Table III—Solubility of Papaverine Hydrochloride at 25°

Fluid	Concentration, mg/ml
1.0 *N* HCl	1.5
0.50 *N* HCl	2.7
0.25 *N* HCl	4.6
0.10 *N* HCl	12.4
Gastric	10.6
pH 2.45[a]	22.8
pH 3.10[a]	23.1
pH 4.50[b]	30.0
pH 6.70[a]	<0.1
Intestinal	<0.1

[a] Mixture of gastric and intestinal fluids. [b] Test fluid.

dependency and apparently confirms the results of the first part of the experiment. The difference in the total amount of papaverine released between Products A and B was largely a result of the difference in the amount released in gastric fluid. Product C showed a greater release in pH 4.50 fluid.

The pKa of papaverine is 6.4 (10). However, the solubility of papaverine reaches a maximum about pH 4.5 and then decreases (Table III). The data indicate a significant common ion effect owing to the addition of excess chloride, which significantly reduces the dissociation of the hydrochloride salt, reducing its solubility.

CONCLUSIONS

The reciprocating basket apparatus with variable speed control has a wide range of usefulness. The stroke rate can be varied to obtain agitation intensities equivalent to those observed in both the continuous flow system and the rotating basket apparatus. Based on the results of this study, this apparatus appears to be suitable for evaluating the dissolution of nondisintegrating dosage forms. It fulfills the requirements recognized as necessary for an *in vitro* test. There is a controlled fluid flow rate past the dosage form. The agitation intensity can be varied as required, and the apparatus can be easily automated. The basket rack assembly has a modified top plate to provide sufficient room for sampling and replacement tubing.

The commercial sustained-release papaverine products had varied release rates in the test methods and pH fluids. Although no correlations with *in vivo* data were made, a general statement concerning these preparations is possible. It appears that the residence time of the pellets in the stomach and in the transition pH between the stomach and the intestines determines the amount of papaverine available for absorption. Little additional papaverine would be released from the pellets in the intestines because of its low solubility in this basic environment. Therefore, it may be possible to obtain an equivalent therapeutic effect from a standard dosage form of papaverine hydrochloride. Data reported (11) in a recent monograph on sustained-release papaverine hydrochloride are in agreement.

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Influence of Wax Coatings on Release Rate of Anions from Ion-Exchange Resin Beads

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Abstract □ Ion-exchange resin beads were coated with various waxes to improve and control their release. The *in vitro* release rates of benzoate ions from the coated resin beads were then investigated using a rotating sieve basket technique. The dramatic differences in release rates observed with the different waxes can be discussed in terms of the wax to resin ratio and the solubility characteristics of the waxes. The initial release rates can be expressed in terms of a mathematical expression previously reported for the diffusion of ions in ion-exchange resins, thereby aiding in the elucidation of the effect of the waxes on release.

Keyphrases □ Waxes, various—coated on ion-exchange resin beads, effect on release of benzoate anions □ Resin beads, ion exchange—coated with various waxes, effect on release of benzoate anions □ Benzoate anions—release from ion-exchange resin beads, effect of coating with various waxes □ Release rates—benzoate anions from ion-exchange resin beads, effect of coating with various waxes

Ion-exchange resins are currently used as vehicles for preparing prolonged-release medication. Saunders and coworkers (1–3) investigated the effect of binding of drugs to ion-exchange resins and employed drug–resin complexes to prolong drug release, thereby increasing its duration of action. Abrahams and Linnell (4) indicated that drug release from the resin depends on the availability of ions within the GI tract. Subsequent papers indicated the value of employing ion-exchange resins to prolong the release of ephedrine (5) and amphetamine (6).

Table I—Characteristics of the Wax-Coated Resin Complex

Wax	Wax, g / Resin Complex, g[a]	Benzoate Released[b], mg/g of Resin Complex
No wax	0.0000	366.4
Beeswax	0.2460	363.9
Polyethylene glycol 6000	0.3630	353.9
Carnauba wax	0.1850	354.5
Hard paraffin	0.0813	359.8
Stearic acid	0.5920	369.9
Stearyl alcohol	0.0664	355.1

[a] Average values of triplicate determinations on three different preparations. [b] Expressed as milligrams of sodium benzoate per gram of resin complex exclusive of wax. These are average values of triplicate determinations on three different preparations.

