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PREPARATION AND DISSOLUTION CHARACTERISTICS OF PROLONGED RELEASE MEBEVERINE-HCL BEADS

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ABSTRACT

Different batches of slow release mebeverine-HCl beads were prepared by pan coating technique using different release retarding polymers viz Eudragit RL_{100}, Eudragit RS_{100} and Ethyl cellulose. The thickness of the coats was controlled by changing the amounts of the added polymers. Pre- and overcoating of the beads with bees wax was also carried out. Mixtures of pre-waxed Eudragit RS_{100} coated and uncoated beads in different ratios were prepared to control both drug content and release.

Dissolution profiles of mebeverine HCl from the prepared beads were investigated using USP XX rotating basket method. Prolonged release of mebeverine-HCl was obtained from different batches of the coated beads with the advantage of no initial dumping of the water soluble drug. The release of mebeverine-HCl from the beads coated with acrylic resins and ethyl cellulose as well as waxed acrylic resins coated beads was diffusion controlled according to Higuchi model. Beads coated with ethyl cellulose showed a different release pattern when pre- or overcoated with wax. By altering the

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ratios of prewaxed Eudragit Rs_{100} coated and uncoated beads in formulated mixtures, it was possible to control both mebeverine-HCl content and release rate.

INTRODUCTION

Beads offer the advantage over other sustained release systems where the coated particles can be widely distributed throughout the gastrointestinal tract. This improves drug absorption and reduces the side effects related to localized build up of irritating drug in G.I.T. mucosa(1). Nevertheless, the importance of beads is also due to possible wide range of drug levels and the high drug loading that can be obtained with this physical form(2). Conventional pan coating method has been described in the literature, and has been applied to polymers such as Polyvinylacetate(3), Eudragits(4,5), Hydroxypropylmethylcellulose(6) and Microcrystalline cellulose(7).

Mebeverine HCl is an effective antispasmodic drug used to relieve irritable bowel syndrome(8,9) with selective effect on the G.I.T. smooth muscle specially the colon(10). The drug is water soluble, has a short biological half-life of 1.7+0.17 hrs(11) and normally prescribed 3-4 times daily. Therefore, sustained release mebeverine-HCl is an important therapeutic aspects because it would be possible to maintain steady plasma level of the drug and reduce the frequency of administration especially in the treatment of chronic cases.

The objective of this study was to prepare sustained release mebeverine-HCl beads coated with different polymers namely acrylic resins and Ethylcellulose as drug release controlling materials. The effect of precoating as well as overcoating of the beads with hydrophobic waxy material, to prevent lumps formation during beads production, on the in-vitro release and release kinetics of mebeverine-HCl from the beads were also investigated. Furthermore, mixtures containing various ratios of coated and uncoated beads were prepared and evaluated in order to control both drug content and drug release rate from the final product.

EXPERIMENTAL

MATERIALS

Mebeverine-HCl powder (Duphar, B.V. Weesp, Holland), Eudragit RL_{100} and RS_{100} (Rohm. Pharm. GMBH, Weiterstadt, Germany), carboxymethylcellulose sodium

(BDH, Poole, England), ethylcellulose (10 cps viscosity grade, FMC Corporation, Philadelphia, USA), talc (Charles, B. Chrylstal Company, Inc., New York, N.Y.), bees wax (E. Merck, Darmstadt, Germany), corn starch USP (FMC, Corporation, Philadelphia, PA, USA), and sucrose (Food grade) were used as received. Other chemicals and solvents were of analytical reagent grade.

METHODS

Preparation of mebeverine-HCl beads:

Mebeverine-HCl beads were prepared from a powdered mixture containing 90 gm sucrose (0.5-0.8 mm), 3 gm carboxymethylcellulose sodium, 15 gm corn starch, 15 gm talc and 78 gm mebeverine-HCl using the conventional pan coating method that was previously described(4). Distilled water was used as a wetting agent while, 2 parts of talc and 1 part of corn starch were used as a dusting mixture. Size screening and size selection was performed and those beads having particle size range of 0.8-1 mm were selected for preparation of mebeverine-HCl sustained release beads. The drug loaded beads were coated by spraying different concentrations (10 and 20% w/w) of Eudragit RL_{100}, RS_{100} or ethylcellulose that was dissolved in 1:1 isopropanol-acetone mixture in the coating pan using hot stream of air. The effect of applying another release retarding coat of bees wax (3.3% w/w) as pre or overcoat was also studied by spraying its chloroformic solution before or after polymer coating of the beads.

