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RELEASE KINETICS AND AVAILABILITY OF MEBEVERINE HYDROCHLORIDE FROM POLYCARBOPHIL LOADED BY SWELLING

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ABSTRACT

The release rate and mechanism of release of mebeverine hydrochloride were studied for commercial "Duspatalin" tablets and for different tablet formulations (F_1, F_2 & F_3) containing 20, 40 and 65% polycarbophil, respectively. The formulated granules were obtained by freeze drying of polycarbophil granules loaded with aqueous solution of the drug at 25°C by swelling of the polymer. The release of mebeverine hydrochloride from prepared tablet formulations was faster than that of Duspatalin tablets. The release rate of the drug increased as the polycarbophil content of the tablets increased. The calculated correlation coefficients for the release data fitted to various models showed that the release from Duspatalin tablets and F_2 follow first order kinetics, while release of F_1 approaches that of zero order. The release mechanism from F_3 could not be determined. DSC thermograms showed that there is an interaction between the drug and the polymer in aqueous medium, but not in the solid state.

The in-vivo guinea-pig studies revealed that mebeverine hydrochloride was released and absorbed from the tested formula (F_3), depressed the agonists-induced contractions 2 hrs after treatment but not after 4 hrs indicating rapid absorption and metabolism. The percentage inhibitions ranged from

40-85%. The treatment seems to antagonise barium chloride ($BaCl_2$)-induced contractions more than those induced by carbochol.

INTRODUCTION

Mebeverine Hydrochloride is a musculotropic spasmolytic with strong and selective action on the smooth muscle spasm of the gastrointestinal tract, particularly the colon[1,2].

Matrices can be prepared by evaporation of solutions of polymers in which the drug is dissolved or dispersed[3,4], by adding the drug to monomer:cross-linking agent[5] and by compression of the polymer-drug mixture[6-10]. Also, matrices can be prepared by swelling of polymers with solvents in which drugs are dissolved[11-13]. The last technique is used in this study using mebeverine hydrochloride which is very soluble in water and of very bitter taste. Polycarbophil[14], being a synthetic polymer, of polyacrylic acid loosely crosslinked with about 0.15-1% (w/w) divinylglycol, that is insoluble but can swell to varying degrees in water, common organic solvents, strong mineral acids and bases makes it a candidate polymer to be used in this study. The swelling characteristics of polycarbophil in water are pH dependent, swelling increases, as pH increases. At low pH (1-3) polycarbophil absorbs about 15-35 ml of water per gram. The purpose of this study is the preparation and evaluation of release rate and availability of mebeverine hydrochloride tablets prepared by the above mentioned technique.

MATERIALS AND METHODS

Materials

Mebeverine hydrochloride powder and tablets were a kind gift from Duphar B.V. (Weesp, Holland). Polycarbophil was kindly provided by Lee Laboratories (Petersburg, V.A., USA). All other chemicals and reagents were of analytical grade.

Loading of Polymer

The loading of polycarbophil (pc) granules (30-40 mesh) was carried out at 20°C by allowing the granules to swell in aqueous solutions of different concentrations of mebeverine hydrochloride. The water was then

evaporated by freeze-drying. This method of loading ensures the loading of the desired amount of the drug within polymer granules[15,16]. The amounts of mebeverine hydrochloride loaded in polycarbophil granules by swelling the polymer were 135 mg drug per 35, 90 and 250 mg dry polymer in formulae F_1, F_2 and F_3, respectively (Table 1).The resulting freeze dried granules were subjected to sieving through a 30/40 mesh screen and mixed with 1% talc and 2% magnesium stearate, just before direct compression into tablets using a single punch tabletting machine (Korsch, type EKO, Frankfurt, Germany) fitted with a 6 mm flat faced punch. The hardness was measured in Kp in a hardness tester (Erweka, Type TB 24, Frankfurt, Germany) and was adjusted to the range of 4-6 Kp.

Drug Content Determination

A known weight of the granules was dissolved in 0.1N HCl, filtered through a 0.45 Um pore size filter, and assayed using a Pye Unicam SP 8800 (Cambridge, U.K.) at 263 nm for its drug content. Blank experiments showed no interference from polycarbophil in 0.1N HCl at the above wavelength.

