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STUDIES ON THE MICROENCAPSULATION OF DEXTROPROPOXYPHENE HYDROCHLORIDE. PART 1. PREPARATION BY COACERVATION AND THE IN VITRO EVALUATION.

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ABSTRACT

The main purpose of our study is to achieve the release at a slower rate and the prolonged action of dextropropoxyphene hydrochloride through microencapsulation. Besides this, microencapsulation of this active agent can prevent the incompatibility in the presence of aspirin, and the local anesthetic effect on the tongue.

Microcapsules of dextropropoxyphene hydrochloride (D-PRX·HCl) were prepared by coacervation method with core-shell ratios of 1:1 and 1:2, and the in vitro release rate experiments were carried on in 0.1 N hydrochloric acid solution.

INTRODUCTION

D-PRX·HCl is a widely used non-narcotic analgesic since 1957 when it was first put into use (1). It has a very bitter taste and a local anesthetic effect on the tongue. Even though it is classified under non-narcotics, attention was drawn with its abused use (2,3). D-PRX·HCl is absorbed rapidly when administered orally. Its usual dose is 65 mg, 3-4 times a day. By slowing down the release rate, the prolonged action of D-PRX·HCl can be achieved. It is

usually used in combination with other analgesics and aspirin is the one used most commonly. However, D-PRX·HCl is reported to be chemically incompatible with aspirin (4).

To bring a solution to all of these problems, microencapsulation was proposed in this study. Most of the microencapsulation techniques cited in the literature were investigated, particularly those for the water-soluble drugs. Amongst the simpler techniques and those applicable in our laboratory conditions, the method developed by Jalsenjak and others (5) was chosen. Only the particles greater than 180 μm (>180 μm) and smaller than 63 μm (<63 μm) were used.

The dissolution parameters of the microcapsules obtained were then examined. For this purpose the release rate studies were carried on the following samples: E_1= D-PRX·HCl powder with a particle size 63 μm; E_2= D-PRX·HCl powder with a particle size >180 μm; M_1= microencapsulated E_1 with a core-shell ratio of 1:1; M_2= microencapsulated E_1 with a core-shell ratio of 1:2; M_3= microencapsulated E_2 with a core-shell ratio of 1:1; M_4=microencapsulated E_2 with a core-shell ratio of 1:2.

MATERIALS

D-PRX·HCl (Eczacıbaşı) was tested by thin-layer-chromatography, U.V. spectrophotometry, I.R. spectrophotometry, and melting point measurements for standardization. The spectra and the melting point values fit the data given in the literature (6-9). Ethyl cellulose (Hercules 22 NF) was used as a coating agent and cyclohexane (E. Merck) as the organic solvent. All the materials were of analitical grade.

The apparatus used throughout the experiments were: mechanical stirrer (Heidolph RZR 2000), thermostatic circulator (Euromex, Ex-003), dissolution apparatus (Aymes), mechanical shaker with the sieves (Endecott BS410), sieve for microcapsules (Erweka No.5), U.V. spectrophotometer (Schimadzu-UV-240 Graphicord), I.R. spectrophotometer (Schimadzu IR-435), melting point apparatus (Gallenkamp).

METHOD

Microencapsulation

The method developed by Jalsenjak and others (5) was used for microencapsulation. For this purpose, two batches of D-PRX·HCl with different particle sizes (<63 μm and >180 μm) were used as the core material, and after microencapsulation four batches of microcapsules were obtained with 1:1 and 1:2 core-shell ratios. The yields of microcapsules were calculated. Particle size distribution studies were carried on by sieving technique. To find the percentage of the active agent encapsulated extraction with water was preceeded by the rupture of the microcapsules.

