Development of Sustained Release Microcapsules Containing Ion Exchange Resin-Dextromethorphan Hydrobromide Complex

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(Received April 18, 1989)

이온교환수지 – 브롬화수소산덱스트로메토르판 복합체의 서방성 마이크로캡셀 개발에 관한 연구

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(1989년 4월 18일 접수)

In order to develop a pediatric liquid preparation with sustained release properties, dextromethorphan hydrobromide (DEXT) was complexed with strong cation exchange resin (CG 120) and the complex was coated with Eudragit RS using a phase separation method by non-solvent addition. The effect of pH, ionic strength of the release medium and drug/resin ratio on the release rate of DEXT was studied. The release rate of free drug from the uncoated complex, and coated complexes with 9.5 and 18.5% Eudragit RS in artificial gastric juice were measured. The release rate from the uncoated complex was faster with higher pH, higher ionic strength of the release medium and higher drug/resin ratio. The release rate from the coated complex could be controlled by the amount of coating material, and the surface after release did not rupture into.

Keywords—drug-resin complex, dextromethorphan hydrobromide, microencapsulation, Eudragit RS, drug-release, microscopic observation

The concept of using ion exchange resins (IER) to obtain controlled release of drugs has been available for at least 20 years[1,2]. A more continuous and uniform release over a long period of time is likely to result if the drug is chemically bound to a solid carrier, from which it is slowly released by the action of the digestive fluids. Ion exchangers are solid and suitably insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. These resins consist of two principal parts: a structural portion consisting of a polymer matrix, usually styrene cross-linked with divinylbenzene; and a

functional portion, which is the ion-active group to which the drug is bound. The functional group may be acidic (sulfonic or carboxylic) or basic (usually an amine)[3-5].

In general all acidic and basic drugs, especially having short biological half-lives are potential candidates, and a wide range of cationic (for the basic drugs) or anionic (for the acidic drugs) exchange resins can be used to form the drug-resin complexes[6,7].

With amine containing drugs, weak acid exchangers are not very useful in slow release formulations because their carboxylic groups have a

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pKa of about 6.5 and the drug is quickly set free, especially in the strong acidic medium of the stomach. It has been found that salts formed with resins having a pKa less than 5.2 are most adaptable to slow elution and hence sustained release of dextromethorphan hydrobromide (DEXT)[8].

Keating[9] listed the following advantages of adsorbing basic nitrogen-containing drugs onto sulfonic acid cation exchange resins and using them in dosage forms: a) prolong availability by releasing the drug from the complex over 12 hours in the gastrointestinal (GI) tract; b) reduce toxicity by slowing drug absorption; c) increase stability by protecting the drug from hydrolysis or other degradative changes in the GI tract; d) improve palatibility; and e) enable formulation of liquid and solid sustained release dosage forms.

However, such uncoated complexes provide only a relatively short delay of drug release in comparison with the preparations of coated complexes and provide no means for selectively modifying the release profile. It has now been found that a selective, prolonged continuous release of pharmacologically active drugs, under conditions such as those encountered in the GI tract, can be achieved by applying diffusion barrier coatings to drug-resin complex. Although there are available long acting agents, the availability of a sustained release drug in a liquid formulation would be of value in cases where solid medication cannot be taken, especially in the case of children.

The purpose of this research is to prepare a sustained release product of DEXT in the form of a coated drug-resin complex. This product may then be considered for use in an aqueous suspension containing no ions.

