found here. Nonetheless, the ultrasonic solution analyzer method offers great promise as a single, rapid, and accurate control procedure for determining the alcohol and soluble solids content of mouthwashes.

A distinct advantage over conventional methods of analysis is the test's simplicity. No alcohol distillation is necessary; in a one-step procedure, with the latest models of the instrument, values for two parameters are available within 5 min on a direct readout display.

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In Vitro Evaluation of Three Commercial Sustained-Release Papaverine Hydrochloride Products

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Abstract □ Three commercial sustained-release papaverine hydrochloride products in the form of microencapsulated pellets were evaluated. Three different dissolution apparatuses were used: a continuous flow apparatus, the USP rotating basket apparatus, and a modified reciprocating basket apparatus. The frequency rate of the reciprocating basket apparatus could be varied from 0 to 32 strokes/min. Salicylic acid compacts were used as a standard to characterize each apparatus. A linear log–log correlation between dissolution rate and apparatus speed or flow rate was obtained. Release of papaverine hydrochloride from the commercial preparations was affected significantly by the pH of the dissolution media but not by the agitation intensity.

Keyphrases □ Papaverine hydrochloride—dissolution, three commercial sustained-release products, three different apparatuses compared □ Dissolution—papaverine hydrochloride, three commercial sustained-release products, three different apparatuses compared □ Apparatus, dissolution—three types compared, papaverine hydrochloride, three commercial sustained-release products □ Relaxants, smooth muscle—papaverine hydrochloride, dissolution, three commercial sustained-release products, three different apparatuses compared

In recent years, the study of dissolution of drugs from solid dosage forms has become increasingly important. The rate and extent of dissolution from tablets, capsules, and pellets affect both the absorption and therapeutic effect of a drug. Different formulations of the same drug may exhibit different absorption characteristics and, subsequently, different therapeutic activity (1).

Although it is agreed that dissolution testing is important, there is disagreement as to the apparatus and method that should be used as a standard. A simple inexpensive apparatus and method that could be used for most products would be ideal. Such a development is a difficult task, however, because of the numerous factors influencing dissolution testing. Some of these factors are related to the product, such as the physical–chemical properties of the drug and variations in formulation; others, such as the amount and type of solvent and the geometry of the container, are unrelated to the product.

The objective of this study was to evaluate the *in vitro* release characteristics of sustained-release papaverine hydrochloride pellets, produced by various manufacturers, under a variety of conditions. This evaluation was made in three different dissolution apparatuses using a nondisintegrating compact as a standard.

EXPERIMENTAL

Materials—Standard nondisintegrating disks have been used (2, 3) as a means of comparing different dissolution apparatuses. In this study, salicylic acid compacts were chosen as the standard and were used to characterize each apparatus under varying experimental conditions.

About 350 mg of salicylic acid powder[1] was compressed at 1860 kg, using a hydraulic press[2] with a motorized attachment operated at 1.0 cm/sec. Standard 0.95-cm concave punches were employed, and the die was held in place with an acrylic[3] mold. The compacts had an initial average weight of 345 mg with an average thickness and diameter of 0.465 and 0.961 cm, respectively.

The sustained-release papaverine products, A–C[4], were encapsulated pellets containing 150 mg of papaverine hydrochloride/capsule.

Test Fluids—Gastric fluid was prepared according to the method described in USP XIX without the addition of enzyme.

The other test fluids, pH 4.50, 6.00, and 7.00, contained 6.8 g of monobasic potassium phosphate/liter. The monobasic potassium phosphate was dissolved in about 950 ml of water, the pH was adjusted to the desired value with 36.5% (w/w) HCl or 5% (w/v) NaOH, and the volume was brought to 1 liter.

Assay Method—Beer's law curves were constructed for papaverine hydrochloride and salicylic acid. The maximum wavelengths for the two test materials are: salicylic acid in gastric fluid, λ = 302 nm; papaverine hydrochloride in gastric fluid, λ = 309 nm; papaverine hydrochloride in pH 4.50 fluid, λ = 309 nm; papaverine hydrochloride in pH 6.00 fluid, λ = 310 nm; and papaverine hydrochloride in pH 7.00 fluid, λ = 325 nm.

