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PREPARATION AND IN VITRO EVALUATION OF SALTS OF AN ANTIHYPERTENSIVE AGENT TO OBTAIN SLOW RELEASE

E. J. Benjamin* and L-H. Lin

Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304

ABSTRACT

The hydrochloride, acetate, tartrate, sulfate, p-hydroxy- benzoate, ebonate, napsylate, 3-hydroxy naphthoate and methacrylic acid-methacrylate copolymer salts of 9-[2-(indol-3-yl)ethyl]-1-oxa-3-oxo-4, 9-diazaspiro[5,5] undecane (I) were prepared. In vitro dissolution rates for the pure salts and the capsule formulation were determined using rotating disk method and USP method 2, respectively, in 0.1 N HCL, water and 0.05 M phosphate buffer pH 7.5. The intrinsic dissolution rates in all media showed dramatic differences among various salts corresponding to the differences in their solubilities in water. The in vitro dissolution

*Author to whom correspondence should be addressed.

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rates from capsules in neutral media showed marked differences among salts, however, there were no significant differences in dissolution rates from capsules when 0.1 N HCL was used as the medium. The data indicated that the ebonate, 3-hydroxy naphthoate and napsylate salts when formulated in an enteric coated dosage form would provide a slow release of I.

INTRODUCTION

The first step in the absorption process of an orally administered solid form of the drug is its dissolution in the gastrointestinal (G.I.) tract fluid. The drug in solution then passes through the lipoidal gut wall into the general circulation. Generally this transport is by a passive diffusion, hence, the unionized form of the drug is absorbed more readily than the ionized form. A basic drug such as a strong amine would undergo a rapid dissolution in acidic pH of the stomach.

Solid drug in G.I. tract fluid	Dissolution	Drug in solution G.I. tract	Absorption	Drug in general circulation

Scheme I

However, being ionized it is not absorbed from the stomach until it reaches the neutral or alkaline part of the intestine where significant amount of the unionized form is present. The rate limiting step in the overall absorption process (Scheme I) is diffusion through the gut wall. If the dissolution rate of the drug can be slowed down then the overall absorption process could become dissolution rate limited. Thus the intensity and duration of action could be controlled by the dissolution rate.

There are numerous ways to modify a drug substance achieve slow release characteristics and this topic has been previously reviewed (1). We chose to utilize the slow release characteristics of slightly soluble salts of the drug substance. This approach has been used successfully for methadone (2) and amitriptyline (3).

Another advantage of using dissolution rate limited delivery is the probability of lower toxicity or G.I. tract adverse side effects (4). In an absorption controlled process, as in the case of rapidly dissolving compounds, the local concentration of the drug is high which can cause local G.I. tract side effects. This has been demonstrated for benzphetamine and etryptamine (5) and clorprenaline (6).

This report describes the preparation and in vitro evaluation of salts of a new potent antihypertensive agent 9-[2-(indol-3-yl)ethyl]-1-oxa-3-oxo-4,9-diazaspiro [5,5] undecane (I).

MATERIAL AND METHODS

Materials: Compound I was obtained from the Institute of Organic Chemistry, Syntex Research. The excipients used were corn starch USP, spray dried lactose USP, magnesium stearate USP, microcrystalline cellulose USP and polyvinylpyrolidine USP. All other chemicals were reagent grade and were used as such.

Preparation of the Salts: The salts were prepared by reacting either I hydrochloride and the sodium salt of the acid (Method A) or I free base and the acid (method B) following general methods described below:

Method A - I hydrochloride (3.5 g, 0.01 M) was dissolved in water (120 mL) with stirring. The appropriate acid (0.005-0.01 M) was suspended in water (50 mL) and neutralized with 10 mL of 1.0 N sodium hydroxide solution to obtain a clear solution. This solution was added slowly to a stirred solution of I hydrochloride. The resulting

precipitate or paste (paste solidified on standing) was separated by filtration and dried in a vacuum oven over Drierite® at 25°C overnight. After initial drying the temperature was slowly increased to 35-40°C for further removal of water. Additional purification was done by crystallization or trituration using organic solvents as indicated.

