Journal of Controlled Release, 9 (1989) 169–175
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

GEL–MATRIX SYSTEMS EXHIBITING BIMODAL CONTROLLED RELEASE FOR ORAL DRUG DELIVERY

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(Received June 9, 1988; accepted in revised form December 19, 1988)

Certain types of hydroxypropyl methylcellulose ethers, when admixed with a therapeutic agent and compressed into a solid dosage form, are found to display a bimodal drug release profile. The bimodal profile is characterized by a rapid initial release of drug, followed by a constant rate of release, and then a second mode of fast drug release at the terminal phase. Release profiles can be selectively modified by varying the viscosity, concentration, and the combination of methylcellulose polymers. The mechanism of release appears to involve initial surface erosion, polymer gelation, a steady-state counter-current permeation of water and dissolved drug across the gel layer, dissolution of gel from the outer surface, and subsequent disintegration of the gel. A bimodal oral controlled release delivery system which produces an increased rate of drug release in the latter phases of dissolution, may offer some advantages over constant zero-order release systems for maintaining uniform drug levels in the body. Bimodal release profiles were obtained for aspirin, ibuprofen, adinazolam, flurbiprofen, and other investigational drugs.

INTRODUCTION

An oral controlled release system which releases drug at a zero-order rate is often considered an ideal system for maintaining constant drug levels. This is based on the assumption that drug absorption occurs rapidly through the entire GI tract, so that the rate of elimination dictates the rate at which the drug must release from the dosage form. However, for many drugs, absorption is moderately slow in the stomach, rapid in the proximal intestine, and it declines sharply in the distal segment of the intestine. This means that to maintain constant drug levels, the delivery system should release drug in such a way that it is able to compensate for the changing drug absorption pattern in the GI tract by increasing the drug release rate in regions of slow absorption. Thus, a release system with a variable rate of release may indeed be more desirable than a constant zero-order release system. The bimodal release system provides such a variable rate system. For drugs where gastrointestinal absorption is uniformly rapid, serum concentrations can be produced which will closely reflect the differential tempered release rates of the bimodal dosage form.

Bimodal release is characterized by a rapid initial release, followed by a period of constant release, then a second phase of rapid drug release. The bimodal release system can offer two major advantages over the other systems: (1) it produces rapid drug release during the initial and later phase to provide rapid onset of action and to compensate for the relatively slow absorption in the stomach and large intestine; (2)

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0168-3659/89/$03.50

it can be used to design programmed pulse release oral drug delivery systems for the therapeutic agents that perform more effectively when drug levels undergo periodic changes.

In this study, a group of hydroxypropyl methylcellulose polymers have been identified that exhibit bimodal release profiles when combined with therapeutic agent in a solid dosage formulation. Although some of these polymers have been widely used and studied [1] for their application in oral controlled release drug delivery, their ability to provide bimodal drug release has not been previously reported.

MATERIALS AND METHODS

Materials

Bimodal hydroxypropyl methylcellulose ethers (HPMCs) which have been used in these studies include Metolose 65SH-50, 65SH-400, 65SH-1500, 65SH-4000, Metolose 60SH-4000, 90SH-100, and 90SH-15,000 (Shin-Etsu Ltd., Japan) as well as Methocel F4-M (Dow Chemical Company, MI).

The following non-bimodal HPMCs were tested: Methocel A4-C, A4-M, A15-LV, A15-C, E4-M, E5, E50, E15-LV, E50-LV, K4-M, K15-M, K100-M, and K100-LV (Dow Chemical Company). Metolose SM-1500, a methylcellulose, was evaluated as a release rate modifier. The drugs utilized were adinazolam, flurbiprofen, aspirin, and ibuprofen.

Tablet preparation

Tablet preparation consisted of through mixing of one or more of the hydroxypropyl methylcellulose ethers with therapeutic agent and ingredients conventional in tablet making such as stearic acid, magnesium stearate, silicon dioxide, etc. The content of the bimodal polymer(s) comprised anywhere from 5 to 99% by weight of the total formulation, depending on the active ingredient and length of drug release desired.

Tablets were manufactured by either direct compaction of the mix on a carver press or on a rotary tablet compressor, after dry granulation.

Dissolution apparatus

Tablets were subjected to dissolution rate testing using an automated six-place rotating filter–stationary basket system [2], a water bath with Tecam C-400 circulator, a 10-place Master Flex pump, a Perkin-Elmer Lambda 3 UV-Visible spectrophotometer, and an IBM–AT computer.