BACKGROUND

An alternative approach to prolonged-release medication is drug dispersal within inert matrixes such as polyvinyl chloride, polyethylene (7, 8), and wax consisting of propylene glycol monostearate and hydrogenated castor oil (9). Various factors influence drug release such as the matrix, the drug, the drug concentration in the tablet, drug solubility, matrix additives, and solvents.

Spray-congealing procedures also were used to prepare sustained-release powders and tablets. The effect of selected formulations and production variables on the physical characteristics and dissolution behavior of the spray-congealed particles was investigated. The effect of various waxes, *e.g.*, white wax, carnauba wax, and cetyl alcohol, on a particular formulation was dependent upon the physical properties of the wax and drug–wax particles, the wax composition, and the dissolution medium (10). Modifiers in the spray-congealed wax formulations such as surfactant and hydrogenated castor oil altered the release rate significantly (11, 12).

Another method employed to obtain prolonged-release coated particles is simply to incorporate the drug particles with the melted wax. The coated drug particles are then obtained either by granulation (13) or dispersion (14).

The coating of ion-exchange resins has received considerably less attention and has generally been regarded as an example of a solid being coated by coacervation (15, 16). Coatings of ion-exchange resins also were employed to alter the taste characteristics of the drug product (17).

The purposes of this research were to investigate the coating of an ion-exchange resin–anion complex with different materials by a simple procedure and to determine the effect of the different coating materials on the release rate of the organic anion from the anion–resin complex. It was expected that by employing different materials, the release rate of the model drug, benzoate anion, already affected by the ion-exchange resin, would be further altered to an appreciable extent, depending on the properties of the coating material. This preparation method of sustained-release pharmaceuticals would permit control of drug release by both the ion-exchange resin and the external coating.

EXPERIMENTAL

Materials—The strongly basic, 20–50-mesh, ion-exchange resin[1] was screened wet, and the beads that passed through a 35-mesh but were retained on a 40-mesh screen were used. The resin was washed thoroughly several times with distilled water, and the floating beads were rejected. The resin was then dried in a vacuum desiccator over sodium hydroxide for about 5 days. The resin was purified by washing with absolute ethanol, ethanol–water mixtures, and eventually with water over 1 week.

The resin was conditioned in a column by conversion to the hydroxide form with 2 *N* NaOH and to the chloride form with 2 *N* HCl. This procedure was repeated once, and then the resin was thoroughly washed with water. The resin was then converted to the benzoate form by adding 0.05 *N* sodium benzoate USP solution until the effluent concentration was the same as the eluant concentration. The resin complex was washed thoroughly with distilled water, dried, washed with methanol, and dried. The average particle size, as determined by microscopic measurement of 30 resin beads, was 0.402 mm for wet beads and 0.363 mm for dry beads.

The coating waxes or materials, beeswax (white), polyethylene glycol 6000[2], carnauba wax, hard paraffin, stearic acid, and stearyl alcohol of USP standard or commercial quality, were used without further purification. The coated resin beads were prepared by adding 4 g of melted wax to 1.5 g of resin complex in a funnel fitted with a coarse-porosity fritted disk. The mixture was maintained in the liquid state by the use of a heating jacket and was stirred for 30 min. The excess wax was removed by suction, and the coating on the beads was allowed to harden. The mixture then was stirred with a glass rod to separate the beads after cooling or gently ground with mortar and pestle to separate beads when carnauba wax was used to produce a coarse powder.

The amount of wax covering on the beads was determined by extracting the coated beads (0.25 g) with about 500 ml of warm chloroform in a heated fritted funnel over 2 hr. The extracted beads were then dried to constant weight in a vacuum desiccator. The extraction of each preparation was carried out in triplicate.

Kinetic Studies—The release rate of the benzoate anion from the coated resin complex was determined by placing a known quantity (0.25 g) of the resin into a metal basket apparatus made with an 80-mesh screen similar to that described by Kressman and Kitchener (18). The basket, placed into a 500-ml round-bottom flask containing 200 ml of phosphate buffer maintained at 30° with a constant-temperature bath, was rotated at 1240 rpm. The phosphate buffer contained 12.095 g of dibasic potassium phosphate/liter of aqueous solution. The elution procedure was carried out in triplicate on a single wax preparation.