The problem of this research is that the parent resin of CG-120 is a gel-type divinylbenzenesulfonic acid cation exchange resin which swells in water with a pH range of 0-14. Thus, diffusion barrier coatings were relatively ineffective since the coating tended to peel rapidly and the coated particle swelled and tended to fracture when contacted by water biological fluids[6,7]. Pretreatment of drug-resin complex particles with an agent such as polyeth-
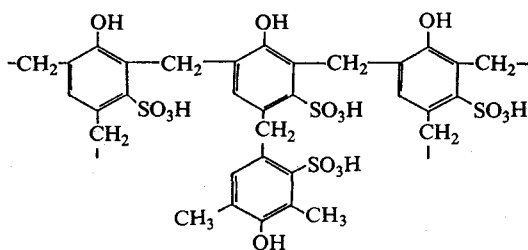

Figure 1—Chemical structure of CG 120.

ylene glycol provided for the particles to retain their geometry and coating during dissolution[10]

The aim of this study was to elucidate the possiblity of manufacturing of coated drug-resin complex using Eudragit RS. Eudragit RS lacquer films, although insoluble, swell in water, in nature and artificial digestive juices and in suitable buffer solutions, and release drugs independent of pH values. Thus, in this study, the method for preparing drug-resin complex and coating drug-resin complex was developed, and dissolution profile in vitro in simulated GI fluids was examined.

EXPERIMENTAL

Materials

Strongly acidic cation-exchange resins (Amberlite® CG 120, wet mesh: 100-200, 8% cross-linked, Röhm and Hass Co), polyacrylate-polymethacrylate copolymer with low content of quarternary ammonium groups (Eudragit Retard-RS 100, Röhm Pharma GmbH, Darmstadt, West Germany), and polyisobutylene (Oppanol B50, BASF, Ludwigshafen, West Germany) were used. Dextromethorphan hydrobromide, non-narcotic antitussive agent, was kindly supplied by Yuhan Corp. All other materials used were chemically pure analytical reagents. The chemical structure of CG 120 is shown in Fig. 1.

Instruments

Scanning electron microscope (JEOL JSM-35), dissolution tester (DST-200, Fine Scientific Instrument), and UV-spectrophotometer (Pye Unicam PU 8800) were used.

Pretreatment of Resin

Strongly acidic cation-exchange resin in sodium form was purified by rinsing 100g of dry resin (approx. moisture content 16%) with 3×1000 ml portion of deionized distilled water (DDW), 2×1000 ml of 95% methanol and 1×1000 ml of DDW; each treatment takes 5 hr by the batch process. After further rinsing with DDW, the resin was conditioned in a chromatographic column with 2×10 ml of 2N HCl, 1000 ml of DDW, 2×100 ml of 2N NaOH solution and 1000 ml of DDW. This cycle was repeated, and to desired state, the resin in the sodium form was washed with DDW until the eluate was essentially free of sodium ions. After filtration, the resin was dried at 110 °C to a constant weight.

Preparation of Drug-Resin Complexes

The drug-resin complexes were prepared by the batch process as described by Keating[9]. 160mg of dry resin in sodium form was placed in 10 ml of DDW in a suitable beaker and mixed for 30 min to hydrate. 100mg of DEXT was gradually added to the resin slurry with mixing, and agitated at 25 °C and 1,000 rpm until apparent equilibrium was reached. This was determined by analyzing for the unadsorbed DEXT, spectrophotometrically. When there was no significant change in the amount of unadsorbed DEXT, apparent equilibrium was assumed to be established. The amount of DEXT adsorbed was calculated as the difference between the initial and the unadsorbed amount of DEXT. The supernatant was taken at scheduled intervals and analyzed spectrophotometrically at 278 nm, which is the maximum absorption wavelength of DEXT. The drug-resin complex was washed free of any unreacted drug with DDW. Excess liquid was drained from the resin bed by suction, and the wet adsorbate was transferred to Petri dish. It was then dried in an oven at 50 °C to be a constant weight.

Effect of Concentration on Drug Loading Efficiency—100mg of dry resin in sodium form was placed in each 10, 20 and 40 ml of DDW in a suitable beaker. To make the complex containing a 50% drug load, 100mg of DEXT was added with mixing and agitated for 2 hr.

Effect of Temperature on Drug Loading Efficienty—100 mg of dry resin in sodium form was mixed with 1.76 ml of 0.028M DEXT solution to make the complex containing a 15% drug load and agitated 2 hr at 27, 35 and 50 °C, respectively.