Melting Point Determination

The melting point of the granules was determined using the melting point apparatus (Mettler FP 800, Mettler Instruments AG, Griefensee, Switzerland).

Differential Scanning Calorimetry (DSC) Analysis

The DSC thermograms were recorded on a General V1.oJ Dupont 9900 thermal analyzer, calibrated with indium (99.999%). The DSC studies on the samples were performed by heating 2 mg of sample at a heating rate of 10°C/min over a temperature range of 25-350°C in closed aluminium pans under an argon purge.

Dissolution Studies

In-vitro release studies of commercial and prepared tablets of mebeverine hydrochloride were performed using the USP dissolution apparatus (Erweka, type DT6, Frankfurt, Germany) at 100 rpm and 37°C. The dissolution medium was 900 ml of 0.1N HCl. Aliquots withdrawn periodically over 2 hours, were filtered through 0.45 um pore size filter, properly diluted with 0.1N HCl and assayed as mentioned above.

TABLE 1

Formulation of Mebeverine Hydrochloride Tablets

Ingredient (mg)	Formulation		
	F_1	F_2	F_3
Mebeverine HCl	135	135	135
Polycarbophil	35	90	250
Talc (1%)	1.70	2.25	3.85
Magnesium stearate (2%)	3.40	4.50	7.70

Study of Spasmolytic Activity of Mebeverine Hydrochloride in Guinea-Pig

a. Preparation of the Isolated Guinea-Pig Ileum From Control Animals:

Six guinea-pigs (500 g) fasted for 15 hours were anaesthetized with aqueous urethane (25% w/v) using a dose of 1.5 g/kg i.p. A small incision was made in the upper part of the abdomen and the stomach was located and withdrawn out. A small incision was made in the fundal area, then sutured and the stomach was returned to its normal position in the abdomen. The abdominal incision was then sutured. Two or 4 hrs later, the animals were killed. The abdomen opened, segments of its terminal ileum (2 cm long) were cut and suspended in oxygenated Tyrode's solution at 37°C. Each tissue was then attached to an isometric transducer fitted to a Narco Physiograph and left to stabilize for 20 min. Thereafter dose-response curves for $BaCl_2$ (20-80 ug/ml) and carbochol (20-80 ng/ml) were obtained using a contact time of 20 sec and a dose cycle of 10 min.

b. Preparation of the Isolated Guinea-Pig Ileum From Treated Animals:

Six guinea-pigs were prepared as described above except that half tablet of mebeverine