Spectrophotometric analysis of the eluted benzoate was carried out by removing 5-ml samples from the flask at suitable intervals. The samples were appropriately diluted with the phosphate buffer, and the absorbance was measured[3] at 224.5 nm, the wavelength of maximum absorption for benzoate anion (19, 20). The concentration of the solution was determined from a Beer–Lambert plot of sodium benzoate in phosphate buffer.

The concentration of the benzoate at 24 hr was taken to be the equilibrium concentration since this period was suitable from an experimental point of view and also relevant to prolonged-release medication. The amount of benzoate released from the resin complex during a kinetic run was determined by taking into account both the concentration of benzoate in the eluting solution and the amount of benzoate periodically removed for analysis.

RESULTS AND DISCUSSION

The ratios of wax to resin complexes are given in Table I. In general, the amount of wax bound per gram of resin was reasonably consistent; all except two values were within 20% of the average. In these two cases, however, the deviation was considerably greater. One sample of resin complex coated with stearyl alcohol was 35% greater than the average, and one sample of carnauba wax was 57% greater than the average. There were large differences among the wax to resin ratios for different waxes, even though the same coating procedure was employed.

The amount of wax covering the surface appeared to depend on the polar character of the wax. The most polar compounds, such as stearic acid and polyethylene glycol, were bound to a much greater extent than the less polar compounds, such as hard paraffin and stearyl alcohol. The other waxes, carnauba and beeswax, were bound to an intermediate extent. The wax to resin ratio was used to calculate the amount of resin complex, exclusive of wax, that was added to the basket for the kinetic studies during elution. Under microscopic examination, the coated resin complex beads had the following characteristics: paraffin, a smooth consistent surface; beeswax and stearic acid, a coherent slightly irregular layer; polyethylene glycol, irregular surface and agglomerated particles; and stearyl alcohol and carnauba wax, sharp edges and agglomerated particles. After elution with the buffer solution, the beads coated with carnauba wax, hard paraffin, and beeswax had a few particles of wax still adhering to the surface; in the other cases, all of the coating had been removed from the resin beads.

The total amount of benzoate, expressed as the amount of sodium salt, released per gram of resin complex after 24 hr of extraction is given in Table I. All values were within 7% of the average value. These results indicate that the amount of benzoate released after 24 hr is essentially independent of the kind or the amount of wax covering the resin complex since the total amounts released were all close to the value for the uncoated resin complex. The amount of benzoate released after 120 min was very close (>99%) to the amount released after 24 hr for the uncoated

[1] Dowex 1-X8, Dow Chemical Co., Midland, Mich.

[2] Carbowax.

[3] Beckman DU-2 spectrophotometer.

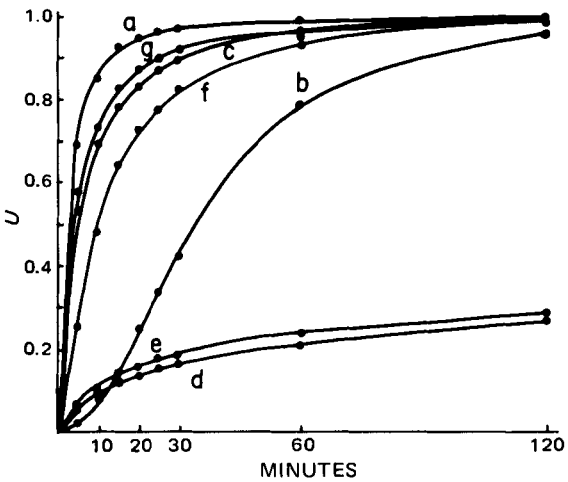

Figure 1—*Effect of a wax coating on the fractional attainment of equilibrium. Each point is the average of three kinetic experiments at the time indicated. Key: a, uncoated resin; b, beeswax; c, polyethylene glycol 6000; d, carnauba wax; e, hard paraffin; f, stearic acid; and g, stearyl alcohol.*

resin. Therefore, 24-hr values can be taken as appropriate equilibrium values for extraction of the coated resin complex as well as the uncoated resin complex under the conditions of the experiment.

