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Preparation and Evaluation of Microencapsulated Ion-Exchange Resin Beads

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Abstract □ Ion-exchange resin beads in the benzoate form were coated by several microencapsulation techniques to alter and improve characteristics, especially the control of drug release, of this type of drug delivery system. The most successful techniques included polymer–polymer interaction, temperature change, and nonsolvent addition. The microencapsulated beads then were studied with respect to the release rate of the organic anion to determine the effects of microencapsulation. The release rate of the organic anion could be controlled over a wide range, depending on the encapsulating material characteristics. Factors affecting the extent and rate of release as a result of microencapsulation are discussed.

Keyphrases □ Microencapsulated ion-exchange resin beads—prepared by various methods, evaluated for release rate □ Ion-exchange microencapsulated resin beads—prepared by various methods, evaluated for release rate □ Delivery systems—microencapsulated ion-exchange resin beads, prepared by various methods, evaluated for release rate □ Dosage forms, potential—microencapsulated ion-exchange resin beads, prepared by various methods, evaluated for release rate

Ion-exchange resins function as effective carriers for prolonging drug release for sustained biological action and for improvement of other pharmacokinetic parameters such as the absorption rate constant (1). In addition, ion-exchange resins are used for binding biological materials such as bile salts and sodium ions within the GI tract (2, 3). While ion-exchange resins form a useful drug delivery system, improvements can be effected in some cases by coating the resin beads with various pharmaceutical adjuvants. Potential improvements are: enhancing the taste of ion-exchange resins (4, 5), decreasing the release rate of drugs from the resins (5, 6), permitting greater saturation of the resin with the drug and a slower elution rate (6), minimizing elution of drug in liquid preparations of ion-exchange resin–drug complexes (6, 7), and minimizing interaction of drugs with resins used as tablet disintegrants (8).

One effective and versatile method of coating small solid particles is microencapsulation, which can be accomplished with various procedures (5, 9, 10). Many researchers discussed the encapsulation of solid particles (11–16), but few applied the process to ion-exchange resins (4, 17). It was deemed appropriate to investigate microencapsulation procedures for the preparation of coated ion-exchange resins to exploit the value of resin beads, such as uniform size and consistent binding of drugs, for improving their pharmaceutical characteristics. Specifically, it was expected that medication with a wide range of prolonged-release characteristics could be prepared. In addition, it was hoped that a uniform coat around the beads could be obtained by various encapsulation methods.

The effect of additives on the characteristics of the film used to coat pharmaceuticals also was investigated. In some cases, additives selected are of such a nature that the rate of transmission or release of drugs is increased (12, 18) or decreased (19). Part of the present research is concerned with employing additives in the preparation of the microencapsulating film to prolong or delay the release so that the coated beads can be considered for other uses in pharmacy besides oral medication.

EXPERIMENTAL

Materials—All experiments were carried out with a 20–50-mesh strongly basic ion-exchange resin[1] in the benzoate form. The resin was screened wet; the beads that passed through a 35-mesh screen but were retained on a 40-mesh screen were used. The resin then was cleaned, conditioned, and converted into the benzoate form by the procedure described previously (20). The average particle size of the resin beads, as determined by microscopic measurement of 30 beads, was 0.366 mm (wet) and 0.325 mm (dry).

Encapsulation Procedures—*Polymer–Polymer Interaction*—The method of Luzzi and Gerraughty (14, 21), adapted from Green and Schleicher (22, 23), was modified for the encapsulation of the resin beads. In this method, the interaction of oppositely charged polyelectrolytes results in the formation of a complex of considerably reduced solubility such that phase separation occurs. The specific procedure used consisted of dissolving 3 g of acacia[2] and 3 g of gelatin[3] separately in 100 ml of distilled water each. The solutions were warmed to 55° and mixed, and the pH was adjusted to 6.5 with 20% NaOH. The resin beads (2 g) then were added, and the pH of the mixture was altered to 4.5 by the dropwise addition of dilute hydrochloric acid with stirring.