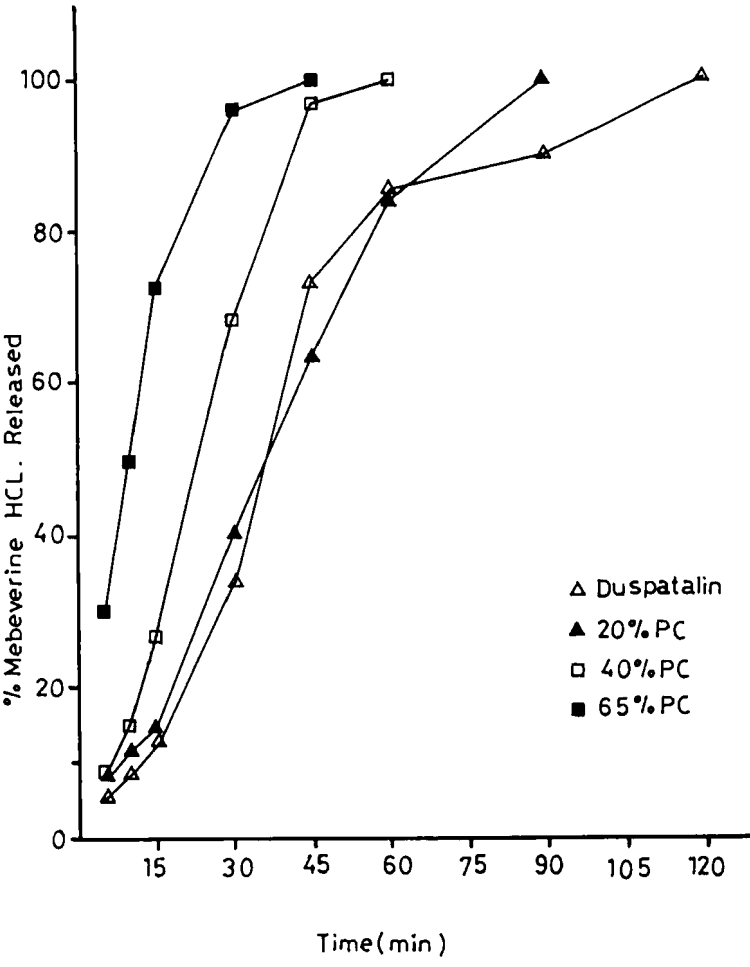

FIGURE 1

Release profile of Mebeverine HCl from commercial tablets and prepared formulations.

hydrochloride (F_3) was inserted in each stomach. The animals were killed 2 or 4 hrs after treatment. Segments of the terminal ileum (2 cm long) were then cut, and suspended in oxygenated Tyrode's solution. The dose-response curves of $BaCl_2$ and carbachol were then obtained. The percentage decrease in the induced contractions were calculated in reference to the response obtained from the control animals (Sham-operated).

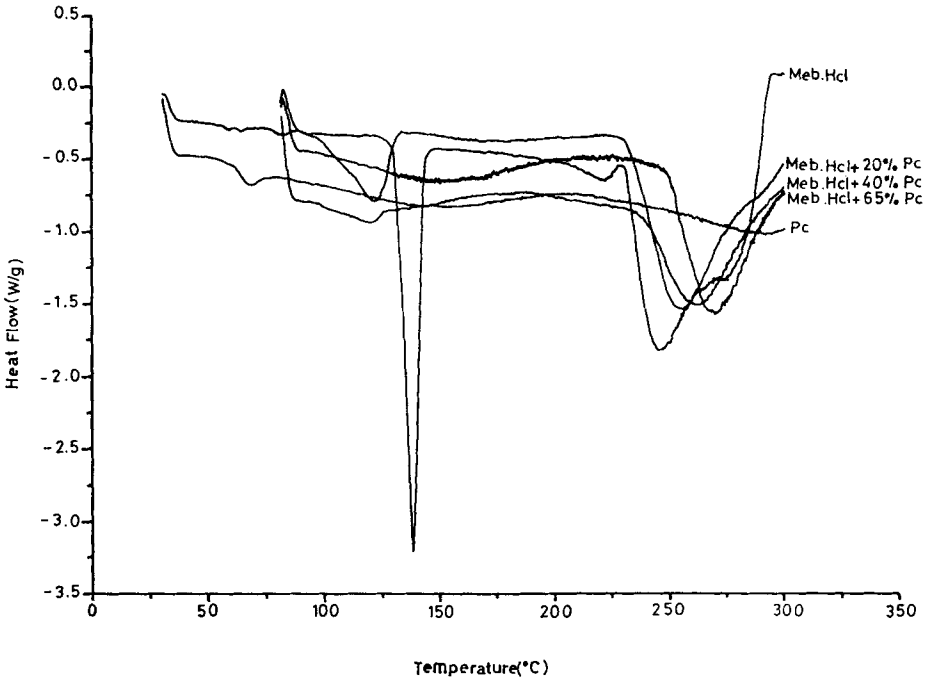

FIGURE 2

DSC thermograms of Mebeverine HCl, polycarbophil and their combination product in F_1, F_2 and F_3.

RESULTS AND DISCUSSION

The prepared tablets were found to comply with the USP specifications for tablet content uniformity. Figure 1 shows that the release rate of mebeverine hydrochloride from the prepared tablets (F_3) is significantly faster than that from the commercially available Duspatalin tablets, while that of (F_1 and F_2) is non-significantly faster ($p<0.05$, student t-test). This could be attributed, in part, to the light and porous nature of the granules of the prepared tablets which were produced by freeze drying. The porosity gives ready solubility and consequently higher rate of release. This is because the drug inside the polymer occupies the same volume as the original solution[15,16]. It is also evident from Fig.