Method B - I hydrochloride (3.5 g, 0.01 M) was dissolved in water (120 mL). The solution was made basic with 1.0 N sodium hydroxide solution. The free base of I separated out as a paste. The mixture was cooled and the supernatant decanted off. The residue was dissolved in methylene chloride (for acetate, p-hydroxybenzoate and napsylate), methanol (for sulfate and tartarate) or isopropanol (for polymer salts). An equimolar solution of the acid in appropriate solvent was added to the above solution with stirring. The resulting precipitate or paste was processed as in Method A.

Solubility Measurements - Excess salt was suspended in 1 mL water contained in 1 mL glass vials. The vials were stoppered using rubber stoppers and sealed with aluminum seals. The vials were rotated in a water bath maintained at 25°C ± 0.5 C for 89 hours. At the end of the equilibrium time

the suspension was filtered using syringe filter (polyvinyl chloride, 2 μ). An aliquot (0.5 mL) of the filtrate was diluted with the mobile phase and injected onto the HPLC for quantitation.

Intrinsic Dissolution Rate Determination - The intrinsic dissolution rates were determined using rotating disk method described by Wood et.al. (7). The disks were prepared by transfering 100 mg of the compound into the die-hole and compressing at a pressure of 2000 psi. The disk had a diameter of 0.8 cm. The die and disk assembly was mounted onto the dissolution apparatus (Model 72 R; Hanson Research Corp., Northridge, CA). The dissolution media was 300 mL of 0.1 N HCl, 0.05 M phosphate buffer (pH 7.5) or water contained in a 1 L round-bottom, plastic flask (Elanco, Indianapolis, Ind.) and maintained at 37°C. The rotation speed was 200 rpm. A continuous recording of the absorbance changes at 279 nm was obtained by circulating the dissolution media through 1 mm flow cells of an automatic sample changer/spectrophotometer (Model 25; Beckman Instruments, Fullerton, CA) using a peristaltic pump (Model 1210; Harvard Apparatus, Millis, MA).

Dissolution Rate Determination - Dissolution rates from capsules were determined employing USP

Method 2. Hanson dissolution apparatus described above was used. The capsules were placed into the wire holders and dropped into each dissolution flask. The dissolution media was 600 mL of deaerated 0.1 N HCl, 0.05 M phosphate buffer pH 7.5 or water maintained at 37°C. The paddle speed was adjusted at 50 rpm. The absorbance changes were measured at 279 nm using the automatic set up described above.

Preparation of the Capsules - Small lots of powder mix were prepared by initially mixing the salt with spray dried lactose by geometric dilution on a sheet of glassine paper. This premix was transfered to a glass bottle and mixed with the corn starch and finally with magnesium stearate. The powder mixture was tested for homogeneity by assaying 5 samples for I. Each capsule was individually hand filled with the powder.

Analytical Methods - Samples for solubility measurements, and for the determination of free base contents of salts were assayed by reverse-phase high performance liquid chromatography using an octylsilane column (Ultrasphere, 4.6 x 250 mm, 5μ; Beckman, USA) and a mobile phase of methanol - 0.025 M sodium acetate buffer pH 4.9 (30:70).

Preparation of the Granules - Small lot of granules containing pamoate salt were prepared by

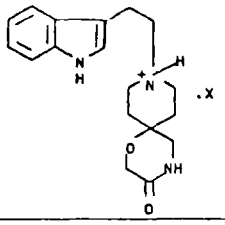
initially mixing the pamoate salt with microcrystalline cellulose by geometric dilution on a glassine paper. The powder mix was transferred to a stainless steel beaker and mixed with polyvinylpyrolidine solution. The wet granules were then passed through 16 mesh sieve and dried at 45°C oven for 3 hours. The dry granules were passed through 20 mesh round hole screen and the granules size between 20-35 mesh and smaller than 35 mesh were collected separately.

RESULTS AND DISCUSSION

Physical Properties of the Salts - Compound I is an amine with pka of 8.5. The I hydrochloride has a solubility of 31.7 mg/mL in water indicating very rapid dissolution in G.I. tract fluid. It had shown some local G.I. tract side effects during early pharmacology studies. Thus, it appeared a good candidate for this approach.

The structures of various salts prepared, their purities and some physical properties are shown in Table I. The solubilities of the salts in water are listed in Table II. The solubilities of ebonate, 3-hydroxy-2-naphthoate, napsylate, salts with

TABLE 1
Physical Properties of the Salts of I.



