:RLPM coprecipitates, in small amounts (DMHP:RLPM of 1:0.5) it was not as effective as RSPM in decreasing DMHP dissolution. As shown in Figure 1c, increase in RLPM (to DMHP:RLPM of 1:1) suppressed the dissolution of DMHP only slightly and any further increase in RLPM concentration did not have much

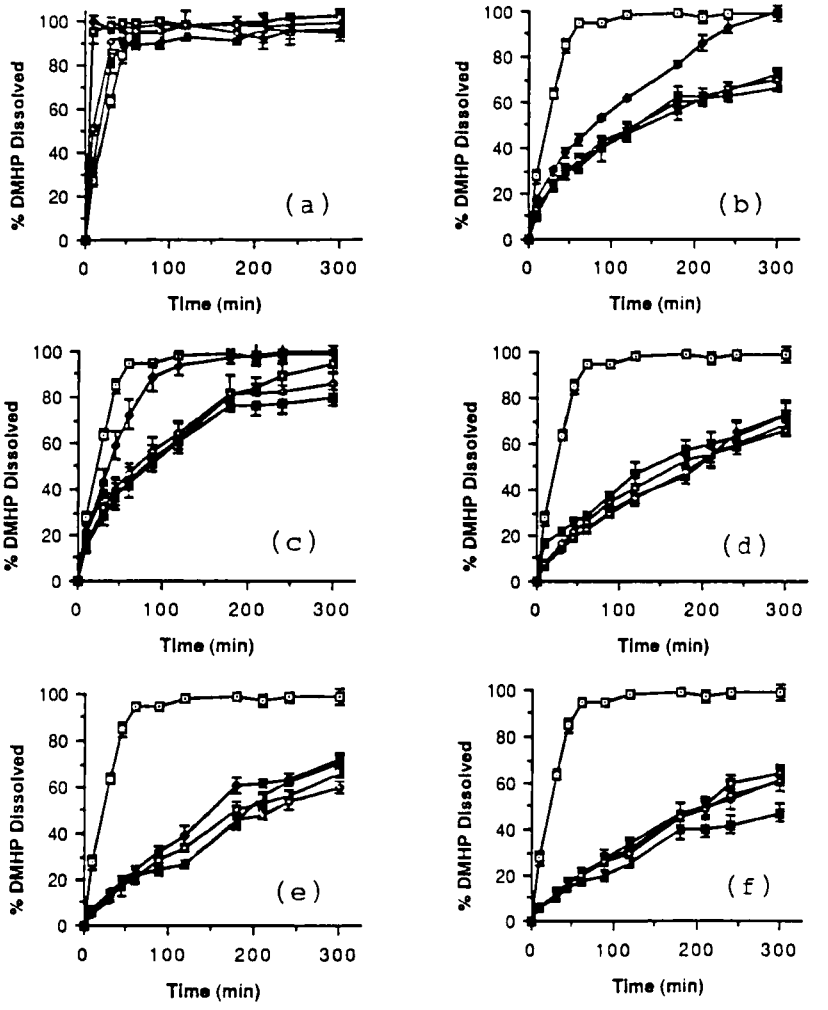

FIGURE 1

DMHP release profile from tablets containing various DMHP:excipient ratios at 37°C in acid buffer.
Key: a = MCC, b = RSPM, c = RLPM, d = HPMC-E4M, e = HPMC-E10M and f = HPMC-K4M.
Key: pure drug; 1:0.5; 1:1; 1:2; 1:4

effect in controlling DMHP release. At all time points and at all ratios, RSPM gave a lower percent released value than the corresponding RLPM system.

In Figures 1d to 1f the results of DMHP release from tablets containing various grades of HPMC are presented. In all cases a plot of percent released versus time seemed linear after an initial burst effect, although not very prominent. The slopes of these lines were nearly the same irrespective of the HPMC grade as shown in Figure 1d (HPMC Grade E4M), Figure 1e (HPMC Grade E10M) and Figure 1f (HPMC Grade K4M). A drastic reduction in DMHP dissolution was observed for all grades of HPMC and at all drug:HPMC ratios ranging from 1:0.5 to 1:4. There were no striking differences between the different grades of HPMC and also between the various concentrations of any given grade.