To compare the effect of the wax coating on the release of benzoate from the resin complexes during the elution procedure as a function of time, the fractional attainment of equilibrium, U, is calculated from:

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

where R is the amount of anion released in time t and R_∞ is the amount released in 24 hr. This information is provided in Fig. 1. Since ion-exchange resins have been used to delay the release of drugs from the resin complex (3), the effect of waxes on further delaying the process is clearly indicated. It can be seen from these data that the order of delay of release of the benzoate was as follows: no wax < stearyl alcohol ~ polyethylene glycol < stearic acid < beeswax < hard paraffin ~ carnauba wax.

A number of physical properties of the waxes such as aqueous solubility, thickness of the wax layer, uniformity of coating, fracturing of the coat due to friction and impact in the elution apparatus, and fracture of the beads during hydration probably influence the release rate of the benzoate anion from the resin complex. The rapid release of the anion by polyethylene glycol can be explained by its high solubility in water (21), which allows the coating to dissolve rapidly and permits ion exchange to take place at only a slightly slower rate than the uncoated resin complex. The polyethylene glycol does, however, decrease the release rate in the early stages of the elution, indicating that even this highly soluble wax exerts some influence on the release rate and a certain amount of time is necessary to dissolve the wax so that the maximum rate can be obtained; overall, the rate was not decreased appreciably.

The relatively high elution rate of the resin complex covered with stearic acid may be attributed to its higher solubility in water [very slightly soluble (21)] compared to the remaining compounds. Another factor is the increase in the dispersibility of stearic acid in the slightly alkaline (pH 9.1) solution used as the elution medium as a result of ionization of this fatty acid.

Beeswax, carnauba wax, stearyl alcohol, and hard paraffin are classified as either practically insoluble or insoluble in water (21, 22). Accordingly, when used as coating materials on the resin complex, all of these compounds delay the release significantly. A comparison can be made among the three waxes that have acid values (21, 23): stearic acid, 206–209; beeswax, 17–24; and carnauba wax, 2.9–9.7. Thus, beeswax occupies an intermediate place both in the release rate and the ease of dispersibility in the medium as indicated by the acid value.

The very low release rate afforded by carnauba wax and hard paraffin can be attributed to their insolubility in water and/or lack of dispersibility in the slightly alkaline medium.

The rapid release by the stearyl alcohol covered beads, in spite of its insoluble nature, may be attributed to its ability to be hydrated to a slight degree and to the comparatively thin coat of stearyl alcohol on the resin complex as indicated by the low wax to resin value.

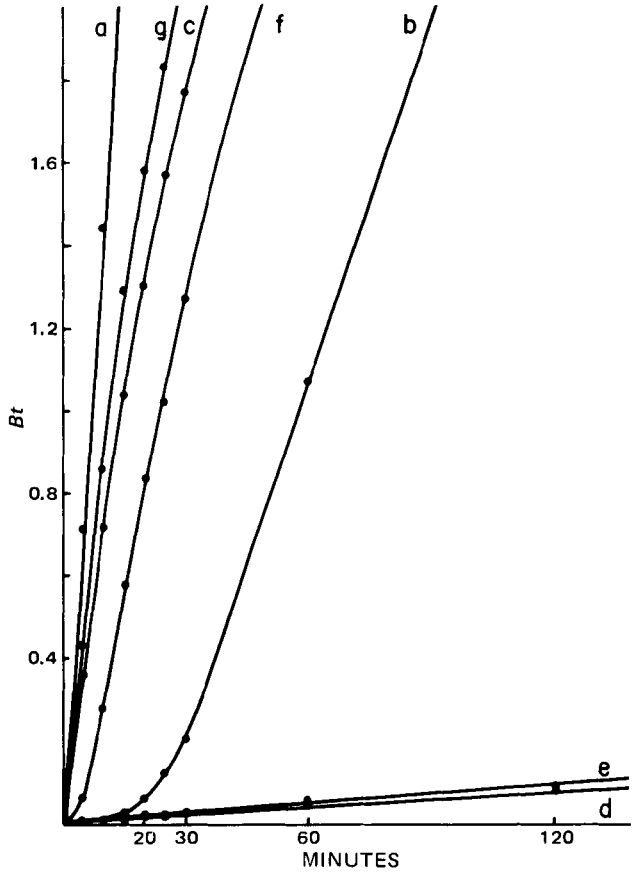

Figure 2—*The* Bt–t *plots for the elution of benzoate anion from coated and uncoated resin beads. Each point is the* Bt *value taken from the* U *values in Fig. 1. Key: a, uncoated resin; b, beeswax; c, polyethylene glycol 6000; d, carnauba wax; e, hard paraffin; f, stearic acid; and g, stearyl alcohol.*