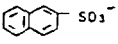
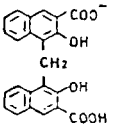
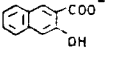
Salts	Structure of X	MW (g)	Melting Point (°C)	Purification Solvent
Acetate	$CH_3C(=O)O^-$	373.4	81-90	Ethylacetate
Hydrochloride	Cl^-	349.8	250-260	Methanol
Tartrate	$HOOC-CH(OH)-CH(OH)-COO^-$	463.4	150-153	Ethanol
Sulfate	HSO_4^-	409.3	245-247	Methanol
P-Hydroxybenzoate	HO-C$_6$H$_4$-COO$^-$	450.3	160	Acetonitrile
Eudragit-L (Polymethacrylic acid - Methacrylic acid Methyl ester)	$\left[-CH_2-C(CH_3)(C(=O)O)-CH_2-C(CH_3)(C(=O)OCH_3)-\right]$	---	---	Isopropanol
Eudragit-S	$\left[-CH_2-C(CH_3)(C(=O)O)-CH_2-C(CH_3)(C(=O)OCH_3)-CH_2-C(CH_3)(C(=O)OCH_3)-\right]$	---	---	Isopropanol
Free Base	---	313.3	97-99	Methanol-Water
Napsylate		520.5	138-145	Isopropanol
Ebonate		1014.3	185-190	Isopropanol
3-Hydroxy-2-Naphthoate		500.5	155-162	Ethylacetate

TABLE 2

Solubilities and Intrinsic Dissolution Rates of the Salts of I

Salts	Solubility in Water (Mg Free Base/mL)	Intrinsic Dissolution Rate (Mg of Free Base/Min/CM^2)		
		0.1 N HCl Solution	0.05 M (pH 7.5) Phosphate Buffer	Water
Acetate	24.20	20.36	15.69	18.60
Hydrochloride	31.70	3.43	7.64	6.32
Tartarate	25.61	13.21	3.65	4.39
Sulfate	10.81	6.25	3.04	2.56
p-Hydroxybenzoate	5.04	12.41	0.83	0.64
Eudragit-L	0.08	0.15	0.27	--
Eudragit-S	0.08	0.17	0.14	--
Free Base	0.32	14.97	0.15	--
Napsylate	0.62	0.13	0.11	--
Ebonate	0.24	0.20	0.06	--
3-Hydroxy-2 -Naphthoate	0.35	0.13	0.04	--

polymeric material and the free base are very small indicating that these salts may have potential to provide a slow release of I.

Dissolution Rates - The results of intrinsic dissolution rates of the salts in 0.1 N HCl, 0.05 M phosphate pH 7.5 buffer and water (Table II, Figures 1-3) indicated that ebonate, napsylate, 3-hydroxy-2-naphthoate and the polymer salts show the desired low intinsic dissolution rates. Inspite of higher solubility in water, the intrinsic dissolution rate of I hydrochloride salt in 0.1 N HCl was lower than that for the free base. Similar results have been seen previously with other amines and are attributed to common ion effect of the chloride (8).

The dissolution rate profiles from the capsules filled with powder mixture of the salt and excipients showed interesting results. Although the intrinsic dissolution rate for the free base in 0.1 N HCl was 75 and 115 times greater than that of the ebonate and the napsylate salt, the difference in the dissolution rates from the capsules was very small (Figure 4). This is due to the larger surface area of the powder salts in the capsule formulation as compared to the compressed disk. In addition, the salts are converted into the rapidly dissolving hydrochloride