Dissolution

The dissolution method used was the USP XX flask method. Two covered flasks which were each filled with 400 ml 0.1 N hydrochloric acid were placed in the dissolution apparatus. The water bath was maintained at 37±0.5°C, and a constant-speed motor was calibrated to provide a 50 rpm stirring rate throughout the test. 5-ml samples of the dissolution medium were withdrawn at selected times with an injector fitted with a Schleicher and Schüll (white-band) filter paper. An equivalent volume of 0.1 N hydrochloric acid was added to the flask after each withdrawal. The samples were then assayed spectrophotometrically at 257 nm.

RESULTS and DISCUSSION

It is known that the size distribution of the microcapsules and the pattern of release of the active agent from the microcapsules depend on the particle size of the core material (10). Therefore microencapsulation procedure was preceeded by the fractioniation of D-PRX·HCl achieved by sieving on a mechanical shaker.

The yield of microcapsules prepared were between 71.69 % and 89.98 %. When the microcapsules were investigated for their coating, it was seen under the microscope also that the capsules formed aggregates during the drying and isolation steps. To get the capsules in standard particle size, every batch was sieved and used in the dissolution rate studies.

TABLE 1.
% Content Of The Microcapsules

Core - shell ratio	Particle size used (μm)	% Content
1 : 1	< 63	66.8
	> 180	54.21
1 : 2	< 63	35.38
	> 180	34.54

Each value is the mean of five experiments.

The percentage of D-PRX·HCl content of the microcapsules were determined spectrophotometrically. The results are given in Table 1.

The results of the dissolution tests are given in Table 2 and demonstrated in Figure 1.

The studies on the in vitro release rates of D-PRX·HCl powder and microcapsules were applied to Lapidus-Lordi (11), Hopfenberg Slab (12), Hopfenberg Spherical (12), Hopfenberg Cylinderical (12), RRSBW (13), zero order and first order kinetics. The data of the kinetics are given in Table 3. According to the correlation coefficients it was decided that the data fit best to the first order kinetics for the microcapsules. However, when evaluated for the samples as a whole, Lapidus-Lordi kinetics seems to give the best fit. Lapidus-Lordi kinetics is given in Table 4 and represented graphically in Figure 2.

TABLE 2

Percentage Of The Amount Released From D-PRX·HCl Powder And Microcapsules, And Their Standard Deviation.

Time / microcapsule code	Percent released						Standard deviation					
	E_1	E_2	M_1	M_2	M_3	M_4	E_1	E_2	M_1	M_2	M_3	M_4
2	90.93	88.26	-	-	-	-	1.191	1.274	-	-	-	-
3	92.29	90.93	-	-	-	-	0.802	0.901	-	-	-	-
4	92.30	91.83	-	-	-	-	0.712	0.820	-	-	-	-
5	94.58	91.38	76.49	40.46	66.14	45.58	0.752	0.796	3.319	6.680	5.014	14.610
10	94.09	92.28	77.18	44.41	67.77	51.94	1.109	0.543	1.918	3.159	4.808	4.947
15	97.28	93.19	78.26	49.65	69.22	53.13	0.592	0.704	3.196	1.810	4.665	4.162
30	-	-	78.81	61.47	71.57	59.17	-	-	4.230	2.877	3.475	4.701
45	-	-	79.24	66.90	71.56	64.73	-	-	4.736	2.638	4.152	11.330
60	-	-	83.46	71.29	70.84	64.87	-	-	5.738	3.903	4.453	11.553
90	-	-	86.1	74.91	75.8	65.28	-	-	3.369	3.395	4.900	10.609
120	-	-	91.59	80.71	80.12	65.66	-	-	5.115	2.135	7.264	7.863
150	-	-	93.60	77.58	82.20	68.8	-	-	7.169	3.575	10.709	11.728
180	-	-	94.81	82.64	83.91	71.34	-	-	8.292	2.903	10.580	7.070

Each value is the mean of five experiments.