The temperature was allowed to drop, and the polymers coalesced around the resin beads. Subsequently, 10 ml of formaldehyde solution USP was added, and the mixture was cooled to 10° by immersion in an ice bath with constant stirring. The pH then was adjusted to 9.0 by the dropwise addition of 20% NaOH. The mixture was diluted to approximately 400 ml with distilled water, left overnight, and then centrifuged for 30 min at 2700 rpm.

The supernate was decanted, and the microencapsulated beads were transferred to a 60-mesh screen and washed with water to remove the empty capsules. The capsules remaining on the screen were poured into a flask along with 100 ml of distilled water. After settling, water was removed by rinsing the capsules with three 50-ml portions of 95% ethanol. The mixture was filtered, washed with ethanol, and dried in a desiccator.

Temperature Change—Five methods of preparation were evaluated.

[1] Dowex 1-X8, Dow Chemical Co., Midland, Mich.
[2] Gum Acacia BP, British Drug Houses (Canada) Ltd., Toronto, Canada.
[3] Gelatin, Pharmagel A., American Agricultural Co., Detroit, Mich.

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Table I—Data on the Microencapsulation of Ion-Exchange Resins

Abbreviation	Encapsulating Material	Encapsulating Material[a], g / Resin Complex, g	Radius of Encapsulated Bead, mm[b]	B, min^{-1} [c]	D, cm^2 sec^{-1} [d]
I	No coat	—	0.1830	0.0748	4.23×10^{-8}
II	Ethylcellulose standard 20[e]	0.1485	0.1916	0.0417	2.58×10^{-8}
III	Ethylcellulose standard 100	0.1419	0.1913	0.0422	2.60×10^{-8}
IV	Ethylcellulose medium 50	0.1274	0.1905	0.00923	5.65×10^{-9}
V	Ethylcellulose medium 100	0.1198	0.1900	0.00613	3.73×10^{-9}
VI	Gelatin–acacia	0.3963	0.2045	0.0548	3.87×10^{-8}
VII	Cellulose acetate butyrate	0.1289	0.1905	0.00564	3.45×10^{-9}
VIII	II plus butyl stearate	0.1587	0.1922	0.0124	7.73×10^{-9}
IX	II plus castor oil	0.2332	0.1963	0.0393	2.55×10^{-8}
X	II plus polyethylene	0.1334	0.1908	0.0119	7.31×10^{-9}
XI	II plus polyethylene and paraffin	0.2438	0.1968	0.00124	8.11×10^{-10}
XII	III plus butyl stearate	0.1822	0.1935	0.0202	1.27×10^{-8}
XIII	III plus castor oil	0.1988	0.1944	0.0208	1.32×10^{-8}
XIV	III plus polyethylene	0.1185	0.1900	0.00110	6.70×10^{-10}
XV	III plus polyethylene and paraffin	0.3406	0.2018	0.000690	4.74×10^{-10}

[a] Average values of two different preparations, except for cellulose acetate butyrate where three preparations were used. [b] Radius was calculated with the assumptions that the resin bead was wet and the density of the bead and the coating materials in the buffer solution was 1. [c] The values of B were obtained from the initial slopes of the Bt–t plots using observed data of values 2 hr and less and fractional attainment of equilibrium 0.9 or less; see text for discussion. [d] D is the diffusion coefficient. [e] Simple coats are II–VII; complex or mixed coats are VIII–XV.

1. The method of Miller *et al.* (24) utilizes the phase separation coacervation of a binary system of ethylcellulose and cyclohexane. At high temperature, a single homogeneous phase exists; upon cooling, phase separation occurs. The polymer at the appropriate concentration, temperature, and agitation conditions coalesces around the dispersed core particles. Ethylcellulose standard[4], 20 or 100 cps, 0.4 g, with an ethoxyl content of 48–49.5% was dispersed in 25 ml of cyclohexane and heated under reflux at about 80° until the ethylcellulose dissolved. Then 2 g of resin beads was added, and the mixture was refluxed for 2 hr. Throughout the whole procedure, the mixture was stirred with a magnetic stirring bar. The mixture was allowed to cool slowly to room temperature, and the encapsulated beads were separated from the solvent by filtration, air dried, and sieved.