Effect of Drug Amount on Exchange Rate—100 mg of dry resin in sodium form was mixed with 1.76, 3.3 and 10 ml of 0.028M DEXT solution to make the complex containing a 15, 25 and 50% drug load and agitated for 60 min.

Preparation of Coated Drug-Resin Complex

To an Erlenmeyer flask containing 10g of 3% (w/w) polyisobutylene (PIB) in methylene chloride-n-hexane cosolvent, 0.1g of Eudragit RS was added and dissolved for 30 min. After 0.9g of drug-resin complex was added, 15 ml of 3% (w/w) PIB in n-hexane as a non-solvent solution was dropped into the flask at a constant rate of 1 ml/min thereby gradually reducing the solubility of the Eudragit RS and futher stirred for 30 min. A constant stirring rate (1000 rpm) and temperature (25 °C) were maintained throughout the production. 50 ml of n-hexane was added to the product and the coated complex was sedimentated and were separated by decantation and rinsed twice with 100 ml portions of n-hexane to remove any PIB adsorbed at the coated complex interface and any empty wall polymer droplets. By means of additional 50ml of n-hexane, they were transferred, filtered and solvent traces were finally dried on filter paper at room temperature.

Determination of Wall to Core Ratio

The amount of material covering the complex was determined by dissolving the coating material from a known weight of the coated complex. Eudragit RS was dissolved with methylene chloride. The decapsulated complex was then dried and weighed. The amount of coating was taken to be the difference in dry weight before and after decapsulation.

In Vitro Release Studies

Dissolution testing used the USP paddle method at 100 rpm in 500 ml of 0.1N HCl or other suitable ionic dissolution medium. Before the dissolution test, the uncoated or coated complex was slurried in 2 ml of 1% Tween 80 in DDW solution for 24 hr to enhance wetting and dispersion into the dissolu-

tion medium. The drug-resin complex was added to each vessel. 5 ml samples of the dissolution solution were removed (free of any polymer particles) and assayed by determining the absorbance periodically at 278 nm and fresh dissolution media were added to make constant volume.

The method is of the type described by Chaundry et al.[1] as the replacement closed tube method.

Effect of pH on Release Rate from Uncoated Complex—A sample of the complex equivalent to 49.6mg of DEXT (a complex containing a 24.8% drug load) was used. The pH 1.2, 4.0 and 6.8 buffer solutions (ionic strength $\mu = 0.1$) was used as dissolution medium.

Effect of Ionic Strength on Release Rate from Uncoated Complex—A sample of the complex equivalent to 49.6 mg of DEXT (a complex containing a 24.8% drug load) was used. 0.1N HCl containing different amount of sodium chloride ($\mu = 0.1$, 0.2, 0.3, 0.4) solution was used as dissolution medium.

Drug Release from the Complex Containing a Different Amount of Drug—Each 200mg of the complex containing a 14.9, 24.8 and 43.4% drug load was used. Artificial gastric juice was used as dissolution medium.

Effect of Coating on Release Rate—A weight of the complex equivalent to 99.2mg of DEXT (a complex containing a 24.8% drug load) in the uncoated and coated complexes with 9.5 and 18.5% Eudragit RS was used. Artificial gastric juice was used as dissolution medium.

Effect of pH on Release Rate from Coated Complex—A sample of the coated complex with 9.5% Eudragit RS equivalent to 99.2mg of DEXT (a complex containing a 24.8% drug load) was used. The pH 1.2, 4.0 and 6.8 buffer solutions ($\mu = 0.1$) were used as dissolution media.

Microscopic Studies

Scanning electron microscopy was used to evaluate the quality of the coating. Thus, the particle of the uncoated complex, coated complex, and the surface of coated drug-resin complex after release were observed.

RESULTS AND DISCUSSION

Preparation of Drug-Resin Complex

The drug-resin complexes were prepared by the batch process. When an amount of DEXT equivalent to yield the complex containing a 15, 25 and 45% drug load were added, the complexes containing a 14.9, 24.8 and 43.4% drug load were obtained.