Kinetics of drug release

The dissolution data were analyzed according to the Higuchi equation which predicts a linear relationship between the amount released versus the square root of time for diffusion controlled mechanism of release (14). However, only certain segments of this graph may exhibit linearity depending on whether diffusion alone or diffusion and relaxation mechanisms predominate. In addition, Higuchi plot requires the line to pass through the origin. All polymers at all ratios used in this study showed excellent linearity (δ^2 = 0.94 or better in most cases) between the percent released versus square root of time. However, all compositions exhibited a positive or a negative intercept indicating a burst

effect or a lag time before linearity is reached. The intercepts were typically smaller for RSPM and RLPM as compared to HPMC. The release rate constants (K) are summarized in Table 1 and show a general trend in that, increasing the polymer concentration in the coprecipitate results in a decrease in the release rate constant. This is easily understood by measuring t_{25} and t_{50}, the times taken for 25% and 50% of the drug content to be released. The t_{25} and t_{50} values for pure DMHP tablets were 14 and 34 minutes respectively. Addition of microcrystalline cellulose at various ratios, as expected, produced much smaller t_{25} values and had slightly variable effect on t_{50} values. This can be attributed to the fact that these tablets readily disintegrated to yield secondary particles of varying surface area. Incorporation of the drug in a polymer matrix showed a profound increase in the t_{25} and t_{50} values indicating their importance and effectiveness in providing sustained release of a water soluble drug such as DMHP. The longest t_{25} and t_{50} were observed with HPMC-K4M (118.0 and 330.0 min respectively) at a DMHP:HPMC-K4M ratio of 1:4.0. In most cases as the polymer concentration was increased the t_{25} and t_{50} values increased correspondingly. But an anomalous behavior was seen with HPMC-E4M which showed a slight decrease in t_{25} as its concentration in the coprecipitate was increased and this cannot be readily explained.

The release of drug was also studied according to the following equation (15):

$$\frac{Mt}{M\infty} = K't^n$$

TABLE 1

Dissolution Kinetic Parameters K and n, and the Times Taken for 25% and 50% DMHP Dissolution in pH 2.0 Buffer from Tablets made from Various Formulations

Formulation	n	Release Rate Constant K ($min^{-1/2}$)	t_{25} (min)	t_{50} (min)
Pure DMHP*	-	-	14.0	34.0
DMHP:MCC*				
1:0.5	-	-	2.5	10.0
1:1	-	-	3.0	22.0
1:2	-	-	5.0	43.0
1:4	-	-	6.0	37.0
DMHP:RSPM				
1:0.5	0.5261	5.9153	21.0	75.0
1:1	0.5081	4.2823	30.0	119.0
1:2	0.5005	4.1720	30.0	126.0
1:4	0.5354	4.0466	32.0	134.0
DMHP:RLPM				
1:0.5	0.4507	6.0699	13.0	35.0
1:1	0.5509	5.8398	24.0	75.0
1:2	0.4991	5.3121	21.0	66.0
1:4	0.4139	4.7423	26.0	80.0
DMHP:E4M				
1:0.5	0.6919	4.3274	66.0	228.0
1:1	0.6718	4.1159	66.0	260.0
1:2	0.6213	4.0358	56.0	228.0
1:4	0.4608	4.1577	48.0	265.0
DMHP:E10M				
1:0.5	0.7062	4.5643	68.0	148.0
1:1	0.6758	4.0207	98.0	177.0
1:2	0.6794	3.6646	96.0	190.0
1:4	0.7260	3.2274	104.0	214.0
DMHP:K4M				
1:0.5	0.6672	3.9993	81.0	204.0
1:1	0.7200	3.9743	84.0	210.0
1:2	0.6977	3.7371	84.0	214.0
1:4	0.6354	2.9297	118.0	330.0

*'K' and 'n' for these formulations could not be determined since the tablets disintegrated soon after exposure to the dissolution medium.

Where the fraction of drug released is proportional to a matrix constant (K') which is dependent on the drug's diffusion coefficient in the matrix. The constant, n, depends on the polymer swelling characteristics and relaxation rate at the swelling front. The value of n indicates the mechanism of release ranging from Fickian (n = 0.45 to 0.5) to non-Fickian or anomalous release (n = 0.5 to 0.89) to zero-order release (n = 1). Hydrophilic polymers that show a fast transition from the dry glassy state to a swollen rubbery state may approach n = 1, which in practice, is difficult to attain. As shown in Table 1, the value of n for all the systems studied ranged from 0.45 to 0.73. Typically the Eudragit polymers showed values closer to Fickian behavior than HPMC. This is perhaps due to the fact that Eudragit acrylic resins do not swell as much as HPMC hydrogels and in the latter case this swelling is also associated with a transition from the dry glassy state to a rubbery state upon hydration.

CONCLUSIONS

The results from our studies show that all grades of HPMC and Eudragit that were tested perform well as matrices for sustained release tablets even when present in small proportions e.g. Drug:HPMC/Eudragit of 1:0.5. Eudragit RSPM was better than RLPM at all concentrations in the tablets in decreasing the release rates of DMHP. All release profiles were found to be non-Fickian, Eudragits approaching Fickian behavior. The results also demonstrate the ability of obtaining directly compressible tablet formulations using these polymers incorporated by coprecipitation.

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