2. A similar procedure was used when ethylcellulose medium[5], 50 or 100 cps, with an ethoxyl content of 45–46.5% was employed as the polymer; however, 5 ml of 95% ethanol was added to improve the solubility characteristics of the solvent.

3. The temperature change technique was modified to alter the film characteristics by using a low molecular weight polyethylene, which was reported to be a phase separation-inducing material (25, 26). Ethylcellulose standard[4], 20 or 100 cps, 0.4 g, and polyethylene[6], 0.4 g, were dispersed in 25 ml of cyclohexane at room temperature and solubilized by raising the temperature to 80°. The procedure was continued as described for Method 1.

4. Method 3 may be modified since the hydrophobic walls can be made more impervious by treating the ethylcellulose capsules with a solution of wax in a solvent capable of swelling, but not dissolving, the capsule wall so that the wax solution penetrates the swollen capsule wall. The capsules are then separated from the solvent and dried so that the wax is entrapped in the polymeric capsule wall (25). The microencapsulated resin beads prepared by Method 3 were dispersed in a 20% solution of hard paraffin in cyclohexane, agitated at room temperature for 30 min, separated from the wax-containing solvent system by suction filtration, and air dried. The dry beads were sieved through a convenient mesh size screen to get rid of dust and broken particles.

5. Ethylcellulose is compatible with many common plasticizers. The plasticizer, when added to the polymer, is capable of forcing the polymer chains apart, thus producing a softening effect. Castor oil and butyl stearate, which produce a considerable softening effect, were employed (27). The ethylcellulose standard[4], 20 or 100 cps, 0.4 g, was dispersed in 25 ml of cyclohexane, and the mixture was refluxed until the polymer dissolved. Then 0.2 g of butyl stearate or 0.2 g of castor oil and 2 g of dry resin were added, and the mixture was refluxed for 2 hr. The mixture was stirred constantly with a magnetic stirring bar during the heating process and for 1 additional hr during cooling. The separation of the beads from the solvent was the same as described for Method 1.

Nonsolvent Addition—This technique is used to induce phase separation by the addition of a liquid that is a nonsolvent for the polymer (28). Cellulose acetate butyrate[7], 0.5 g, was dissolved in 20 ml of methyl ethyl ketone by heating. The dry resin beads (2 g) were then added and dispersed in the solution. The mixture was heated to 55°, and 30 ml of isopropyl ether was added dropwise. The system was allowed to cool slowly to room temperature, and the encapsulated beads were separated by centrifugation, washed with isopropyl ether, and dried in a vacuum.

All microencapsulated beads were stored in a desiccator.

Kinetic Studies—The *in vitro* evaluation of the release rate from the microencapsulated resin beads was carried out by the following procedure. The release pattern of the microencapsulated resin samples was determined by using a centrifugal basket stirrer similar to that used for ion-exchange rate measurements (29). The top and bottom of the cylindrical basket, 1 cm in diameter and 1.5 cm high, were made from 80 wire mesh screen. The basket was enclosed in a cylindrical aluminum body with an opening at the bottom and a series of horizontal holes above the basket. Upon rotation, the water flowed through the bottom of the basket out of the top and then through the holes in the aluminum body as a result of centrifugal force.

About 0.1 g of the microencapsulated resin was weighed accurately and placed into the basket. The basket, in the aluminum body attached to an electric stirrer, was then introduced into a two-neck, round-bottom, 500-ml flask containing 200 ml of a pH 9.2 buffer (containing 12.095 g of dibasic potassium phosphate in 1 liter of solution) previously equilibrated and maintained at 30° with a constant-temperature water bath. The basket was rotated at 1400 rpm. Samples (5 ml) were removed at suitable times and diluted to 50 or 100 ml with the phosphate buffer.