Dissolution procedure

Dissolution studies were conducted in a medium of 0.05 *M* phosphate buffer, pH 7.2, temperature 37°C, and at a stirring speed of 300 rpm. Release rates were determined by continuous spectrophotometric analysis of the dissolved drug.

Viscosity measurements

Viscosity testing was performed on selected HPMC samples. 2.0% solutions were prepared by dissolving the polymer in water at 60°C. Samples were refrigerated for 12 hours, then warmed to 20°C prior to analysis. Measurements were made using a Schott Geräte AVS 400 automated viscometer.

Clinical study procedure

Ten normal male volunteers were enrolled in a crossover trial to evaluate the pharmokinetics of the bimodal sustained release adinazolam and conventional formulations. Each dosing sequence was separated by a one week interval. Venous blood specimens were collected by individual venipunctures at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24 and 30 hours after dosing, to measure plasma drug concentration.

RESULTS AND DISCUSSION

Cellulose ethers are being utilized extensively in the design of oral controlled release dosage forms [3]. In the present study, a series of hydroxypropylmethylcellulose ether polymers that provide bimodal and non-bimodal release profiles from polymer–drug matrix tablets have been identified. As seen in Table 1, bimodal release was observed from some polymers supplied by Shin-Etsu Ltd., while most of the polymers obtained from Dow Chemical Company, with almost identical specifications, gave non-bimodal release profiles. It is not clear yet why these differences in release characteristics exist. Methods of manufacture, ionic composition, variations in the distribution of substituent groups, or distribution of molecular weight fractions may be the cause. Viscosity measurements were conducted on selected polymer lots. Experimental viscosity values were found to be well within the manufacturer's specified ranges.

Conventional oral sustained release formulations usually exhibit either a zero-order release profile, where the rate of drug release is essentially constant, or a profile where the rate of release decreases with time. Figure 1 compares declining, constant, and bimodal release profiles.

TABLE 1

HPMC polymers exhibiting bimodal and non-bimodal release

Bimodal	Non-bimodal
60SH-4000	A4-C
65SH-50	A4-M
65SH-400	A15-LV
65SH-1500	A15-C
65SH-4000	E4-M
90SH-100	E5
90SH-15000	E50
F4-M	E50-LV
	E15-LV
	K4-M
	K15-M
	K100-M
	K100-LV

Figure 2 illustrates the bimodal release of a controlled release aspirin tablet containing 40% Metolose 65SH-4000. The upper curve is the cumulative amount of drug released as a function of time, while the bar graph comprises the same data presented as the rate of release as a function of time. A similar bimodal release profile is shown in Fig. 3 for an ibuprofen tablet made with 60% Metolose 65SH-4000. The bar graph clearly shows an initial rapid release of drug, followed by a period of constant release, and then a second mode of fast drug release, that are characteristic of bimodal release.

The rate of drug release and the shape of the release profile can be selectively modified by varying the viscosity, concentration, and combination of hydroxypropyl methylcellulose used. Other excipients such as methylcellulose, sodium carboxymethylcellulose, hydroxypropyl

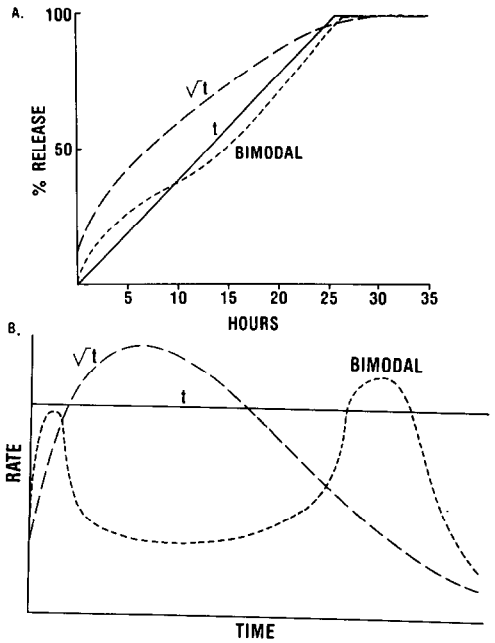

Fig. 1. Comparison of bimodal release with constant (t) and declining ($\sqrt{t}$) release profiles. A: Cumulative drug release. B: Rate of release as a function of time.