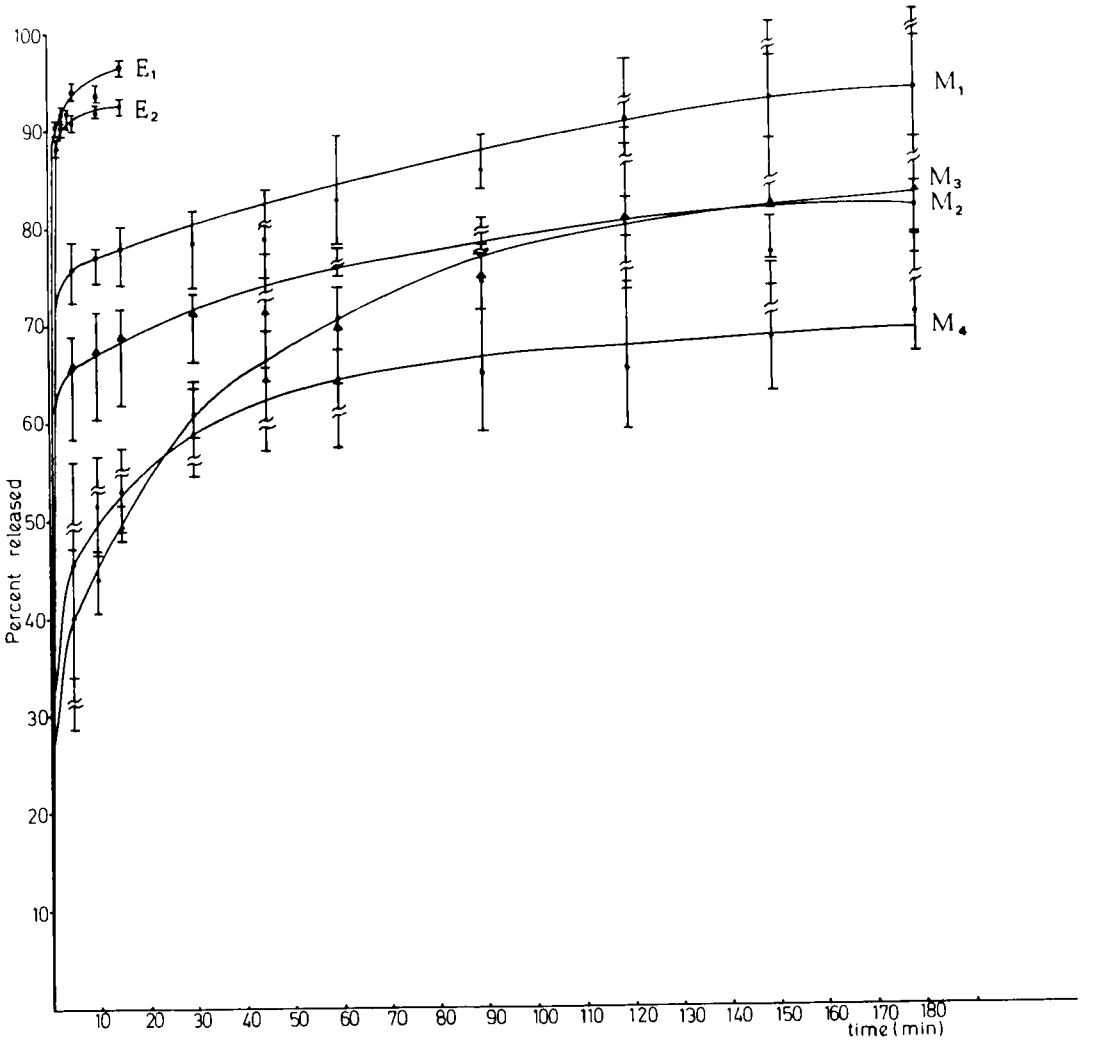

FIGURE 1
The Release Profiles Of D-PRX·HCl Powder And Microcapsules.