The amount of benzoate released from the resin was determined spectrophotometrically at 224.5 nm from a standard calibration curve for sodium benzoate in the phosphate buffer. The amount released was expressed in terms of sodium benzoate per gram of dry uncoated resin. Each kinetic run, up to 168 hr, was carried out in triplicate. The absorbances of the coating materials at the dilutions used for analysis were negligible.

The amount of material covering the resin beads was determined by dissolving the encapsulating material from a known weight of the encapsulated beads; ethylcellulose and films containing castor oil and butyl stearate dissolved with 95% ethanol; films containing polyethylene, paraffin, and cellulose acetate butyrate dissolved with chloroform; and gelatin–acacia film dissolved with 0.1 N NaOH in water and 95% ethanol. The decapsulated resin was then dried and weighed.

RESULTS AND DISCUSSION

Microscopic examination, a loss of weight upon extraction, and slower rates of release of benzoate ion from the beads indicated that microencapsulation does, in fact, occur and can be accomplished by several methods. Microscopic observation showed that the beads were covered uniformly with the encapsulating material in all cases. Thus, microencapsulation tends to give a more uniform and more consistent coat than other procedures (20).

The ratio of encapsulating material to resin complex was reasonably

[4] Ethocel Standard 20 or Ethocel Standard 100, Dow Chemical Co., Midland, Mich.

[5] Ethocel Medium 50 or Ethocel Medium 100, Dow Chemical Co., Midland, Mich.

[6] Molecular weight 5000, Allied Chemicals, Toronto, Canada.

[7] Cellulose acetate butyrate, Eastman Kodak Co., Rochester, N.Y.

Table II—Elution Data

Encapsulating[d] Material	Amount of Benzoate (Milligrams) Released[a] per Gram of Resin Complex[b] as a Function of Time[c]												
	Minutes						Hours						
	5	10	15	20	25	30	1	2	24	48	72	96	168
I	236	291	320	336	345	352	370	375	379	381	—[e]	—	—
II	130	202	243	273	293	307	348	368	375	377	380	—	—
III	134	206	245	274	293	303	342	359	370	374	—	—	—
IV	46	82	114	139	150	168	234	291	369	—	—	—	—
V	32	60	82	100	114	129	192	255	369	370	—	—	371
VI	134	190	220	237	249	257	273	280	286	291			
VII	46	76	97	112	127	135	179	236	314	315	320	327	348
VIII	61	104	134	158	176	194	271	327	383	—	—	—	384
IX	149	218	261	288	310	325	367	390	398	406	—	—	—
X	80	131	164	190	207	222	268	299	347	—	—	—	349
XI						69	102	135	246	271	368	—	369
XII	82	138	177	207	232	250	313	359	388	—	—	—	—
XIII	85	144	183	217	242	260	330	373	405	—	—	—	—
XIV	3	13	20	28	34	40	67	113	239	274	308	318	329
XV						3	9	15	65	76	152	167	182

[a] Expressed as sodium benzoate. [b] Expressed in terms of resin complex, exclusive of encapsulating material. [c] These are average values of triplicate determinations on a single preparation. [d] See Table I for key. [e] Dashes indicate no further appreciable change.

consistent since the values for individual preparations were within 10% of the average value (Table I), except with cellulose acetate butyrate and ethylcellulose standard 100 when combined with castor oil or butyl stearate where individual values were within 20% of the average value. In general, many ratios were close to a value of 0.12 for the simple encapsulating agents except gelatin, which had a value of 0.39. The addition of butyl stearate, castor oil, and the polyethylene–paraffin combination increased the ratio considerably in conjunction with either cellulose material.