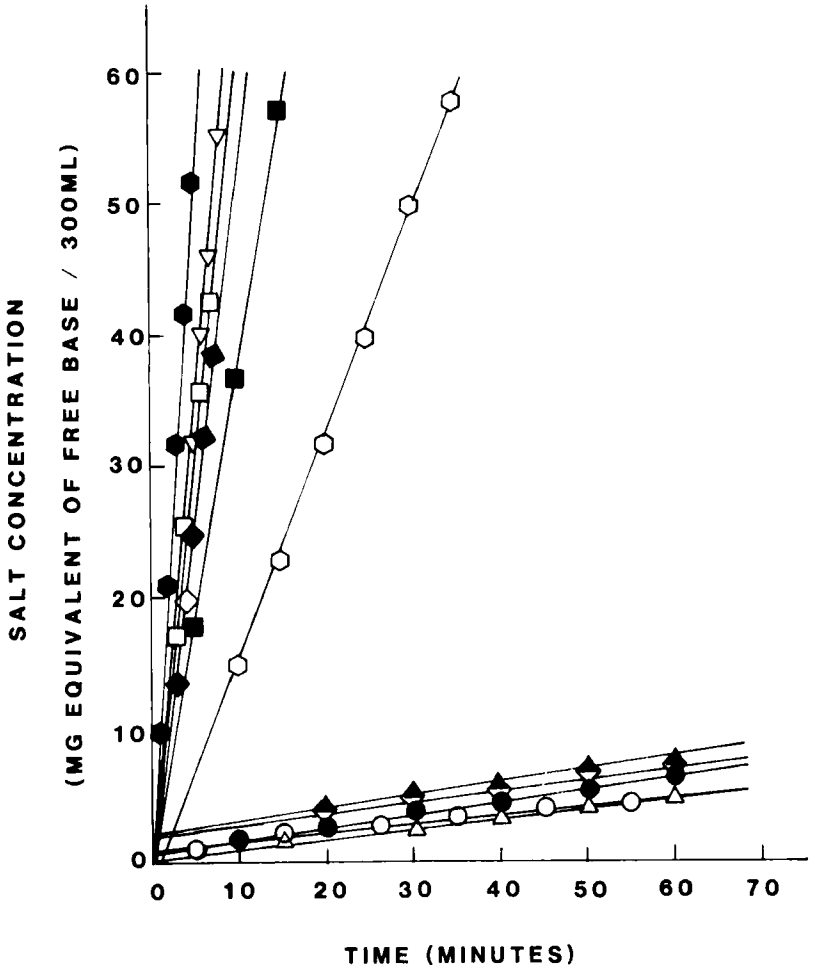


FIGURE 1.

Intrinsic Dissolution of Salts of I in 0.1 N HCl Solution

(⬢) Acetate, (⬡) Hydrochloride, (□) Tartrate, (■) Sulfate, (▽) Free Base, (◆) Hydroxybenzoate, (◇) Eudragit-L, (▲) Eudragit-S, (△) Napsylate, (●) Ebonate, (○) 3-Hydroxy-2-Naphthoate