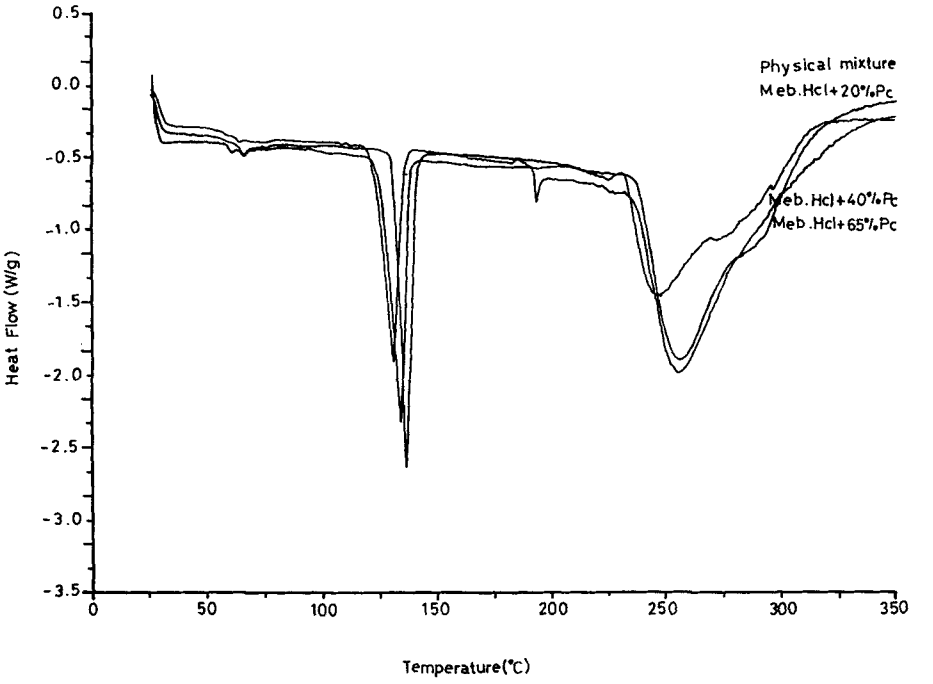

FIGURE 3

DSC thermograms of physical mixtures of Mebeverine HCl and polycarbophil in same ratios as in F_1, F_2 and F_3.

1, that as the polycarbophil content increased in the prepared tablets, the release rate increased. This can be explained by the fact that polycarbophil particles have a high concentration of ionic groups inside which cause a large influx of water by osmosis, swelling the particles until the crosslinks are strained[14]. This will lead to rapid diffusion of soluble drug out of the polymer.

The results obtained from DSC thermograms (Fig. 2) show that there is an endothermic melting peak max at 135°C for mebeverine hydrochloride, in addition, the polymer shows an endothermic physical change at about 67°C which could be due to melting or dehydration of existing moisture. Thermograms also show interaction between the drug and the polymer due to for-

TABLE 2

Analysis of Release Data of Mebeverine Hydrochloride From Duspatalin and Prepared Tablet Fomulations.

Formula	Model	Coefficient	Slope	Intercept	Release Mechanism
Duspatalin	Zero	0.9829	1.8509	-14.6308	
	First	0.9966	0.0274	0.6570	First
	Higuchi's	-0.9623	-17.9540	154.6299	
	Release exponent	-0.8821	-0.7435	2.7769	
F_1	Zero	0.9964	1.5349	-6.1233	
	First	0.9853	0.0222	0.85016	Zero
	Higuchi's	-0.9809	-15.0766	140.1954	
	Release exponent	-0.9456	-0.5727	2.5657	
F_2	Zero	0.9145	2.1401	-11.1142	
	First	0.9507	0.0205	1.0075	First
	Higuchi's	-0.8814	-20.4337	155.7997	
	Release exponent	-0.7749	-1.8381	3.9686	
F_3	Zero	0.2331	0.2929	61.9033	
	First	0.2593	0.0020	1.7773	-----
	Higuchi's	-0.3197	-3.9801	49.8998	
	Release exponent	-0.3641	-0.6061	2.1510	