The amount of benzoate, expressed as the sodium salt in milligrams released per gram of resin complex as a function of time, is given in Table II. Samples of the buffer solution were analyzed for benzoate until there was no appreciable change or periodically up to 168 hr; these values were taken to be the equilibrium values. A comparison of the amounts released over this period of 168 hr is useful in terms of the potential use of the encapsulated resin complex as implants or in certain pharmaceutical suspensions.

Table II indicates that, even after 168 hr of elution, a considerable amount of the anion was contained within the resin when it was coated with ethylcellulose standard 100 in combination with polyethylene or both polyethylene and paraffin. The absorbancies of the eluant from the gelatin–acacia-covered resin complex began to decrease after 48 hr, suggesting that some other process such as decomposition or binding was occurring.

The release from the uncoated resin complex was almost complete at 1 hr and had reached an equilibrium within 24 hr; these results are similar to reported findings (20). All coatings decreased the rate of release of the anion from the resin complex. A comparison of the amounts released at the end of the 24-hr period is useful in terms of the potential use of the resin complex as an oral prolonged-release agent where the prolongation of action of the resin itself is further enhanced by the encapsulating material. At the end of 24 hr, two simple coats, cellulose acetate butyrate and gelatin–acacia, and four mixed coats, ethylcellulose standard 20 or 100 in combination with polyethylene or polyethylene and paraffin, prevented the full release of the anion from the resin complex. All ethylcelluloses and the ethylcelluloses in combination with the plasticizers butyl stearate and castor oil released the anion within 24 hr. The plasticizers tended to decrease the initial rate of release and yet permit full release within the 24-hr period.

A comparison of the effect of the encapsulating material on the release of the benzoate during the elution procedure in terms of equilibrium values can be made from the values of the fractional attainment of equilibrium, U, calculated from:

$$U = \frac{R}{R_\infty} \qquad \text{(Eq. 1)}$$

where R is the amount of benzoate released at time t and R_∞ is the amount released at equilibrium as already defined. Representative data (Figs. 1 and 2) clearly indicate the delaying action of the encapsulating materials on the resin complex over a period of time. Ion exchange took place almost immediately, in most cases due to the thin film and the uptake of moisture by the encapsulating materials.

A comparison of the fractional attainment of equilibrium (Fig. 1) of the simple coating material at 1 hr showed that the order of increasing prolongation was as follows: no coat, gelatin–acacia, ethylcellulose standard 20 ~ ethylcellulose standard 100, ethylcellulose medium 50, ethylcellulose medium 100, and cellulose acetate butyrate. All of these coatings had approximately the same ratio of encapsulating material to resin complex except gelatin–acacia; consequently, the properties of the films themselves were primarily responsible for the observed effects rather than the thickness of the coat.

The viscosity numbers (in organic solvents), which are the suffixes of the ethylcellulose compounds listed, are roughly indicative of the size of the ethylcellulose molecule and, within limits, the toughness of the deposited film. In addition, ethylcellulose medium at equivalent molecular weights is reported to be tougher than the standard and have a slightly higher specific gravity (27). The experimental results are in agreement with the concept that tough dense films of large molecular weight compounds delay the release of the anions. For a series of cellulose ester films, water permeability decreased with an increase in the chain length of the nonpolar acid moiety (30). The decrease in the diffusion of ions with an increase of the density of the film also was reported previously (31). The cellulose acetate butyrate film released the anion at a lower rate compared to the cellulose standard, which had a lower specific gravity (32). Thus, the decrease in the exchange rate of phosphate and benzoate ions across the film probably was due to the increase in the molecular weight, the more nonpolar character, and the higher specific gravity of the film, and these properties are related to the decreased water permeability. Gelatin–acacia, the thickest coat, provided the fastest initial rate of release. This effect can be partially explained by the polar character of the film and its ability to swell in water (33).