It is usual to express the amount of exchanges as a fraction (F) of the amount which occurs after time t (Q_t) to that after infinite time (Q_∞), thus;

$$F = \frac{Q_t}{Q_\infty} \tag{1}$$

In the present work, the results were calculated in terms of X[11];

$$X = \frac{\text{amount of exchange after time t}}{\text{amount of exchange after equilibrium was obtained}} \tag{2}$$

Assuming that all the resin particles were uniform spheres and the sole rate-controlling process was particle diffusion, calcaulation of results followed the equation derived by Boyd et al.[11]. The equation of this theory is shown in Eq. (3)

$$F = \frac{Q_t}{Q_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{\exp(-n^2 Bt)}{n^2} \tag{3}$$

Where n is an integer; B, the rate constant is defined as $B = \pi^2 D/r^2$ where D is the effective diffusion coefficient of the ion exchange process and r is the mean particle radius of the resin.
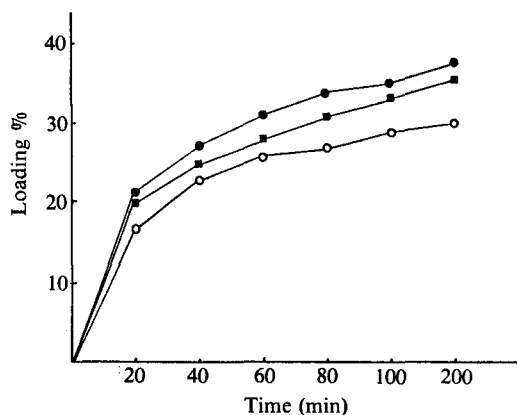
To calculate the rate constants from the experiments, values of F are calculated from the mesurements and the corresponding theoretical values of Bt are found from Table I.

Preliminary experiments were conducted to determine the effect of DEXT concentration and temperature on the drug loading efficiency in preparing the complex.

As DEXT concentration was increased, the drug loading efficiency was increased (Fig. 2). A study of these data led to the selection of a 0.028M DEXT solution, considering the drug solubility in preparing the complex. The effect of temperature on the
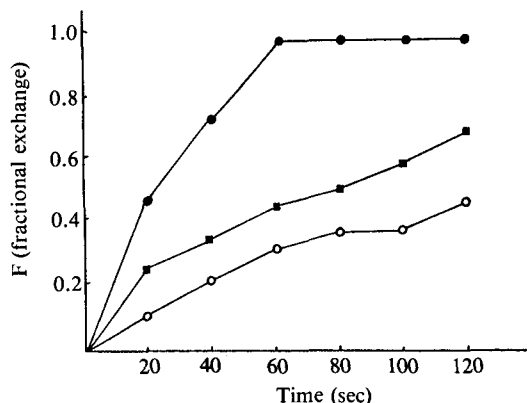
F	Bt	F	Bt	F	Bt	F	Bt
0	0	0.25	0.0623	0.50	0.301	0.75	0.905
0.01	0.00009	0.26	0.0678	0.51	0.316	0.76	0.944
0.02	0.00036	0.27	0.0736	0.52	0.332	0.77	0.985
0.03	0.00079	0.28	0.0797	0.53	0.348	0.78	1.028
0.40	0.00141	0.29	0.0861	0.54	0.365	0.79	1.073
0.05	0.00219	0.30	0.0928	0.55	0.382	0.80	1.120
0.06	0.0032	0.31	0.0998	0.56	0.400	0.81	1.171
0.07	0.0044	0.32	0.1070	0.57	0.419	0.82	1.224
0.08	0.0057	0.33	0.1147	0.58	0.438	0.83	1.280
0.09	0.0073	0.34	0.1226	0.59	0.458	0.84	1.340
0.10	0.0091	0.35	0.1308	0.60	0.479	0.85	1.404
0.11	0.0111	0.36	0.1391	0.61	0.500	0.86	1.468
0.12	0.0132	0.37	0.1485	0.62	0.522	0.87	1.543
0.13	0.0156	0.38	1.1577	0.63	0.545	0.88	1.623
0.14	0.0183	0.39	0.167	0.64	0.569	0.89	1.710
0.15	0.0210	0.40	0.177	0.65	0.594	0.90	1.80
0.16	0.0241	0.41	0.188	0.66	0.620	0.91	1.91
0.17	0.0274	0.42	0.199	0.67	0.647	0.92	2.03
0.18	0.0309	0.43	0.210	0.68	0.675	0.93	2.16
0.19	0.0346	0.44	0.222	0.69	0.703	0.94	2.32
0.20	0.0386	0.45	0.234	0.70	0.734	0.95	2.50
0.21	0.0428	0.46	0.246	0.71	0.765	0.96	2.72
0.22	0.0473	0.47	0.259	0.72	0.798	0.97	3.01
0.23	0.0520	0.48	0.273	0.73	0.832	0.98	3.41
0.24	0.0570	0.49	0.287	0.74	0.868	0.99	4.11