In most cases, these wavelengths allowed direct absorbance readings under experimental conditions. Linearity was followed in the concentration ranges used.

Dissolution Methods—Each of the three dissolution methods affected

[1] Reagent grade, J. T. Baker Chemical Co., Clifton, N.J.

[2] Model C, Fred S. Carver, Menomonee Falls, Wis.

[3] Lucite.

[4] Product A was lot 3H518, Vitarine Co.; Product B was Pavabid lot 12023, Marion Laboratories; and Product C was Cerespan lot 55282, USV Pharmaceutical Corp.

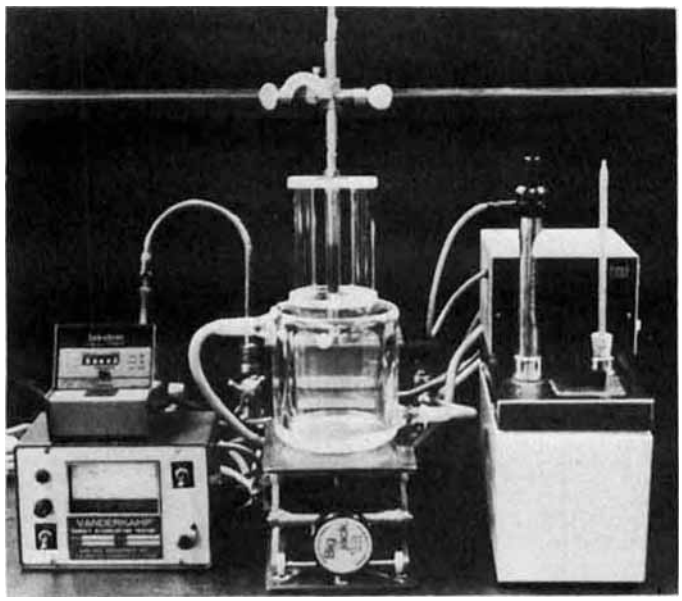

Figure 1—*Reciprocating basket apparatus.*

dissolution by a different mode of agitation. The continuous flow system utilized a flowing stream of liquid, which bathed the dosage form and caused the dissolved drug to be carried away in the effluent. The rotating basket apparatus caused agitation by the rotation of the basket containing the test material. Agitation in a vertical reciprocating apparatus was accomplished by the up and down movement of the basket rack assembly. Liquid moved into the tubes past the dosage form resting on the screen during the down stroke and then back into the bulk solution on the up stroke.

The continuous flow system was similar in design to the apparatus described by Tingstad *et al.* (2). The dissolution medium reservoir consisted of a 1-liter jacketed beaker maintained at 37.5 ± 0.5° by a constant-temperature regulator. The solid-state, variable-speed, peristaltic tubing pump[5] had a pump head[6] capable of delivering a maximum of 125 ml/min.

Effluent from the dissolution chamber was either routed with the aid of flexible tubing[7] through a spectrophotometer[8] adapted with a flow cell or collected as fractions. In some experiments, the recorder output of the spectrophotometer, which represents the derivative of the cumulative dissolution curve, was input into an analog computer[9]. The computer integrated the signal and, with a recorder[10], printed cumulative amount *versus* time.

A constant voltage source[11] was used to input an electrical signal of opposite sign and sufficient magnitude into the analog computer to reduce the electrical noise of the system's components to minimal levels. This step reduced the maximum error that might have resulted from the integration of an extraneous signal with the spectrophotometer output to about 1% over 100 min.

When the continuous flow system was operated with the analog attachment, the voltage output of the spectrophotometer was related to the cumulative amount of drug released in milligrams, C, from the dosage form as follows:

$$C = \frac{F}{KS}\int_0^t M\,dt = \frac{F}{KS}Mt \qquad \text{(Eq. 1)}$$

where F is the flow rate (milliliters per second), K is the absorptivity (milliliters per milligram), M is the millivolt output of the system, t is the time (seconds), and S is the millivolts per absorbance unit for the system. For this system, S = 33.33 mv/absorbance unit. The integrator time constant was 100 sec.