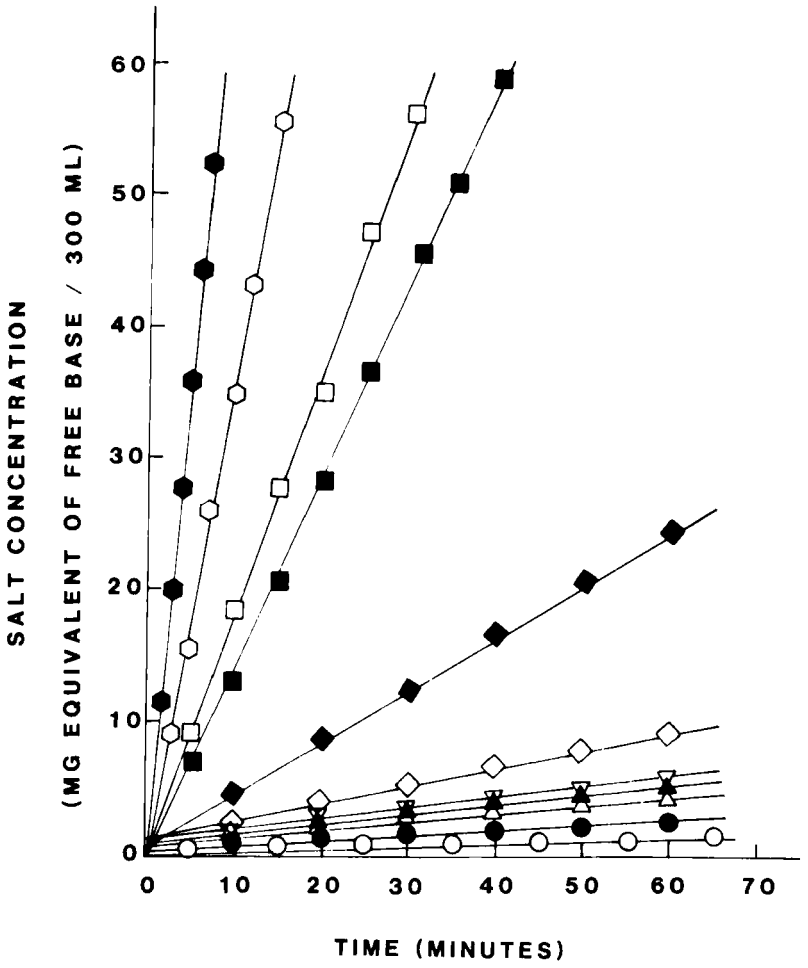


FIGURE 2.

Intrinsic Dissolution of Salts of I in 0.05 M (pH 7.5) Phosphate Buffer

(⬢) Acetate, (⬡) Hydrochloride, (□) Tartrate, (■) Sulfate, (▽) Free Base, (◆) Hydroxybenzoate, (◇) Eudragit-L, (▲) Eudragit-S, (△) Napsylate, (●) Ebonate, (○) 3-Hydroxy-2-Naphthoate

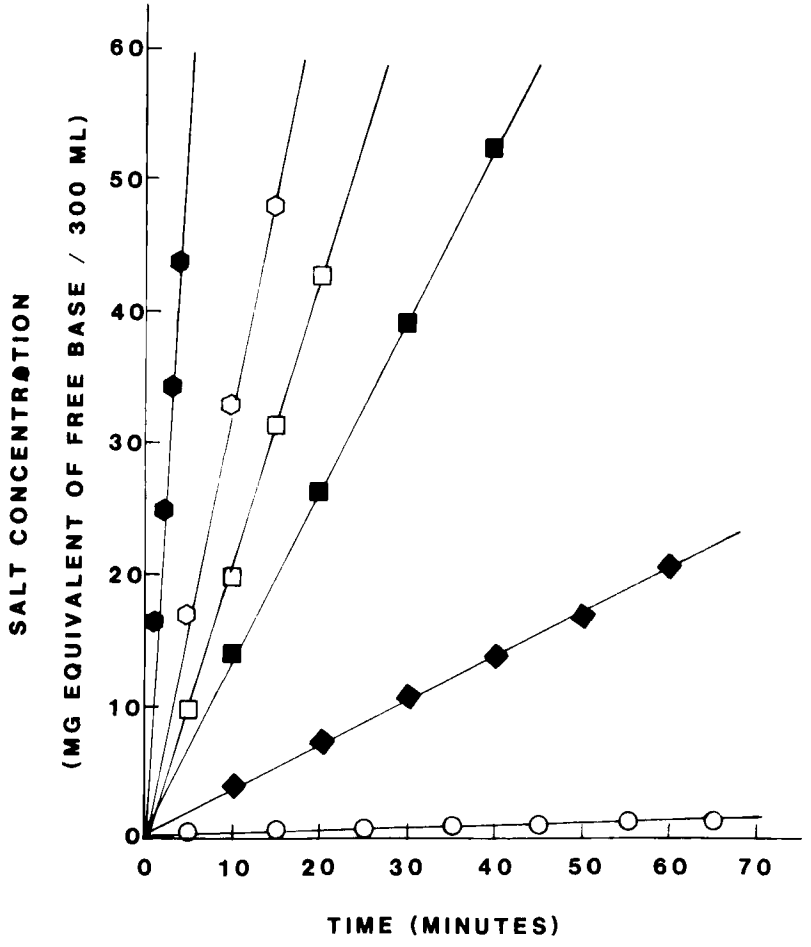


FIGURE 3.

Intrinsic Dissolution of Salts of I in Water

(⬢) Acetate, (⬡) Hydrochloride, (□) Tartrate,
(■) Sulfate, (◆) Hydroxybenzoate,
(○) 3-Hydroxy-2-Naphthoate

salt by reaction with the dissolution media in the diffusion layer (9,10).