Figure 3—Effect of temperature on the drug loading efficiency in preparing the complex containing a 15% drug load.

Key: ●, 50°C, ■, 35°C; ○, 27°C.

Figure 4—Effect of temperature on the drug loading efficiency in preparing the complex containing a 25% drug load.
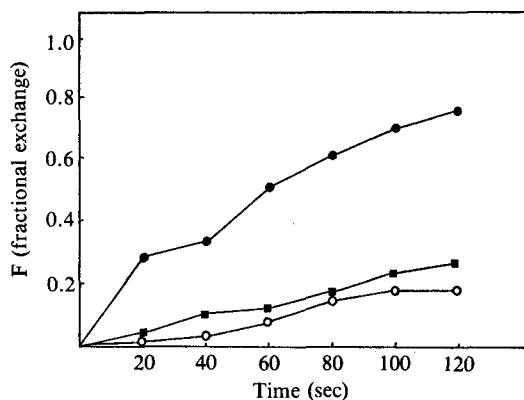
Key: ●, 50°C, ■, 35°C; ○, 27°C.

Figure 2—Effect of DEXT concentration on the drug loading efficiency in preparing drug-resin complex.

Key: ●, 2.8×10^{-2}M; ■, 1.4×10^{-2}M; ○, 0.71×10^{-2}M.

drug loading efficiency in preparing the complex containing a 15 and 25% drug load was studied at 27, 35 and 50°C, respectively.

Figs. 3 and 4 shows the fractional exchange *vs.* time (sec) in preparing the complex containing a 15 and 25% drug load. As shown in Fig. 3, the equilibrium was obtained in 60 sec at 50°C. Fig. 4 shows the fractional exchange at 27 and 50°C was 0.18 and 0.8, respectively.
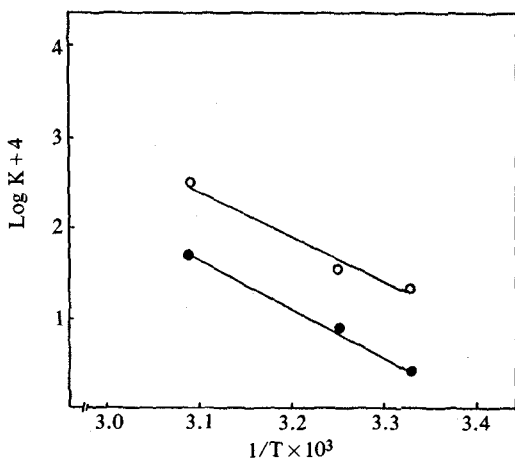
The actual values of B derived (by the method of least square) from the Bt-t plots are shown in Table II. The reaction rate constant B increased by a factor of 1.7 and 2.64 for 35°C as against 27°C in preparing the complex containing a 15 and 25% drug load, respectively.