A comparison of the wax to resin ratio suggests that, except for stearyl alcohol, there appears to be very little relationship between the fraction of attainment of equilibrium at 30 min, for example, and the wax to resin ratio. Hard paraffin and stearyl alcohol have similar ratios and solubilities in water, but the fraction of attainment of equilibrium is considerably different. A similar comparison can be made between beeswax and carnauba wax.

In view of the insolubility of waxes like hard paraffin and the fact that approximately 5% of equilibrium is attained even within a very short period after beginning elution, factors affecting the release rate other than solubility and dispersibility must be considered. After the wax-covered beads were prepared, microscopic examination indicated that the coating was rough in many cases; parts of some beads probably were not completely coated with wax. After elution, beads coated with the least soluble or the least dispersible of the waxes, namely, carnauba wax, hard paraffin, and beeswax, showed evidence of some wax adhering to the beads. Thus, with these harder waxes, fracture of the coating probably takes place during the elution procedure, giving rise to immediate release of the benzoate anion. Another factor to be considered is the cracking or rupture of some resin beads when they are hydrated rapidly or mechanically damaged during elution, thus exposing noncoated surface to the elution medium for immediate extraction.

The theoretical treatment of the kinetics of ion exchange was elucidated (24) and reviewed (25), and the rate equations appropriate to sustained release from ion-exchange resins were developed (3). The mathematical equation deals with the control of ion exchange within resin beads of spherical shape and uniform diameter in a solution of infinite volume. A number of 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, but diffusion would only likely take place where the coating had been removed. It is useful, however, to treat the release rate in this theoretical manner to aid in the interpretation of the effect of waxes.

The method of calculation is fully explained in the references (3, 25). 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 $B = \pi^2 D/r^2$, where D is the effective 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 (26) are plotted against t and the slope of the line yields the rate constant B. These data are plotted in Fig. 2. 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 (26). It can be seen from Fig. 2 that the release rate from the uncoated resin beads yields a linear Bt–t relationship over a major portion of the graph, indicating that the diffusion of ions is controlled by particle diffusion.

While this theory cannot be applied strictly to the coated resin beads since interionic diffusion can hardly be expected to take place through the wax coating and the surface area of the beads exposed to the aqueous electrolyte solution will increase as the wax is dissolved or broken from the bead, it is useful to examine the Bt–t plots to assess diffusion characteristics.

Since the beads are not perfectly coated, it would be expected that release would begin immediately from any exposed surfaces. If the wax is rapidly removed, the maximal release rate should follow shortly thereafter. If the wax is removed at an intermediate rate, then the release rate would be expected to increase with time as the surface area is increased. Finally, if the wax is very slowly or incompletely removed, then the release rate should decrease with time due to the longer path length of diffusion within the resin bead.

The curves of the release from the beads coated with stearyl alcohol and polyethylene glycol 6000 are both similar in that the lines are slightly curved with a slightly smaller slope, indicating that the highly soluble polyethylene glycol 6000 and the thin coat of the stearyl alcohol have a small, but measurable, effect on the release of the benzoate ion compared to the uncoated resin. The curves of stearic acid and, especially, beeswax have very low slopes initially, but the slopes increase as time proceeds, indicating that the diffusion rate increases considerably within the first 10 min for stearic acid and within the first 30 min for beeswax and that some coating material is rapidly removed, thus exposing a greater surface area and allowing the maximum rate to be achieved.

The Bt–t plots of release from beads of resin coated with hard paraffin and carnauba wax are similar in that the release rate is very slow throughout the kinetic process. While the Bt–t plot appears to be linear, on an expanded vertical scale (10×) the curve has a decreasing slope, indicating a decrease in the rate with time due to much slower or incomplete removal of the wax coat from the bead's surface.

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