During the preformulation investigations of drug substances intrinsic dissolution rates are generally used as one of the criteria for salt selection. In

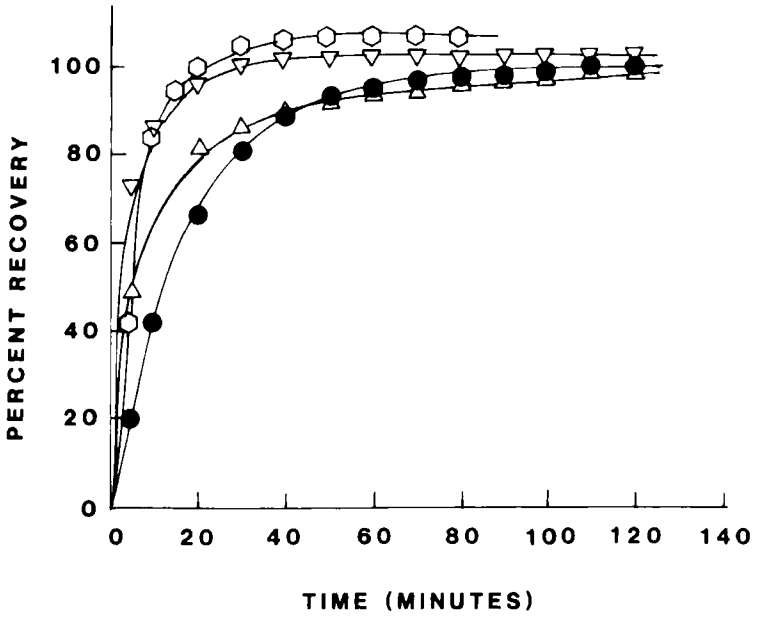


FIGURE 4.

Dissolution of Salts of I from Capsule Formulation in 0.1 N HCl Solution

(⬡) Hydrochloride, (▽) Free Base, (△) Napsylate, (●) Ebonate.

view of the above discussion and a previous report (8) it seems that intrinsic dissolution rates tend to exaggerate the real differences in the dissolution rates which would be obtained from capsule formulations used in phase I clinical studies or tablets that would disintegrate into granules before dissolution. Therefore the intrinsic dissolution rates data should be evaluated very carefully.

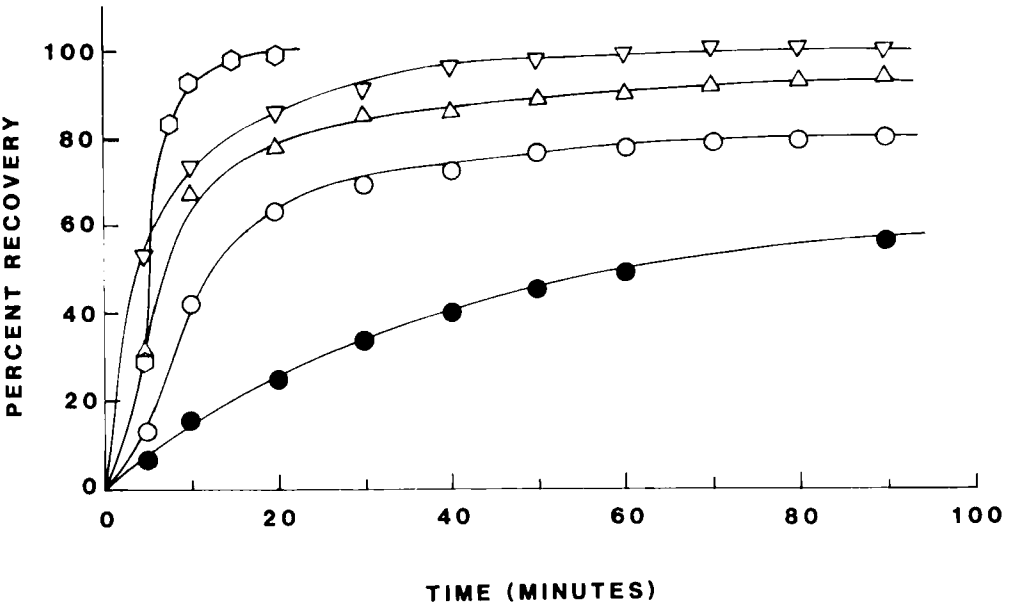


FIGURE 5.