Determination of beads contents:

Approximately 30 mg of mebeverine-HCl beads were sonicated with 100 ml of ethylalcohol for 10 minutes. 10 ml of the solution was filtered and an aliquot, suitably diluted, was analyzed spectrophotometrically at 263 nm for its mebeverine-HCl content. A mean of three assays were recorded.

In-vitro dissolution study:

Dissolution studies were performed on 0.8-1 mm mebeverine-HCl beads using USP/NF dissolution apparatus I with a 50 rpm basket rotational speed and an automated monitoring system (IBM Computer PK 8620 series and PU 9605/60 tablet dissolution system

software, Philips UGV, Vis NIR single beam spectrophotometer PU 8605/50 eight cell program, Epson LX 850 Printer and Matson-Marlow Prestatic Pump). 750 ml phosphate buffer of pH 7.4 was used as dissolution medium at 37°+.5°C. The concentration of the dissoluted mebeverine-HCl from beads equivalent to 200 mg drug was determined spectrophotometrically at 263 nm. All determinations were carried out in triplicate.

RESULTS AND DISCUSSION

From Figure 1 it was clear that the release profile of the drug from the prepared coated beads depends to a great extent on the type of polymer used as well as the coating level of the final product. A significant retardation for release of the water soluble mebeverine-HCl from the polymeric coated beads with the advantage of no drug dumping was observed. While, it was previously reported that drug dumping (60-80%) could be seen with readily soluble drug when encapsulated with polymeric materials (5). Our results are in agreement with data of previous workers (12), and might be due to the uniformity and integrity of deposition of the coating materials. At 10% coating with Eudragit RL_{100}, RS_{100} and ethylcellulose, the amount of mebeverine-HCl released in 3 hours dissolution time was 82.58, 72.79 and 71.83% respectively, while at 20% coating with the same polymers the amount released was 64.92, 61.25 and 59.12%, respectively, compared with 91.5% for the uncoated beads. These results indicate that the high coating level produce significant retardation on drug release ($p<0.05$). Therefore, the polymers, according to their retardation effect, could be arranged in a descending manner as follows: ethylcellulose, Eudragit RS_{100}, then Eudragit RL_{100}.

From Figure 2 it is apparent that 3.3% wax coating caused more pronounced retarding effect in case of beads coated with Ethylcellulose and Eudragit RS_{100} specially when the beads are prewaxed. The wax overcoating expected to be rapidly emulsified and dissolved by the dissolution media (phosphate buffer, pH 7.4) this allowed for faster drug release than from prewax coating where, the wax coat could be dissolved only after a time required for the dissolution media to permeate through the polymeric film.

Table 1 summarizes the correlation coefficients (r) of the different release kinetic models. It is apparent that the release model of mebeverine-HCl from the beads coated with acrylic resins or ethylcellulose were nearly linear for both square root of time and first order release plots as indicated by their cor-