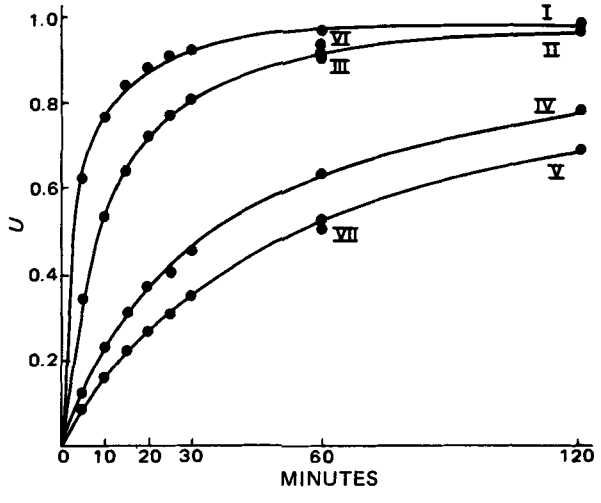

Figure 1—*Typical curves illustrating the effect of simple encapsulating agents on the fractional attainment of equilibrium. Each point is the average of three kinetic experiments at the time indicated. Some curves were omitted for clarity. Key: see Table I.*

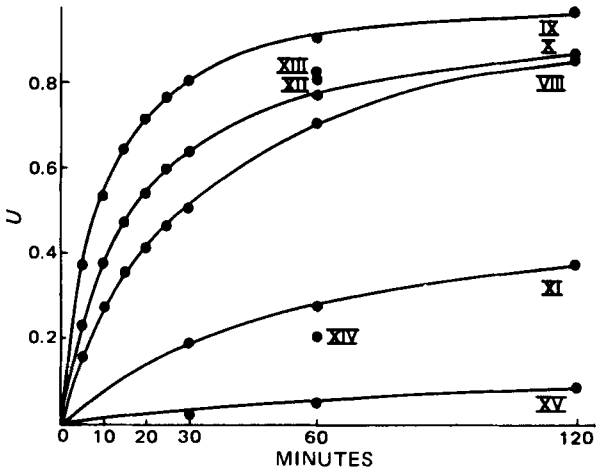

Figure 2—*Typical curves illustrating the effect of complex encapsulating agents on the fractional attainment of equilibrium. Each point is the average of three kinetic experiments at the time indicated. Some curves were omitted for clarity. Key: see Table I.*

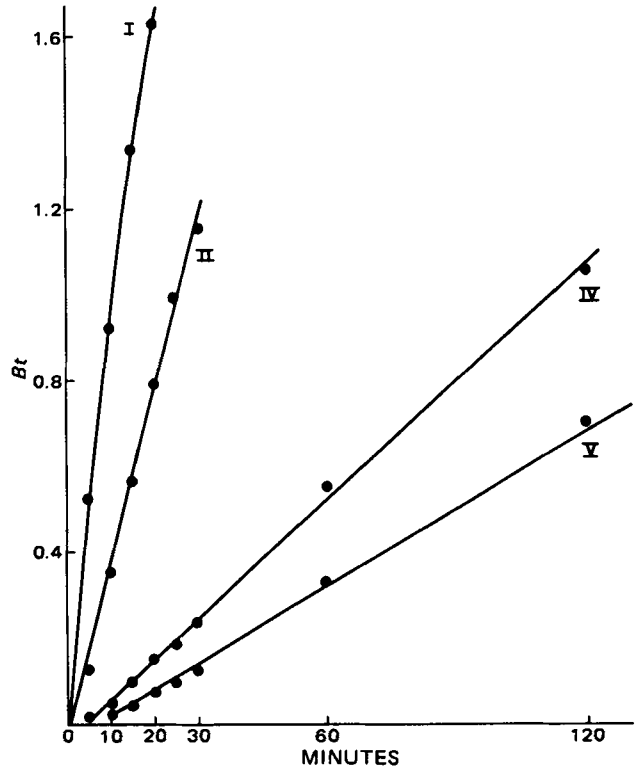

Figure 3—*Typical* Bt-t *plots showing the effect of simple encapsulating agents on the elution of benzoate ion from resin beads. Key: see Table I.*

Figure 2 provides information on the fractional attainment of equilibrium for complex coats. Water probably would be required to permit the transport of ions across the film. Thus, the addition of nonpolar compounds to the ethylcellulose film would decrease the water uptake or water transmission and, hence, lower the rate of anion exchange. Lipophilic films have been found to be less permeable to moisture than hydrophilic systems (19). Other studies indicated that the release rate of water-soluble compounds like neomycin sulfate can be enhanced by increasing the polarity of additives in the films or the celluloses comprising the film (34, 35).