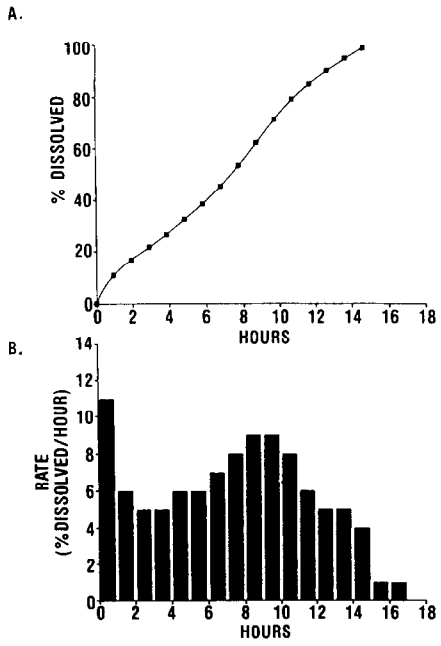

Fig. 2. Bimodal release profiles of 300 mg aspirin tablet. A: Percent drug dissolved versus time. B: Rate of drug release (percent dissolved/hour) versus time.

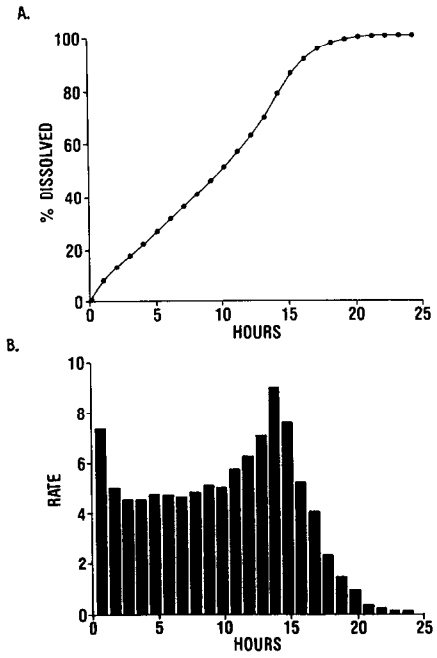

Fig. 3. Bimodal release profile of 60 mg ibuprofen tablet. A: Percent drug dissolved versus time. B: Rate of drug release (percent dissolved/hour) as a function of time.

cellulose, lactose, starch, binders, fillers, and disintegrating agents, may also be added to the formulation in alter the release rate. The effect of polymer viscosity on the time course of bimodal release is demonstrated in Fig. 4. Generally the use of higher viscosity polymers results in slower drug release from the matrix tablets. In Fig. 5, the addition of increasing amount of methylcellulose (1500 cP) to a formulation containing Metolose 65SH-4000, shifts the bimodal profile to the left, increasing the rate of drug release.

Bimodal release is evident in results of *in vitro* dissolution testing of 30 mg adinazolam tablets, prepared by incorporating 65% Metolose 65SH-1500 and 25% Metolose SM-1500 with the drug (Fig. 6). Preliminary evaluation of these tablets in a clinical biopharmaceutical study suggests that the bimodal sustained release is also evident *in vitro*. A comparison of serum levels in normal volunteers, as a result of oral administration of the bimodal tablets and

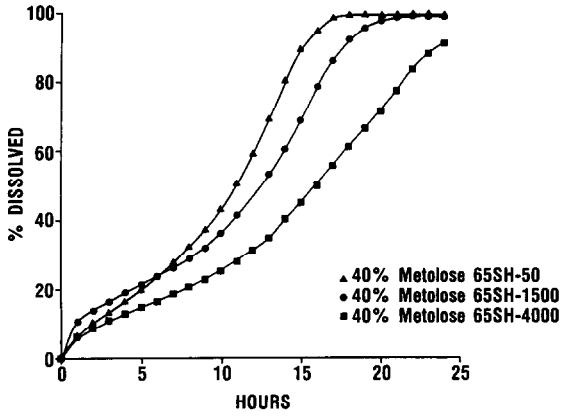

Fig. 4. Effect of polymer viscosity on drug release from 200 mg ansaid tablets.

conventional tablets is given in Fig. 7. The bimodal sustained release tablets provided an initial serum drug level of approximately 20 ng/ml after an hour, which remained essentially constant for seven hours. A subsequent rise was