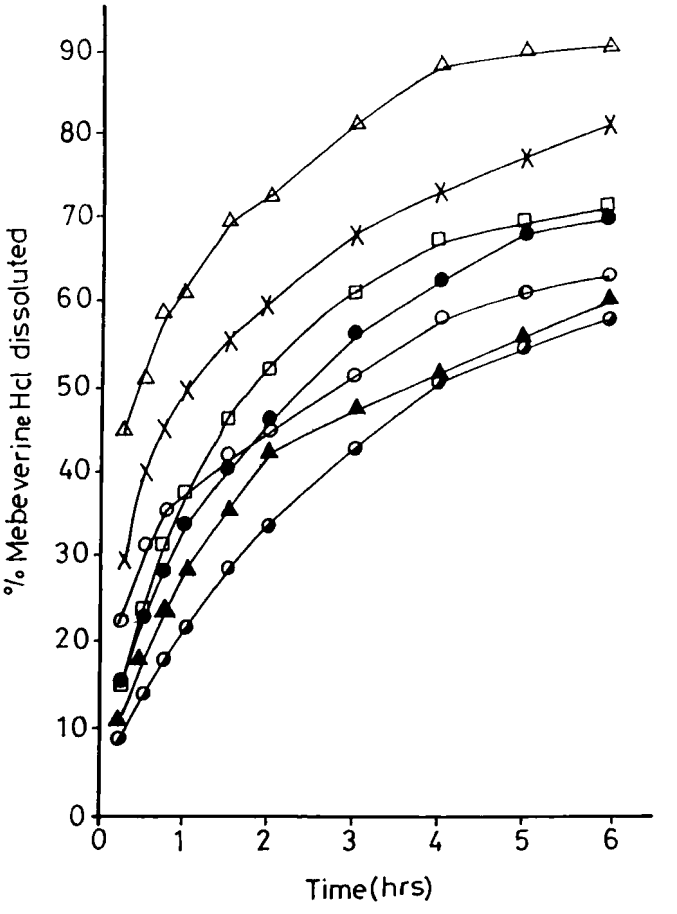

Fig. (1) Dissolution of mebeverine-HCl beads coated with different polymers in phosphate buffer of pH 7.4 at 37°C±0.5 (particle size 0.8-1 mm).

△ Non-coated beads
X Eudragit RL_{100} 10%
□ " " RS_{100} 10%
● Ethylcellulose10%
○ Eudragit RL_{100} 20%
▲ " RS_{100} 20%
◕ Ethylcellulose20%

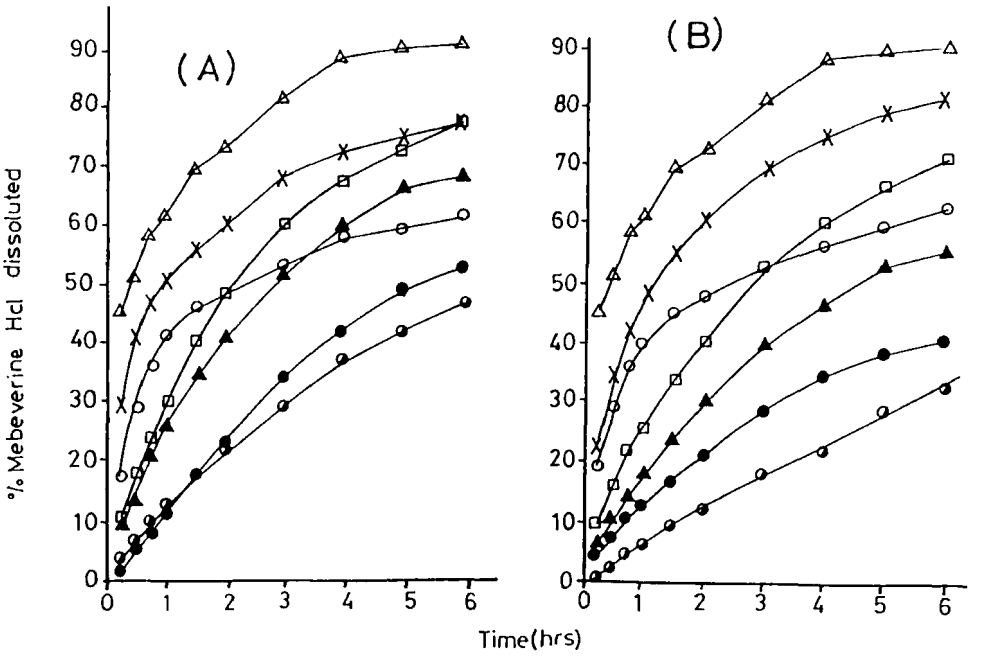

Fig. (2) Dissolution of mebeverine-HCl from prewaxed caoted (A) and overwaxed coated (B) beads in phosphate buffer of pH 7.4 at 37°C±0.5.

△ Non-coated beads
X Eudragit RL_{100} 10% + 3.3% bees wax
○ " RS_{100} 20% + 3.3% " "
□ Eudragit RS_{100} 10% + 3.3% " "
▲ " RL_{100} 20% + 3.3% " "
● Ethylcellulose 10% + 3.3% " "
◕ " " 20% + 3.3% " "

relation coefficients while, zero order plots were significantly far from linearity.

In order to further verify the release model the simple power law expression, that was demonstrated by Korsmeyer et al (13), $Mt/Moo=Kt^n$ was adopted. Although this equation was applied for several defined geometry, it was tried for beads in this study. From Table 1 the values of (n) came to be 0.263-0.626 for Eudragit coated mebeverine-HCl beads and 0.300-0.695 for waxed acrylic resin coated beads, indicating that the release mechanism could be a Fickian diffusion. Ethylcellulose waxed beads gave values of (n) ranging from 0.614-1.137 which indicated a possible zero order or diffusion process.