In the present experiments, the additives with the greatest lipophilic character, polyethylene and paraffin, produced the greatest resistance to ion transfer as compared to the not quite so lipophilic compounds castor oil and butyl stearate (Fig. 2). Thus, the release characteristics and water transmission properties of the films depend on the lipophilic and hydrophilic characteristics of the film as influenced by the additives and matrix. In nearly all cases, ethylcellulose standard 100, a tougher film in combination with additives (except butyl stearate), was more effective than ethylcellulose standard 20 in delaying the release of the anion from the resin.

The theoretical treatment of the rate of ion exchange was described (36) and reviewed in detail (37), and the rate equations suitable for sustained release from ion-exchange resins were developed previously (38). The mathematical equation deals with ion exchange within resin beads of spherical shape and uniform diameter in a solution of infinite volume. Some of the experimental conditions did not meet these criteria; for example, the concentration of benzoate ion increased appreciably during the kinetic study, negating the requirement of infinite solution volume. The beads can be regarded as spherical, and diffusion of the benzoate ion probably could take place through all of the encapsulating materials since they or similar films are permeable to water and can absorb water to some extent (27, 32, 39, 40). It is of value to treat the rate of release in this theoretical manner to assist in the interpretation of the effect of the various films.

The method of calculation was described fully (37, 38). The values of the fractional attainment of equilibrium are related to the rate constant B by a summation equation. The rate constant B is defined as:

$$B = \frac{\pi^2 D}{r^2} \qquad \text{(Eq. 2)}$$

where D is the diffusion coefficient and r is the mean particle radius of the resin beads. To calculate the rate constant, values of Bt corresponding to values of fractional attainment of equilibrium (41) are plotted against t; the slope of the line yields the rate constant B. These data are plotted in Figs. 3 and 4. If the line is straight, it can be assumed that ionic diffusion within the resin bead is the rate-controlling step in the diffusion process (41). The rate of release from the uncoated resin beads and most coated beads yields a Bt–t relationship close to linearity over a major portion of the graph (Figs. 3 and 4), suggesting that the diffusion of ions is controlled by a particle diffusion process. Thus, the encapsulating material, while decreasing the rate of release considerably in a number of cases (Figs. 3 and 4), still permits the rate to follow the particle diffusion process of ion exchange.

The Bt–t plots over the complete timespan show deviation from linearity. Materials that rapidly release the anion show a decrease from linearity when the fractional attainment approaches 0.9, possibly as a result of not satisfying the infinite solution volume conditions. Plots of release of encapsulated resins possessing very slow rates of release also show deviations, probably due to a mechanical breakdown of the film as a result of wear or rupture in the rotating basket, thus causing a considerably greater rate of release as the system approaches equilibrium. Two clear examples are the Bt–t plots for ethylcellulose standard 20 and 100 polyethylene paraffin films, which show a very definite jump over the 48–72-hr period.

For discussion purposes, the resin bead and the encapsulating material can be treated as a homogeneous ion-exchange system in view of the linearity of the Bt–t plots and the relatively small increase in the particle diameter caused by the encapsulating material (Table I). The slopes of the Bt–t plots (Figs. 3 and 4 and Table I) were determined from the initial release, using the observed data of 2 hr and less and values of fractional attainment less than 0.9, corresponding to a Bt value of 1.8. To compare the effectiveness of the various coatings on the particle diffusion, values of B were determined from the slope of the Bt–t plots and the diffusion coefficients were determined from Eq. 2 using the radius of the encapsulated beads listed in Table I.