Comparison of the dissolution profiles of powder and encapsulated drug seems to indicate that microcapsules have delayed the release rate. The time of release was longest with the microcapsules with a core-shell ratio of 1:2. This shows that the release rate is controlled by the wall thickness (Figure 1). This is in accordance with the results found in previous studies (14, 15).

TABLE 3

The Results Of The Dissolution Rate Kinetics Of D-PRX·HCl Powder And Microcapsules.

Kinetics / Code		E_1	E_2	M_1	M_2	M_3	M_4
Lapidus-Lordi	Slope	2.218	1.413	2.953	3.333	2.091	1.713
	r^2	0.947	0.945	0.923	0.964	0.923	0.938
Hopfenberg Slab	Slope	-8.957	-4.275	-1.572	-1.899	-1.007	-1.045
	r^2	0.848	0.704	0.978	0.839	0.968	0.721
Hopfenberg Spherical	Slope	-9.809	-4.299	-1.484	-1.525	-8.535	-8.536
	r^2	0.850	0.716	0.977	0.854	0.968	0.731
Hopfenberg Cylinderical	Slope	-4.115	-2.498	-1.134	-2.208	-9.864	-1.332
	r^2	0.830	0.666	0.974	0.790	0.964	0.686
RRSBW	$\frac{\text{Slope}}{r^2}$	0.813	0.240	0.772	0.982	0.819	0.896
Zero order	Slope	-4.115	-2.498	-1.228	-2.184	-9.883	-1.157
	r^2	0.830	0.667	0.939	0.768	0.965	0.744
First order	Slope	-0.080	-0.029	-0.048	-0.029	-0.034	-0.024
	r^2	0.859	0.740	0.991	0.985	0.994	0.984

TABLE 4
Data Of Lapidus-Lordi Kinetics.

$\sqrt{t}$	Amount released (mg)					
	E_1	E_2	M_1	M_2	M_3	M_4
1.414	90.93	88.66	-	-	-	-
1.732	92.29	90.93	-	-	-	-
2	92.30	91.83	-	-	-	-
2.236	94.58	91.38	127.738	35.787	89.636	39.358
3.162	94.09	92.28	128.891	39.281	91.845	44.850
3.873	97.28	93.19	130.694	43.915	93.810	45.878
5.477	-	-	131.613	54.370	96.995	51.093
6.708	-	-	132.331	59.173	96.982	55.894
7.746	-	-	139.378	63.056	96.006	56.015
9.487	-	-	143.787	66.258	101.752	56.369
10.954	-	-	152.955	71.388	108.583	56.697
12.247	-	-	156.312	68.620	111.402	59.409
13.416	-	-	158.333	73.095	113.719	61.602

Since there was no loss of the shell integrity during the dissolution experiments and it remained intact after an exposure to the dissolution medium, release of drug was presumably by diffusion (16). Also the linear portion seen in Figure 1 may be indicative of drug release through diffusion (17). Diffusion is a physical process where the wall does not dissolve in the medium but penetrates the dissolution fluid.