mulation. F_1 (20% polymer) shows that the endotherm became broader and the intensity of the peak became less sharp. While F_2 and F_3 (40 and 65% polymer), respectively, show complete disappearance of the endothermic melting peak of the drug (135°C). On the other hand their physical mixtures (Fig. 3) show a simple superposition of the thermal pattern of each component. This is in agreement with the melting point determinations.

To study the mechanism of release of the drug from commercial and prepared tablets, the release data

TABLE 3

Effect of Mebeverine Hydrochloride After 2 hrs of Treatment (F_3) on $BaCl_2$ and Carbachol-Induced Contractions in the Isolated Guinea-Pig Ileum.

Drug & Dose		Amplitude (in mm)		Percentage Inhibition
		Control	2 hours after Treatment	
A.	$BaCl_2$:			
-	20 ug/ml	3	1	66.7
-	40 ug/ml	13	2	84.6
-	80 ug/ml	39	15	61.5
B.	Carbachol:			
-	20 ng/ml	28	8	71.4
-	40 ng/ml	55	30	45.4
-	80 ng/ml	65	39	40.0

were tested for zero and first order kinetics as well as Higuchi[17] model. the exponent indicative of release mechanism (n) is also determined[18]. The correlation coefficients as well as slopes and intercepts of tablet formulations release data are shown in Table 2.

The release from the commercial tablets and F_2, containing 40% polycarbophil,was found to follow first order kinetics, while that for F_1, containing 20% polycarbophil, follows that of zero order kinetics. The release from F_3, containing 65% polycarbophil, shows a value of $n<0.5$ which indicate statistical analysis problems[18] or is due to drug release from porous system by combined mechanisms (diffusion partially through a swollen matrix and partially through water-filled pores) which shift the release exponent toward a smaller value.

Figure 3 shows the dose-response curves of $BaCl_2$ and carbachol (a & b), respectively in the isolated