When the analog attachment was not used, effluent from the dissolution cell was collected as fractions and assayed individually because high absorbance values prevented direct readings. Fractions were collected at 2-min intervals for the first 10 min and at 5-min intervals for the next 20 min. Thereafter, effluent was collected in a large cumulating reservoir. A 2-ml aliquot was removed every 15 min for assay for the remainder of the test. As required, either a 1:5 or a 1:10 dilution was made to obtain absorbance readings.

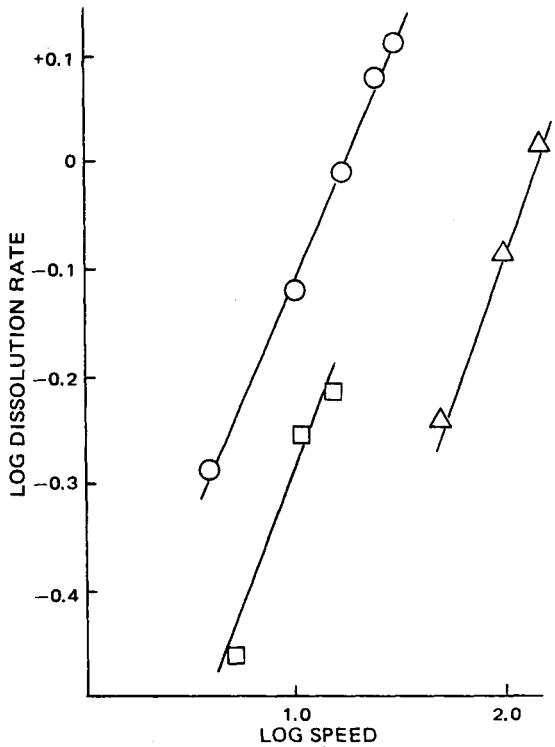

Figure 2—*Correlation of the dissolution rate of the salicylic acid compacts in gastric fluid with apparatus speed or flow rate. Key:* □, *continuous flow system;* ○, *reciprocating basket apparatus; and* △, *rotating basket apparatus.*

A variation in the general apparatus was made while studying the effect of varying pH on a single dosage form. A second jacketed beaker was placed in series with the first and also was maintained at 37.5°; this arrangement allowed for the switching of pH fluids (using additional tubing and a valve) without interrupting solvent flow. This experiment employed three test fluids in the following order: gastric fluid for 60 min, pH 4.50 fluid for 30 min, and pH 7.00 fluid for 60 min. Fractions were collected at 10-min intervals when the pH 4.50 and 7.00 fluids were used.

In the operation of the continuous flow system, the spectrophotometer was set at the desired wavelength, and the pump speed was adjusted to provide the fluid flow rate required. The system was allowed to equilibrate for at least 15 min before use. The recorder was adjusted to zero, and the spectrophotometer was nulled. The electrical noise of the system input to the analog integrator was adjusted with the aid of a constant voltage source to a minimal level so that it would not interfere with the spectrophotometer signal. The pump was then stopped.

The dissolution cell was then removed from the system, disassembled, and dried. The dosage form was placed on the lower support screen, and the cell was reassembled and put back in place. At time zero, the pump was restarted, and the amount of drug released was measured. Effluent was collected in a cumulating reservoir. The final volume of liquid was measured to obtain the average flow rate during the experiment.

The reciprocating basket apparatus (Fig. 1) consisted of a basket rack assembly, a 1-liter jacketed beaker attached to a temperature-regulating device maintained at 37.5 ± 0.5°, and a device[12] for raising and lowering the basket in the dissolution fluid at a constant frequency rate through a stroke distance of 5.5 ± 0.5 cm. The frequency rate of this device could be varied from 0 to 32 strokes/min, depending on the conditions desired.

The specially designed basket rack assembly consisted of two open-end glass tubes, 12 cm long × 21.5 mm i.d., with a wall 2 mm thick. The tubes

[5] Model 7555, Cole-Parmer Instrument Co., Chicago, Ill.
[6] Model 7014-20, Cole-Parmer Instrument Co., Chicago, Ill.
[7] Catalog No. 13-9110-5, Ace Scientific Supply Co., Linden, N.J.
[8] Model 222, Gilford Instrument Laboratories, Oberlin, Ohio.
[9] Model TR-20, Electronic Associates, West Long Branch, N.J.
[10] Mosley model H01-680, Hewlett-Packard, Downers Grove, Ill.
[11] Model EU-80A, Heathkit Corp., Fair Lawn, N.J.
[12] Model 74D-442-6, Van-Kel Industries, Inc., Chatham, N.J.