TABLE 1

Regression coefficients (r) for different kinetic models and (n) values for the release of mebeverine-HCl from coated beads.

Coat	Conc.	Zero order	First order	Diffusion Model	(n) values	dQ/dt vs.1/Q	dQ/dt vs. Q
Eudragit RL_{100}	10%	0.9526	0.9922	0.9903	0.3040	0.8700	0.7664
" "	20%	0.9441	0.9705	0.9821	0.2632	0.8950	0.7910
Eudragit RS_{100}	10%	0.9194	0.9614	0.9739	0.4838	0.9807	0.9647
" "	20%	0.9525	0.9802	0.9906	0.5490	0.9834	0.9445
Ethylcellulose	10%	0.9640	0.9923	0.9954	0.4840	0.9932	0.9622
" "	20%	0.9812	0.9960	0.9994	0.6256	0.9824	0.9560
3.3% wax overcoat+							
Eudragit RL_{100}	10%	0.9280	0.9694	0.9716	0.3000	0.9466	0.8639
Eudragit RL_{100}	20%	0.8911	0.9210	0.9510	0.4366	0.9950	0.9500
Eudragit RS_{100}	10%	0.9603	0.9771	0.9935	0.6110	0.9503	0.9659
Eudragit RS_{100}	20%	0.9667	0.9879	0.9953	0.6395	0.9555	0.9561
Ethylcellulose	10%	0.9899	0.9981	0.9973	0.6140	0.6105	0.9380
Ethylcellulose	20%	0.9908	0.9981	0.9985	0.9011	0.8496	0.9776
3.3% wax precoat+							
Eudragit RL_{100}	10%	0.9283	0.9841	0.9785	0.3970	0.9863	0.9125
Eudragit RL_{100}	20%	0.9148	0.9563	0.9678	0.3451	0.9854	0.9141
Eudragit RS_{100}	10%	0.9617	0.9977	0.9982	0.5020	0.9803	0.8614
Eudragit RS_{100}	20%	0.9799	0.9929	0.9973	0.6952	0.9029	0.8845
Ethylcellulose	10%	0.9801	0.9852	0.9975	0.7165	0.9006	0.9724
Ethylcellulose	20%	0.9925	0.9991	0.9972	1.1370	0.6952	0.8990

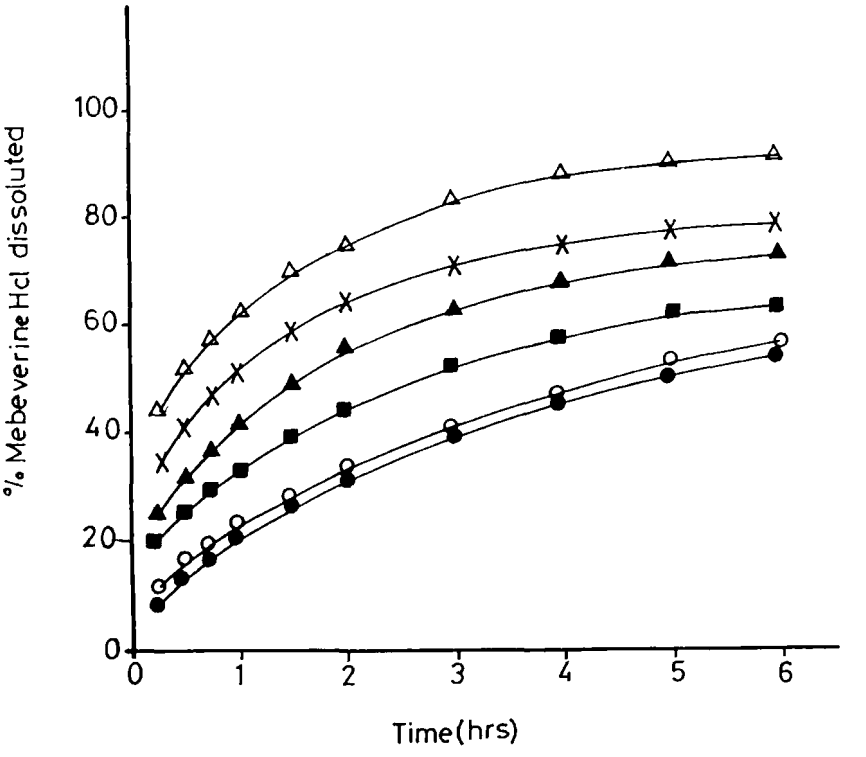

Fig. (3) Dissolution of mebeverine-HCl from mixtures of prewaxed Eudragit RS_{100} coated and uncoated beads in phsopate buffer of pH. 7.4 at 37°C ±0.5.