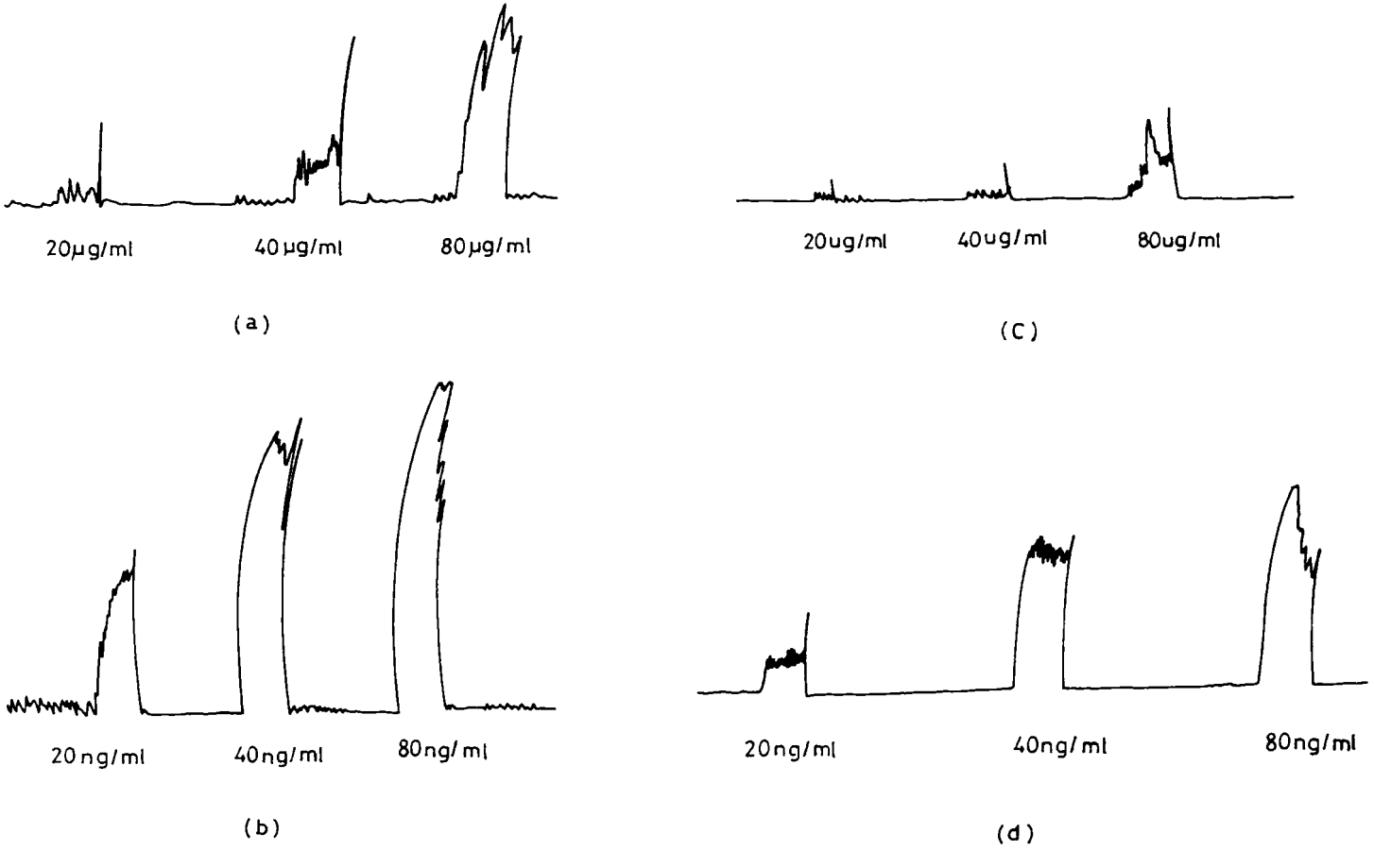

FIGURE 4

Dose-response curve of a) $BaCl_2$, b) Carbachol in guinea-pig ileum from controls and (c & d) 2 hrs after treatment respectively.