Table I—Values of a and b in $R = aS^b$ for the Various Dissolution Apparatuses

Method	a	b
Continuous flow system	0.15	0.54
Reciprocating basket apparatus	0.26	0.48
Rotating basket apparatus	0.067	0.55

were held in the vertical position by two plastic plates. The lower plate was 9 cm in diameter and 8 mm thick with two holes 24 mm in diameter equidistant from the center plate and equally spaced from each other. The upper plate was rectangular with convex sides. It measured 9 cm in length at its widest point and 7.2 cm at the edges, and it was 4.8 cm wide and 8 mm thick with two holes equidistant from the center identical in size to those in the bottom plate. It was held in place by a collar and set screw, which could be easily loosened to remove the glass tubes or screens when necessary.

The central shaft was 14.2 cm in length and 9 mm in diameter. It was attached to the bottom plate with a screw. The upper end could easily be attached to a shank if an extension was required. Two individual screens fit into the bottom plate below the tubes. Forty-mesh stainless steel screens were used.

When the vertical reciprocating apparatus was used, exactly 900.0 ml of test fluid was placed in the dissolution vessel and allowed to equilibrate at 37.5 ± 0.5°. One dosage form was placed in each of the two tubes of the basket. The basket assembly was immersed in the test medium so that it descended to 1 ± 0.1 cm from the bottom of the vessel on the downward stroke. The stroke rate was adjusted to the desired speed, and the test was begun.

Three milliliters of fluid was removed for assay at 15-min intervals for the length of the test. The removed fluid was immediately replaced with fresh liquid to maintain a constant volume. The aliquots were assayed spectrophotometrically at the wavelength required for the test fluid and compound. When necessary, dilutions were prepared. All aliquots were filtered through membrane filters[13] before assay.

The rotating basket apparatus met the requirements described in the official compendia (4, 5). The basket rotation rate was maintained at the desired revolutions per minute by a motor fitted with a speed-regulating device[5]. The entire assembly was immersed in a suitable water bath maintained at 37.5 ± 0.5°. The method of operation was as described in USP XIX. Three milliliters of fluid was removed from the dissolution vessel at 15-min intervals for assay. The removed fluid was immediately replaced with fresh fluid. The samples were assayed in the same manner as described for the reciprocating basket apparatus.

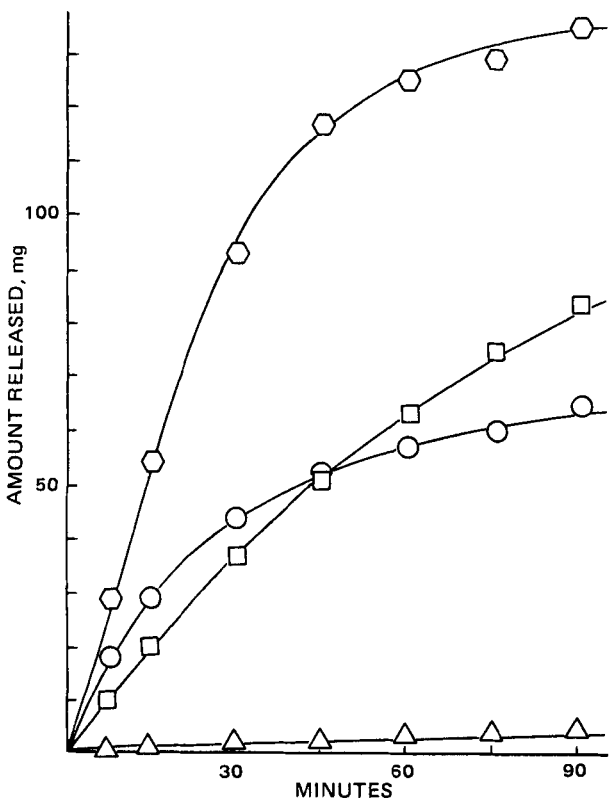

Figure 3—*Release curves for papaverine hydrochloride from Product A in the continuous flow system. Key: □, gastric fluid, flow rate = 10.1 ml/min; ○, pH 4.50 fluid, flow rate = 10.1 ml/min; ○, pH 6.00 fluid, flow rate = 10.3 ml/min; and △, pH 7.00 fluid, flow rate = 10.1 ml/min.*