●	100%	coated beads
○	90:10	coated/uncoated
□	70:30%	coated/uncoated
▲	50:50	coated/uncaoted
X	30:70	coated/uncoated
△	100%	uncoated beads

As the (n) values deviated from 0.5, it was still necessary to distinguish between the possible mechanisms of release using the differential form of the square root of time and first order equations dQ/dt versus both Q and 1/Q, respectively where dQ/dt is the release rate and Q is the amount released (14,15). The high correlation coefficients obtained for the relation dQ/dt versus 1/Q (Table 1) confirmly indicated a diffusion controlled mechanism for the release of the drug from beads coated with acrylic resins, and ethylcellulose as well as for the waxed acrylic resin coated

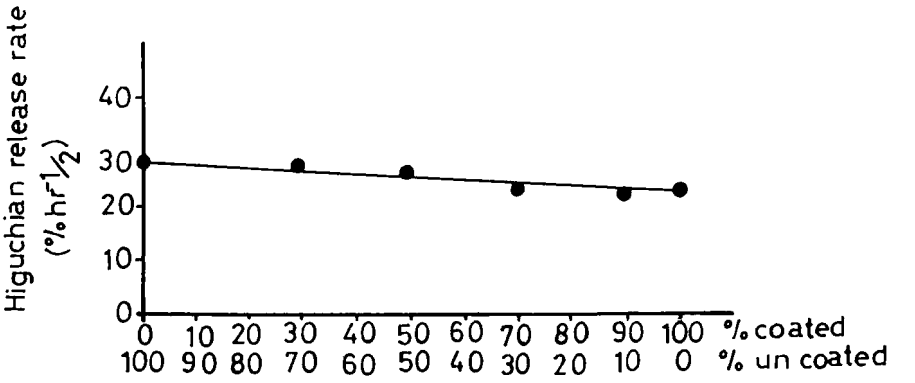

Fig. (4) Higuchian release rate of mebeverine-HCl from different mixtures of prewaxed Eudragit RS_{100} coated and uncoated beads.

beads. Although the above n values were deviating from 0.5, it was proven that the diffusion controlled mechanism is still valid. It was believed that the deviation in n values might be attributed to its dependency on both the release mechanism and the geometry of the system(16), as concern the beads particles are not having a regular smooth surfaced shape.

Beads coated with ethylcellulose showed a different behavior when pre or overcoated with wax compared to acrylic resins. The regression coefficients obtained for the relation dQ/dt versus both Q and 1/Q revealed an overall first order kinetic. This could be explained by the interesting observation for the release which occurs via two phases. An initial zero order release valid for 1.5-2 hours with regression coefficient of 0.999+0.00066 was followed by confirmed diffusion controlled mechanism for the rest of release time with a regression coefficient of 0.946+0.0036. This finding indicates that zero order release mechanism is working as long as wax coat is intact, where it was believed that precoated wax film needs about 2 hours to be dissolved in the dissolution media as shown in Figure 2.

In order to control drug content and drug release from the final preparation, mixtures of prewaxed Eudragit RS_{100} coated and uncoated beads were blended together in various ratios. Figure 3 shows the dissolution of mixtures containing 90, 70, 50 and 30% w/w of the prewaxed Eudragit RS_{100} coated mebeverine-HCl beads with the uncoated beads in phosphate buffer pH 7.4. By

altering the percentage of coated and uncoated beads, it was possible to increase or decrease the rate of drug release. The overall dissolution rate of each of these mixtures were found to obey the diffusion controlled kinetics (best regression coefficient compared to other models). Plotting Higuchi diffusion rate of the mixtures versus the percentage of its compositions gave a linear relationship (Fig. 4), indicating that Fickian diffusion model was regularly valid throughout the whole range of mixtures. This also reveals that the release rate of mebeverine-HCl from prewaxed Eudragit RS_{100} coated beads could be easily adjusted to the required rate by just controlling the ratio of the coated to uncoated beads in a mixture.

Further in-vivo studies are in progress to determine the performance of a suitable formulation of mebeverine-HCl sustained release beads.

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