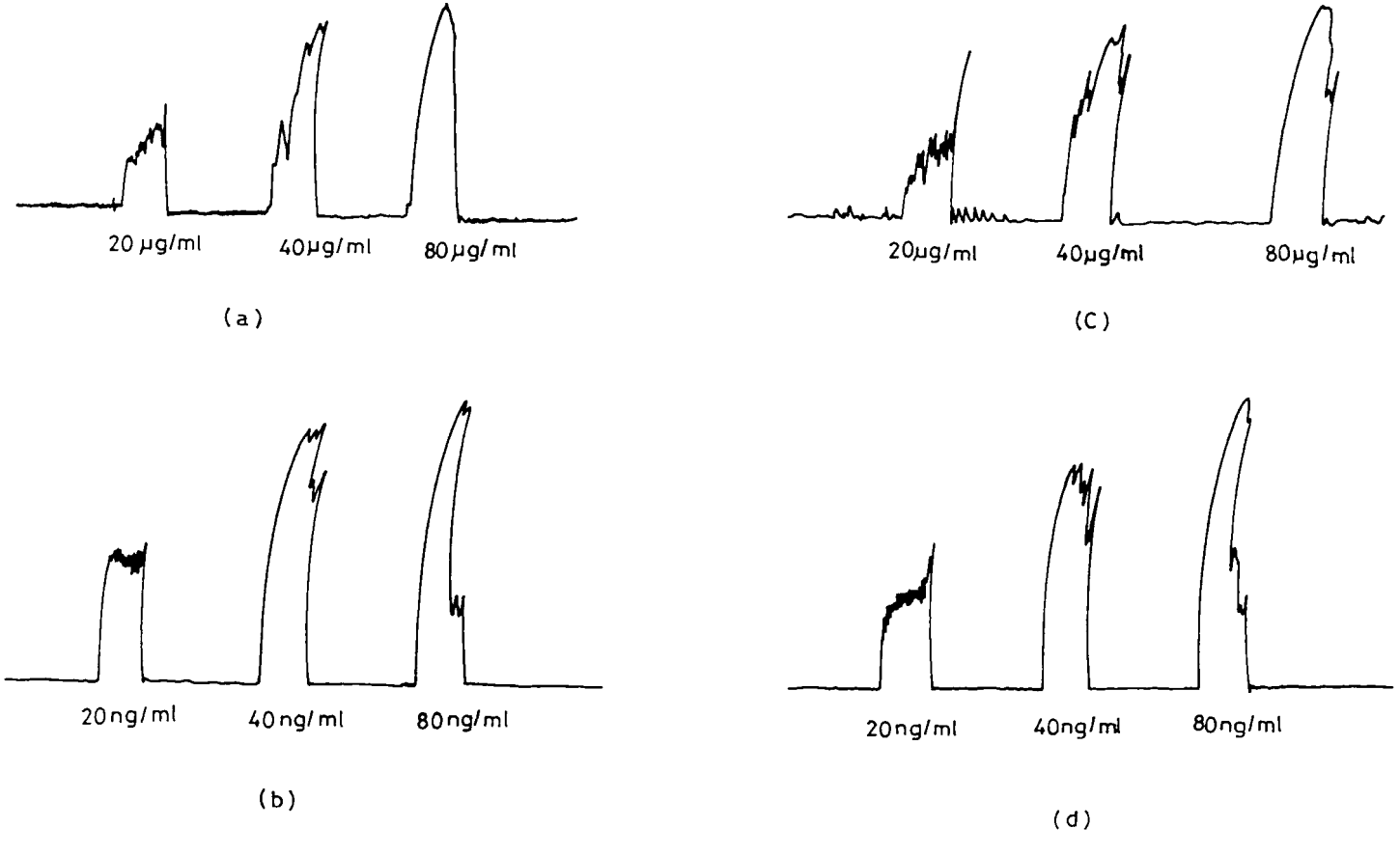

FIGURE 5

Dose-response curve of a) $BaCl_2$, b) Carbachol in guinea-pig ileum from controls and (c & d) 4 hrs after treatment respectively.

TABLE 4

Effect of Mebeverine Hydrochloride After 4 hrs of Treatment (F_3) on $BaCl_2$ and Carbachol-Induced Contractions in the Isolated Guinea-Pig Ileum.

Drug & Dose		Amplitude (in mm)		Percentage Inhibition
		Control	4 hrs after Treatment	
A.	$BaCl_2$:			
	- 20 ug/ml	15	15	Zero
	- 40 ug/ml	37	37	Zero
	- 80 ug/ml	42	43	Zero
B.	Carbachol:			
	- 20 ng/ml	25	22	12.0
	- 40 ng/ml	50	45	10.0
	- 80 ng/ml	55	55	Zero

guinea-pig ileum from the control (Sham-operated) animals. While Fig. 3 (c & d) shows the dose-response curves of both antagonists 2 hrs after treatment with half tablet of F_3. This treatment depressed the agonists-induced contractions. The percentage inhibition ranged from 40 to 84.6% as shown in Table 3. The treatment antagonise $BaCl_2$-induced contractions more than those induced by carbachol.

Similarly, Fig. 4 shows the dose-response curves of both antagonists in isolated guinea-pig ileum from control animals (a & b) and after 4 hrs of treatment (c & d). Testing the ileum after 4 hrs with F_3, failed to reveal normal inhibitory action that was observed after 2 hrs as shown in Table 4.

These results demonstrate clearly the disintegration of F_3 tablets and passage of its mebeverine HCl throughout the intestine. The induced spasmolytic activity of F_3 was demonstrated 2 hrs but not 4 hrs after treatment indicating rapid absorption and metabolism of the drug, so its suppressant activity was terminated before 4 hrs.

As a conclusion, polycarbophil is a useful polymer that could be used as a drug delivery system by inclusion of drugs by swelling.

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