Dissolution of Salts of I from Capsule Formulation in 0.05 M (pH 7.5) Phosphate Buffer

(○) Hydrochloride, (▽) Free Base, (△) Napsylate, (●) 3-Hydroxy-2-Naphthoate, (●) Ebonate.

The dissolution rates from capsules in 0.05 M phosphate buffer pH 7.5 are shown in Figure 5. The hydrochloride salt exhibited the fastest dissolution (complete dissolution in 20 min.) followed by the free base (complete dissolution in 60 min.). The napsylate and 3-hydroxy-2-naphthoate underwent an initial rapid dissolution (60-80% dissolved) followed by a slow phase. The dissolution rate for ebonate salt was especially suitable for providing slow

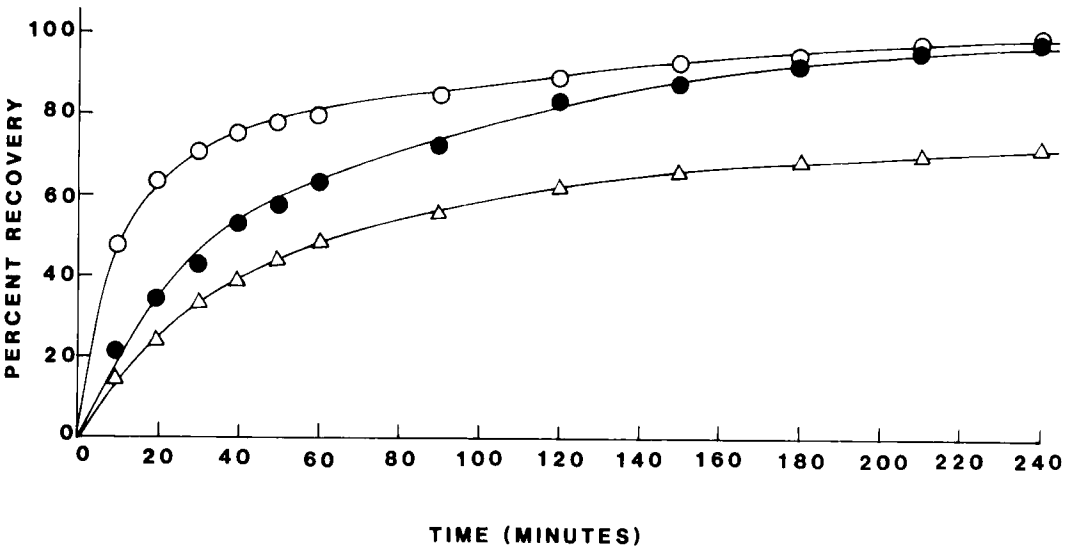


FIGURE 6.

Dissolution of Ebonate Salt of I from Capsule Formulation in 0.05 M (pH 7.5) Phosphate Buffer

(●) Capsule Containing 20-35 Mesh Granules of Ebonate Salt of I. (O) Capsule Containing < 35 Mesh Granules of Ebonate Salt of I. (Δ) Capsule Containing Powder Mix of Ebonate Salt of I with Spray Dried Lactose.

release of I. During the dissolution of 3-hydroxy-2-naphthoate and ebonate salt capsules, as the excipients went into solution, formation of drug aggregates and mass at the bottom of the dissolution flask was noticed, which slowed down the subsequent dissolution.

This problem was solved by replacing spray dried lactose with an insoluble excipient, microcrystalline cellulose and wet granulation of the powder mixture.

The granulation yielded a more consistent and smooth dissolution profile (Fig. 6). The dissolutin of the powder mixture is also included in the figure for comparison. The granulation made with microcrystalline cellulose exhibited a faster dissolution than the powder mix containing spray dried lactose. The dissolution rate varied with the size of the granules. This demonstrates that the dissolution rates of the salts can be further manipulated using formulation techniques.

CONCLUSIONS

This study has demonstrated that a variety of release rates can be obtained by using the appropriate salt of I. Since the difference between dissolution rates are larger in pH 7.5 phosphate buffer than in 0.1 N HCl solution, the formulation for oral dosage form should be protected from the acidic pH of stomach. This can be accomplished by using an enteric coated dosage form designed to release the salt in the neutral or alkaline pH of the small intestine to provide the desired release properties for prolonged action.

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