Table II—*The Reaction Rate of Drug-Resin Complex.*

T (°C)	Reaction rate (sec⁻¹)	
	15% Complex	25% Complex
27	2.0×10^{-3}	2.5×10^{-4}
35	3.4×10^{-3}	6.6×10^{-4}
50	3.3×10^{-2}	5.4×10^{-4}

Table III—*The Activation Energy in Preparing Drug-Resin Complex.*
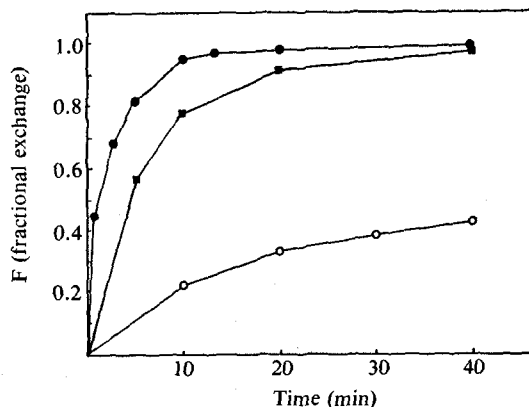
Loading %	Activation energy (Kcal/mol)
15	22.8
25	26.6

Figure 6— Effect of drug amount on the rate of exchange in preparing drug-resin complex.
Key: ●, 15%, ■, 25%; ○, 50%.

Figure 5—A plot of log K againt 1/T for preparing drug-resin complex.
Key: ○, 15%; ●, 25%

Figure 7—Effect of ionic strength on the release rate from the uncoated complex in 0.1N HCl solutions with and without sodium chloride.
Key: ●, $\mu = 0.1$; □, $\mu = 0.2$; ■, $\mu = 0.3$; ○, $\mu = 0.4$.

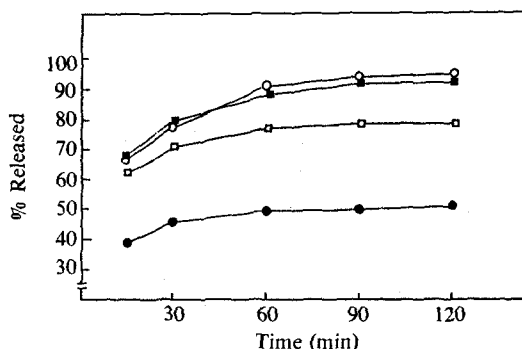The data obtained from Table II were plotted against log K as shown in Fig. 5. By Arrhenius equation, the activation energy (E_a) was calculated. The complex containing a 15% drug load had the smaller E_a than that of the complex containing a 15% drug load in preparing the complex. From the result, although the variation of temperature from 27 to 50 °C had significant effect on the rate of exchange, but had no appreciable effect on the drug loading efficiency. And also considering the drug stability in subsequent work, the room temperature (27 °C) was chos

Fig. 6 shows that the effect of the drug amount

added to a constant amount of resin on the exchange rate in preparing drug-resin complex. The equilibrium was reached at 20 and 40 min in preparing the complex containing a 15 and 25% drug load, respectively. We could know that the more the added drug amount, the slower the exchange rate.

**Variables Affecting Drug Release Rate from Complex.**

Release kinetics depend upon resin inherent properties such as particle size and crosslinking degree, and on the other hand upon test conditions such as electrolyte concentration, pH and so on.