Dissolution and ion exchange, as shown from the Bt–t plots, are important factors governing the rate of drug release. In addition, release of drugs from polymers soluble in the digestive system can be influenced by the permeability of the film and the rate of dissolution of the polymer. Permeability would be a major factor governing the rate of release through a polymer such as ethylcellulose, which is insoluble in water (42). Recent papers (42, 43) indicated that two major mechanisms may be responsible for the diffusion of drugs through films of ethylcellulose, namely, a solubility diffusion process and a transfer through a capillary network. In the present research, both the benzoate and phosphate probably would be transported through the ethylcellulose when the film contains water, thus permitting a greater solubility of the ions.

Previous papers suggest that water vapor transmission and drug release are reduced when the interstices of the film are filled with nonpolar plasticizers such as hexadecyl alcohol, at least over a certain range of concentration of the additive. Somewhat more polar additives like tri-

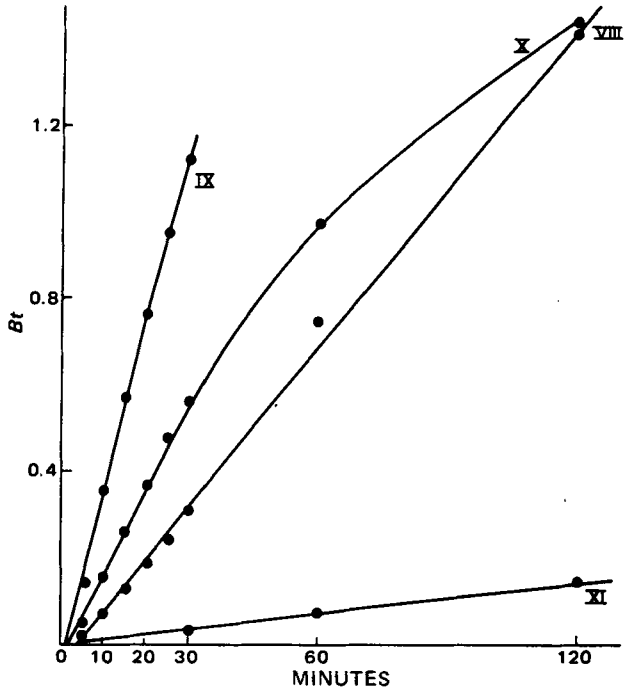

Figure 4—*Typical* Bt-t *plots showing the effect of complex encapsulating agents on the elution of benzoate ion from resin beads. Key: see Table I.*

butyl citrate tend to increase the rate (34, 39). A lipophilic film of *n*-butyl methacrylate was less permeable to moisture than hydrophilic films like hydroxypropylcellulose (19). Large organic ions were released more quickly when the more polar hydroxypropylcellulose content of the cellulose films was increased (44). The permeability of cellulose ester films decreased with the increasing chain length of the acid moiety used, and the plasticizer enhanced or retarded moisture permeation (32).

A review of the rate constants, *B*, or diffusion coefficients, *D*, in Table I supports the suggestion that lipophilic films or the incorporation of lipophilic additives prolongs the release of the anion. The tougher ethylcellulose medium and the nonpolar cellulose acetate butyrate prolonged the release more than the ethylcellulose standard and the polar gelatin films. When additives or plasticizers were added to the ethylcellulose standard 20 and 100 films, the release was further prolonged by the nonpolar compounds. The addition of castor oil to ethylcellulose 20 did not produce appreciable differences but caused almost a 50% decrease in the diffusion coefficient of ethylcellulose standard 100, and butyl stearate provided a generally greater decrease. Polyethylene, especially in conjunction with ethylcellulose standard 100, produced a further reduction; when it was used along with the additive paraffin, the maximum prolongation of release was achieved.

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