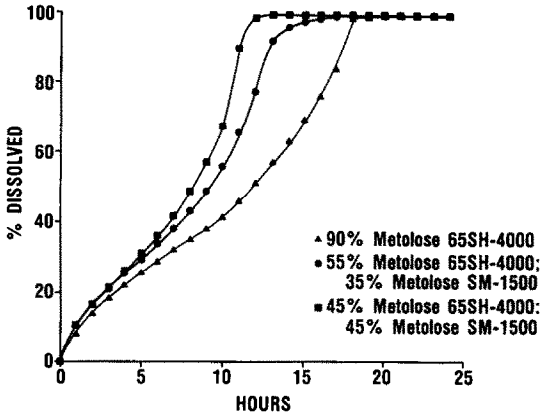

Fig. 5. Effect of rate modifier (Metolose SM-1500) on drug release from 30 mg deracyn tablets.

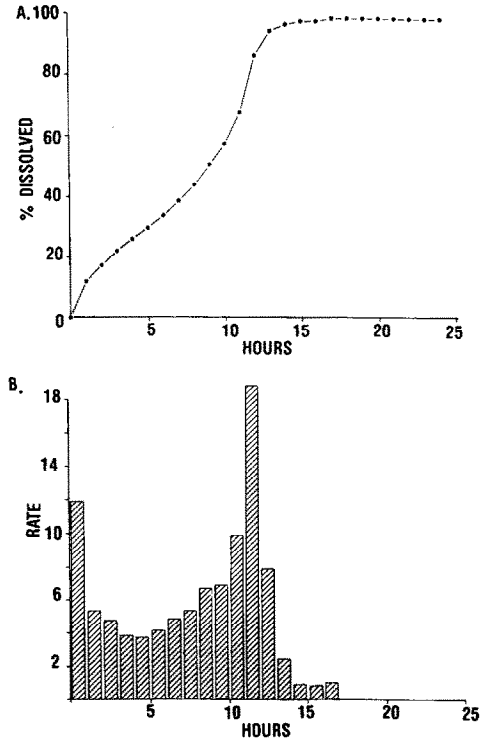

Fig. 6. Bimodal release profile of 30 mg adinazolam tablet. A: Percent drug dissolved versus time. B: Rate of drug release (percent dissolved/hour) as a function of time.

seen at about nine hours, with nearly steady drug levels for the next five hours.

Bimodal drug release from hydroxypropyl methylcellulose gel–matrix seems to involve an

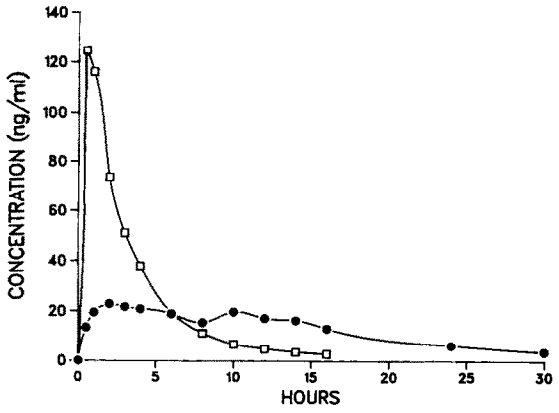

Fig. 7. Comparison of human serum levels of rapid release versus bimodal controlled release adinazolam tablets. Drug concentration in serum (ng/ml) as a function of time. □ = Conventional release tablet; ● = controlled bimodal release tablet.

initial gelation phase during which there is some erosion of the tablet matrix, which provides rapid dissolution. This phase is followed by counter-directional diffusion of dissolved drug and solvent through the polymer gel, substantial swelling, and considerable dissolution of the gel surface. Upon complete hydration of the polymer, disintegration of the gel–matrix occurs. The relative contribution and effects of each of the processes involved needs to be accessed before a comprehensive description of the mechanism of bimodal release is possible.

The kinetics of drug release from an erodible device, in the absence of diffusion, under perfect sink conditions, have been presented by Hopfenberg [4] and by Baker and Lonsdale [5].

Korsmeyer et al. [6,7] developed mathematical models for solute release from noneroding swellable polymer systems, based on a drug diffusion coefficient which is dependent on the concentration of absorbed solvent, in a functional form consistent with the free volume theory of diffusion. Their findings showed an exponential dependence of the solute diffusion coefficient on penetrant concentration.

A mathematical model incorporating the diffusion of solvent in polymer, diffusion of dissolved polymer in solution, and characteriza-

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