[13] Catalog No. HAWP01300, Millipore Corp., Bedford, Mass.

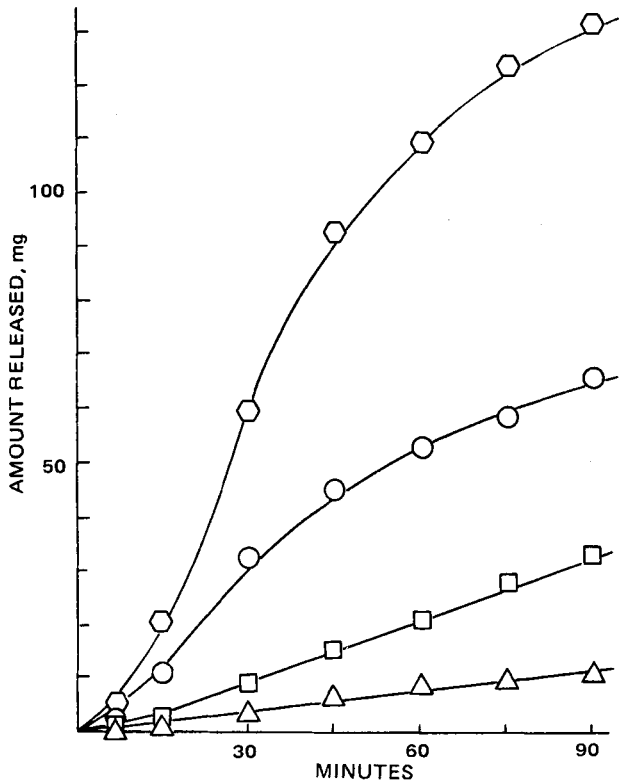

Figure 4—*Release curves for papaverine hydrochloride from Product B in the continuous flow system. Key: □, gastric fluid, flow rate = 10.0 ml/min; ○, pH 4.50 fluid, flow rate = 10.0 ml/min; ○, pH 6.00 fluid, flow rate = 10.4 ml/min; and △, pH 7.00 fluid, flow rate = 10.2 ml/min.*

The sustained-release papaverine hydrochloride pellets were removed from the capsule before placement in the various dissolution apparatuses. The emphasis was on the characterization of the drug release rate from the pellets. Any effect the gelatin capsules might have on the release rate was not considered.

Determinations involving salicylic acid were made in duplicate. Those involving the papaverine hydrochloride preparations were done in triplicate.

Solubility Determinations—The solubility of papaverine hydrochloride was determined in 0.1–1.0 N HCl, the test fluids, and fluids of varying pH obtained by mixing different proportions of gastric fluid USP and intestinal fluid USP, both without enzyme. Excess papaverine hydrochloride was placed in a 50-ml glass-stoppered flask together with 25.0 ml of fluid. The sample was shaken mechanically in a water bath maintained at 25.0 ± 0.5° and allowed to equilibrate. After equilibrium, an aliquot was removed and filtered. It was diluted as required with 0.2 N HCl; the concentration was determined spectrophotometrically at λ 309 nm.

RESULTS AND DISCUSSION

Characterization of Dissolution Methods—Dissolution is affected by many variables such as the degree of agitation, which becomes extremely important when comparing different apparatuses. Some investigations (6, 7) involving agitation led to the empirical relationship:

$$R = aS^b \qquad \text{(Eq. 2)}$$

where R is the dissolution rate (milligrams per minute), S is the apparatus speed (strokes per minute or revolutions per minute) or flow rate (milliliters per minute), and a and b are constants.