Increasing the ionic strength from 0.1 to 0.4 shi-
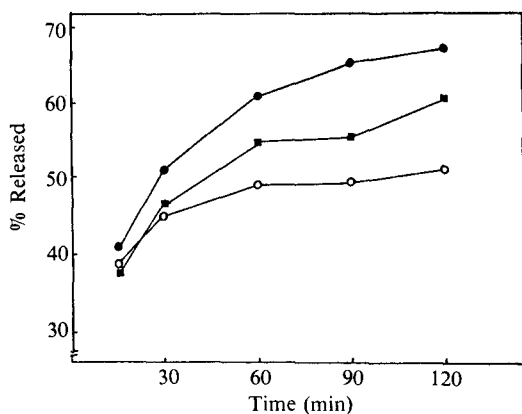
Figure 8—Effect of pH on the release rate from the uncoated complex at various buffer solutions.
Key: ○, pH 1.2; ■, pH 4.0; ●, pH 6.8
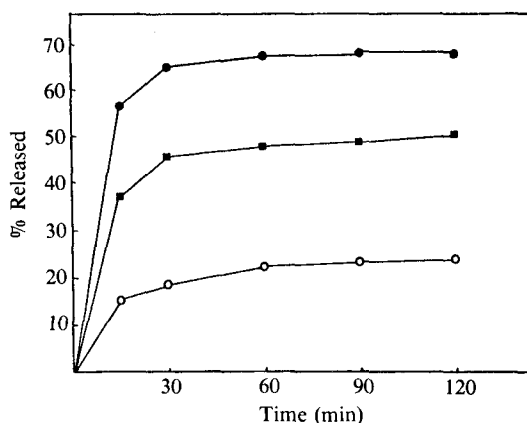
Figure 9—Release of DEXT from the complexes containing a different amount drug in 0.1N HCl.
Key: ●, 43.4%; ■, 24.8%; ○, 14.9% solutions.

fted the equilibrium concentration toward more complete drug release with the drug-resin complex (Fig.7). The release of DEXT after 2 hr was 95 and 50% in a dissolution medium which ionic strength was 0.4 and 0.1, respectively. These results indicate not only the effect of ionic strength on the release rate of DEXT, but also quality of the prepared complex. And also, these results suggest that the complex had no appreciable release in DDW. Most sustained aqueous products release drug on storage, but we could know from the result that this drug-resin complex does not. It is important to develop a liquid preparation with sustained release profile.

Fig. 9 shows the comparative release in 0.1N HCl of DEXT from drug-resin complexes containing a 14.9, 24.8 and 43.4% drug load. Release studies revealed that the complex containing a 43.4% drug load released about 65-70% of the available drug within the initial 60 min of dissolution, but the complex containing a 14.9% drug load released about 20% of the available drug in the same time. In the case of the complex containing a 14.9% drug load, this 20% of the released drug was attributed to the drug on or near the surface of the drug-resin complex; and the remaining 80% of the drug was internally bound by the resin matrix. Therefore, as the loaded amount of drug was increased, the release rate was increased.

Complete drug release cannot be obtained in this system because equilibrium is reached and sink conditions are not obtained. But DEXT was completely bioavailable from this drug-resin complex. It was perhaps due to the continuous absorption of released drug into the blood, resulting in a lower GI tract concentration, which, in turn, permitted more drug release. It was perhaps also due to the continuous passage of the resin through the GI tract.

Microencapsulation

The results indicated the need for a diffusion barrier coating for the complex to modify the drug release profile, essential for the formation of a sustained release liquid dosage form[12].

Eudragit RS was selected as the diffusion barrier film since it has swelling and pH-independent drug properties. Therefore, the complex was coated with Eudragit RS using a phase separation method by non-solvent additions[13,14]

From the preliminary experimental results, it was observed that the presence of PIB at a minimal concentration was vital to the formation of individual microcapsules[15]. The use of PIB concentrations between 0 and 2% failed to give good reproducible microcapsules, but 3% PIB, minimum PIB enabling formation of individually microencapsulated core particles, was sufficient to prevent aggregation of the coated complex.
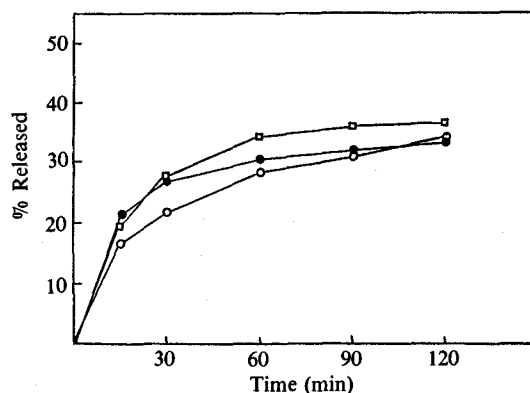
The complex with 9.5 and 18.5% Eudragit RS
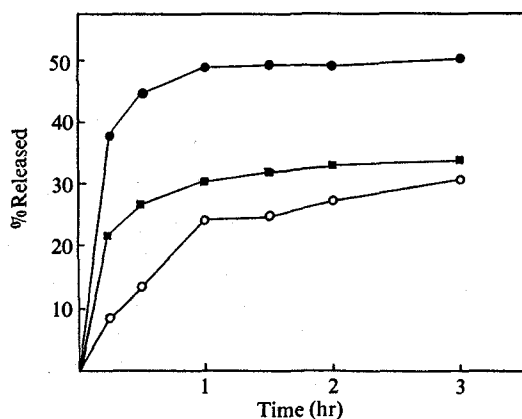
Fugure 10—Release of DEXT from the uncoated and coated complex with 9.5 and 18.5% Eudragit RS in 0.1N HCl.
Key: ●, uncoated; ■, 9.5% coated; ○, 18.5% coated