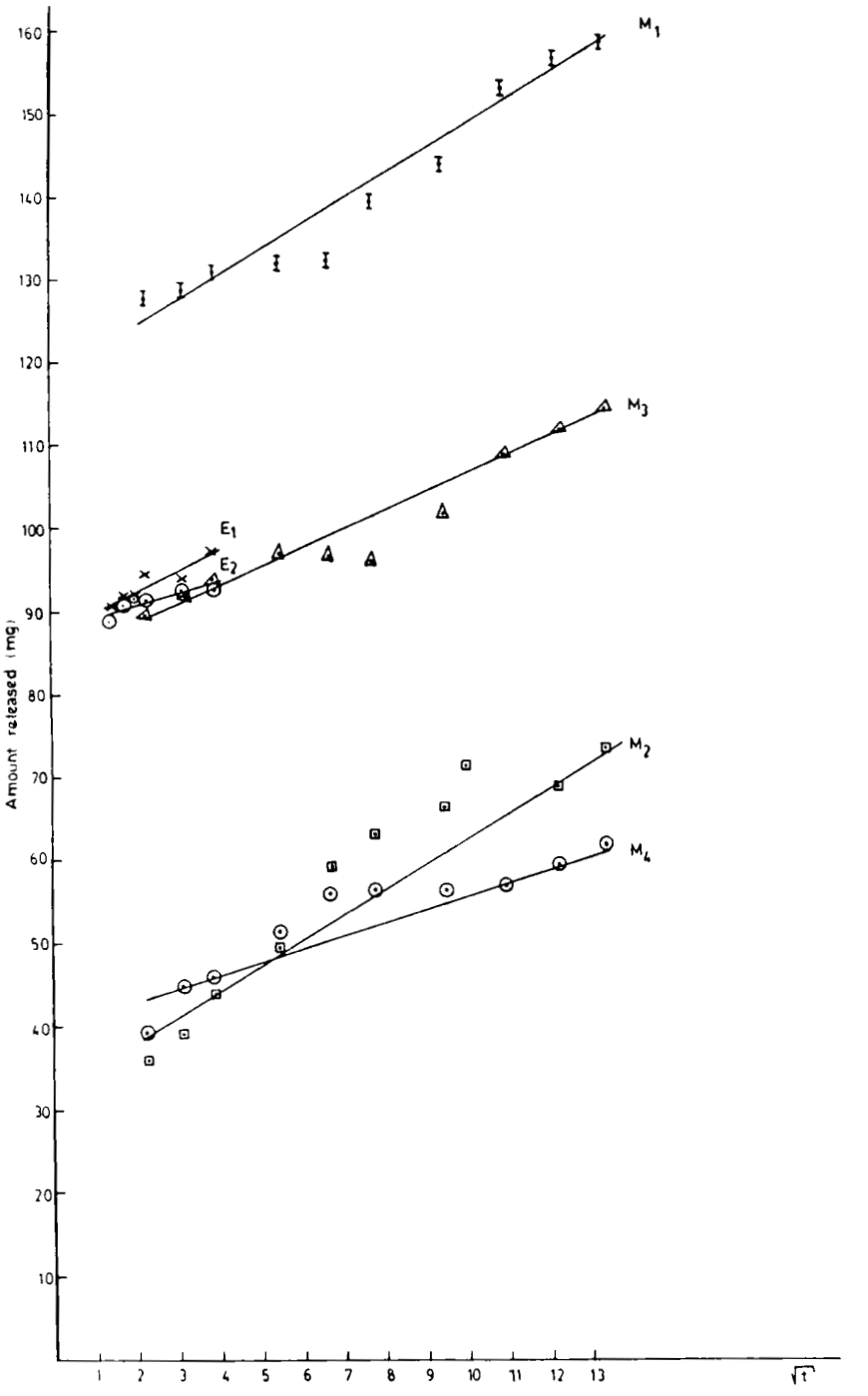

FIGURE 2

The In Vitro Dissolution Profiles According To Lapidus-Lordi Kinetics.

The initial rapid release seen in Figure 1 is due to the unencapsulated D-PRX·HCl. No attempt was done to wash away this portion in order to provide the first dose in further studies. In the first 5 minutes, initial release were as follows: a) powder (92-95 %); b) core-shell ratio 1:1 (66-75 %); 1:2 (41-46 %).

It is obvious that the unencapsulated portion is lower in microcapsules with 1:2 core-shell ratio. This may be due to the excess wall material to prevent the powder drug to fill the defects on the microcapsules as reported before (18,19).

It appears that microcapsules of D-PRX·HCl can be prepared by coacervation. But further studies have to be done to minimize the adhesion problem and to raise the yield since every factor in the system changes the gross appearance and the particle size of the microcapsules.

From the dissolution results obtained in conditions simulating the pH of the stomach, D-PRX·HCl microcapsules appear to be a new dosage form worth further investigation.

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