The salicylic acid compacts exhibited zero-order dissolution rates in gastric fluid in the different apparatuses. As the flow rate or apparatus speed was increased, the dissolution rate of the compacts increased.

Table II—Comparison of Sustained-Release Pellets in the Different Apparatuses

Product	Amount Released after 60 min in Gastric Fluid, mg		
	Continuous Flow System[a]	Reciprocating Basket[b]	Rotating Basket[c]
A	63.5 ± 4.8[d]	90.8 ± 7.8	76.2 ± 6.0
B	20.6 ± 0.8	43.0 ± 1.1	41.9 ± 2.1
C	32.8 ± 2.5	55.7 ± 0.7	53.2 ± 2.9

[a] Average flow rate = 10.0 ml/min. [b] Four strokes per minute. [c] At 50 rpm. [d] Mean ± *SD*.

When the dissolution rates of the compacts were plotted *versus* the flow rate or apparatus speed for the methods, using the logarithmic transformation of Eq. 2, a linear correlation was obtained (Fig. 2). The values of a and b, determined from the intercept and slope, respectively, are shown in Table I.

The constant a in Eq. 2 appears to be related to the velocity of the fluid flowing past the compact. For the continuous flow system, it has the dimensions of $mg/min^{(b-1)}ml^b$. In the reciprocating basket apparatus and the rotating basket apparatus, the solvent flow rate past the compact is determined by the basket stroke rate and basket rotation rate, respectively. Thus, in these instances, the value determined for a is proportional to that observed for the continuous flow system.

The value of the constant b depends on a number of factors including the processes controlling dissolution, the type of agitation, and the substance being studied. Cooper and Kingery (6) calculated a value for b of 0.5 in a diffusion-controlled process. The values determined for b in the different apparatuses are in good agreement with this theoretical value. They are also similar to the value of $b = 0.49$ reported for salicylic acid at pH 1.0 (7) and to the value of $b = 0.537$ reported for salicylic acid in various pH fluids (8).

Measurement of the dimensions of the salicylic acid compacts before and after each experimental run indicated that dissolution in the reciprocating basket and rotating basket apparatuses occurred over the whole compact surface since both its diameter and thickness decreased to the same extent. Fluid was constantly moved across all compact surfaces as a result of the varied solvent flow in both apparatuses. Dissolution in the continuous flow system, however, occurred predominantly from the side of the compact. The diameter of the compact decreased while the thickness remained essentially unchanged. Fluid flowed past the compact in a continuous stream, mainly in contact with only one surface.

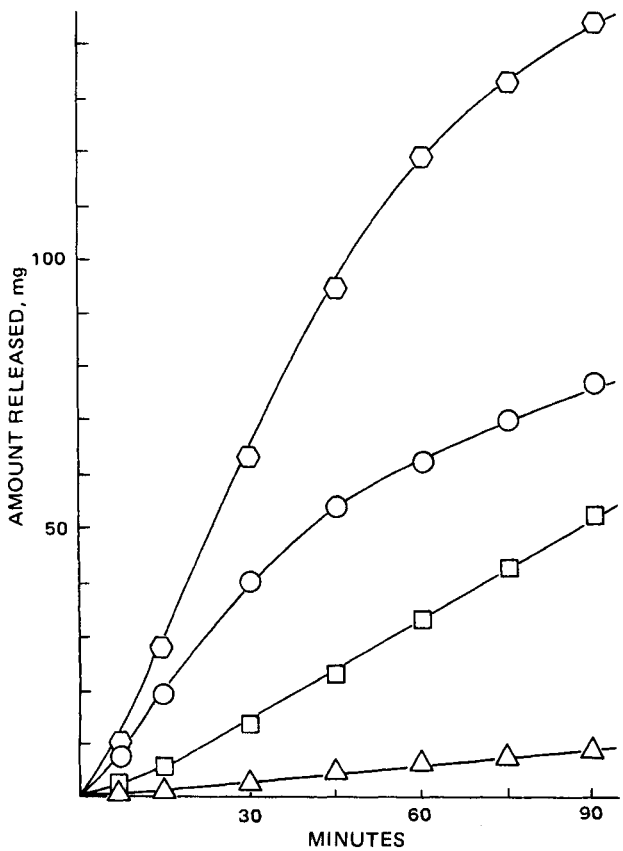

Figure 5—*Release curves for papaverine hydrochloride from Product C in the continuous flow system. Key: □, gastric fluid, flow rate = 10.0 ml/min; ○, pH 4.50 fluid, flow rate = 10.0 ml/min; ○, pH 6.00 fluid, flow rate = 10.2 ml/min; and △, pH 7.00 fluid, flow rate = 10.2 ml/min.*