Figure 11—Effect of pH on the release rate from the coated complex with 9.5% Eudragit RS in various buffer solutions.
Key: □, pH 6.8; ○, pH 4.0; ●, pH 1.2

coat was formed, respectively when as amount of coating material equivalent to yield the complex with 10 and 20% Eudragit RS coat was used.

Drug Release from Coated Complex

Fig. 10 shows the drug release profiles from Eudragit RS coated and uncoated complexes. About 32 and 27% of DEXT were released in 2 hr from the complexes with 9.5 and 18.5% Eudragit RS coat respectively. The data indicates that good retardation of the dissolution from the complex is obtained by the application of a diffusion barrier coating. Effect of pH on the release of DEXT from the coated complex is shown in Fig. 11. This experiment was done to compare the effect of pH on the release of DEXT from the uncoated and coated complexes. While the effect of pH on the release of DEXT
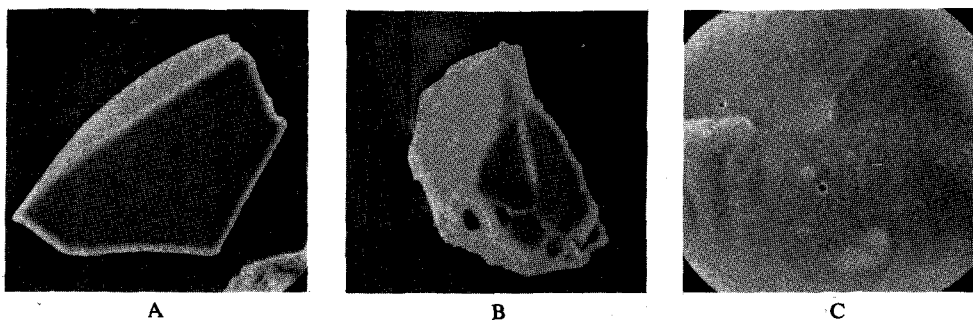
from the uncoated complex was large, the coated complex was very small. It was due to the property of Eudragit RS that releases drug independent of pH values.

Microscopic Studies

Fig. 12 shows microscopic observations of uncoated drug-resin complex (A) and 9.5% Eudragit RS coated drug-resin complexes before (B) and after (C) release test. Scanning electron micrograph (SEM) of the coated complex with 9.5% Eudragit RS revealed that the coating was uniformly applied. SEM confirmed that the coated complex after drug release did not rupture into smaller particles but contained a few small pores on the surface. The release profile and SEM confirmed that the rupture of coating barrier due to rapid swelling of resin in liquid was overcome.

A   B   C

Figure 12—Scanning electron micrograph of uncoated drug-resin complex (A), 9.5% Eudragit RS coated resin complexes before(B) and after (C) release test.

In conclusion, as the release rate from the coated complex could be controlled by the amount of coating, therefore, it was possible to develop a liquid preparation with sustained release properties.

In addition to this study, further work will be necessary to obtain the method to control release pattern from the coated complex and to make release curve straight by adding Eudragit RL coated complex or resin.

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