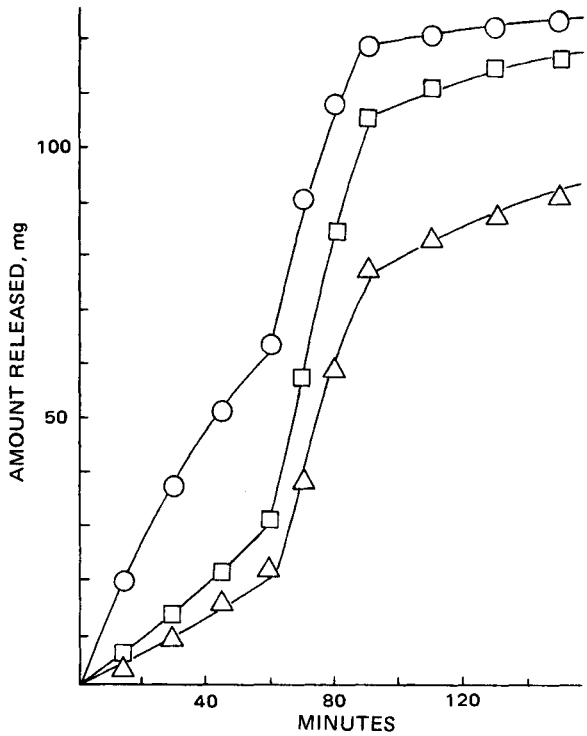

Figure 6—*Release curves for papaverine hydrochloride from the commercial sustained-release products in gastric fluid (60 min), pH 4.50 fluid (30 min), and pH 7.00 fluid (60 min) in the continuous flow system. Key: ○, Product A, flow rate = 10.3 ml/min; △, Product B, flow rate = 10.2 ml/min; and □, Product C, flow rate = 10.1 ml/min.*

Evaluation of Sustained-Release Papaverine Hydrochloride Products—Product A was used to study the effect of variations in agitation intensity on the *in vitro* drug release rate from the pellets. Experiments were conducted in the various dissolution apparatuses with gastric fluid as the test medium. No significant differences in the release rates from the pellets were seen when the apparatus speed or flow rate was varied. However, there was a slight upward trend with increasing agitation in the rotating basket apparatus and the continuous flow system. Preliminary investigations with Products B and C showed similar results.

The amount of papaverine released from the pellets varied among the apparatuses, but the rank order of the products remained unchanged (Table II). Gastric fluid was used as the test medium. An agitation intensity equivalent to a dissolution rate of salicylic acid of about 0.5 mg/min was used in each apparatus.

The effect of the pH of the test medium on the release rate of papaverine hydrochloride from the pellets was studied using the continuous flow system. The flow rate was maintained at 10.2 ● 0.2 ml/min. The effect of a single pH on the release rate was evaluated first (Figs. 3–5).

The sustained-release pellets had varied release rates in gastric fluid. Product A showed a release rate that was linear when the total amount released was plotted *versus* the square root of time. It appeared to follow the theoretical relationship proposed for solid drugs dispersed in solid matrixes (9). Products B and C, after an initial lag period, exhibited pseudo-zero-order release rates since the total amount of papaverine hydrochloride released increased linearly with time.

Release of papaverine hydrochloride from the pellets was greatest in pH 4.50 fluid and least in pH 7.00 fluid. The greatest difference among the products was in gastric fluid. The difference in the amount of papaverine released from the products in the various fluids was a result of both the pH-dependent solubility characteristics of the drug in the test media and the release characteristics of the pellets.

The effect of varying the pH of the test media on a single dosage form was also evaluated (Fig. 6). The release rate for each product showed pH

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).