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DISSOLUTION OF SOME LITHIUM DOSAGE FORMS AND CORRELATION WITH ENSLIN NUMBER

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ABSTRACT

The biopharmaceutic parameters of six conventional and one sustained release lithium carbonate commercial products were determined. From the dissolution data mean residence time, dissolution rate constants, and percent dissolved at 5 and 10 minutes were obtained. The ENSLIN numbers were compared with mean residence time and percent dissolved at 5 and 10 minutes. A good correlation was obtained between ENSLIN number and mean residence time for the conventional preparations.

INTRODUCTION

Lithium carbonate is widely used in the treatment of mania and in preventing the recurrence of both manic and depressive symptoms[1].

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Knowledge of the biopharmaceutic parameters of a dosage form is essential to predict the performance of the dosage form when administered therapeutically. Lithium carbonate is sparingly soluble in water and its absorption is dissolution rate limited. Hence, lithium carbonate is among those solid dosage forms for which the USP requires a dissolution test[2], and bioavailability studies of lithium preparations have been carried out on both the conventional and sustained release products[3-7], and deficiencies were observed for both dosage forms[8-11].

The ENSLIN apparatus permits determination of water uptake into a powder bed as function of time[12]. The use of the ENSLIN apparatus was suggested for drug product development. If the ENSLIN number is determined for the active ingredients and the vehicle substances separately, then for the powder mixture, for granulations by different techniques, and finally for tablets compressed in various shapes and by different compression forces, one may be able to pinpoint which factor is responsible for poor dissolution. These factors may be associated with the powder mixture (particle size, lack of hydrophilating agents), the type of granulation (slugging, wet granulation by various methods, fluidized bed granulation, etc), or with the compression to tablets (shape of tablet, diameter/hight ratio, compression force)[13]. Modifications of the ENSLIN apparatus for testing of hydrophilicity of tablets were suggested[14].

The purpose of this study was: a) to determine the biopharmaceutic parameters of various marketed products of lithium carbonate, and b) to determine the importance of the ENSLIN number

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in predicting the release of a sparingly soluble drug from its dosage forms.

MATERIALS AND METHODS

Material

Commercial 300 mg lithium carbonate tablets and capsules[1]:

Reagents and Chemicals

Deionized distilled water was used throughout the study and all other chemicals were reagent grade. Lithium carbonate A.C.S.[2] was the reference standard.

Physical Measurements

Potency

The percentage of lithium carbonate in each product was determined according to the procedure specified in the USP[2]).

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[1]a. Eskalith® tablets, Lot no. X11J09, Smith Kline and French Laboratories, Philadelphia, PA 19101.

b. Eskalith® capsules, Lot no. 251J07, Smith Kline and French Laboratories, Philadelphia, PA 19101.

c. Lithane® tablets, Lot no. 9Y159, Dome Division, Miles Laboratories, Inc., West Haven, CT 06516.

d. Lithonate® capsules, Lot no. 64826, Rowell Laboratories, Inc., Baudette, MN 56623.

e. Lithobid® tablets, Lot no. 64354, Rowell Laboratories, Inc., Baudette, MN 56623.

f. Lithotabs®, Lot no. 64002, Rowell Laboratories, Inc., Baudette, MN 56623.

g. Lithium Carbonate Capsules USP, 300 mg, Lot no. 820040, Philips Roxane Laboratories, Inc., Columbus, OH 43216.

[2]Lithium carbonate A.C.S., Fisher Scientific Company, Fair Lawn, NJ 07410.

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pH Determination

One gram of powdered tablets or emptied capsule contents was placed in 10 ml of water, mixed for two minutes, and the pH recorded[3].

Water Content

Ten grams of powdered tablets or emptied capsule contents were placed on aluminum foil under light intensity setting of 6.5. Every ten minutes the weight was checked until a constant weight was obtained. The percentage of moisture was then directly recorded from the scale of the moisture determining balance[4].

Friability

Ten dedusted tablets were weighed and placed into the friabilator[5]. The tablets were given 5, 10, 20 and 30 minutes treatment at 20 rpm. The percentage of friability was determined at 5, 10, 20 and 30 minutes.

Pressure Resistance

The pressure resistance of ten tablets from each commercial batch was determined using the Pfizer hardness tester[6].

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[3]Fisher Accumet® pH meter, Model 142, Fisher Scientific Company, Pittsburgh, PA 15219

[4]Moisture determining balance, model 6010, Ohaus Corporation, Florham Park, NJ

[5]Friability tester, Erweka, Type TA33, Heusenstamm, West Germany

[6]Pfizer hardness tester, Chas. Pfizer and Co., Inc., Brooklyn, NY 10017

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ENSLIN Number

A Buchner funnel with a porous sintered glass plate, size F, was connected to a one ml volumetric pipette. The pipette was mounted horizontally so that the upper inner wall of the pipette was level with the upper surface of the porous filter plate. The instrument was filled with water and any trapped air bubbles were removed. Ten tablets were powdered using mortar and pestle, or the powder content of ten capsules was mixed well. One gram of powdered tablets or capsule contents was placed on the porous filter plate and immediately leveled. Water absorption was then read from the pipette at two minute intervals for 10 minutes. A schematic diagram of the ENSLIN apparatus is shown in Fig. 1.

Disintegration Time

The disintegration time was determined as specified in the USP[15] using the Erweka disintegration test apparatus[7].

Dissolution

The dissolution test was performed by the rotating basket method[8]. The dissolution medium (900 ml) was maintained at 37°C and the basket rotated at 100 rpm. The samples were collected after 1.5, 3, 5, 8 minutes and then in 15 minute intervals. The samples

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[7]Disintegration test apparatus, Erweka, type 2T4, Heusenstamm, West Germany

[8]Dissolution test apparatus, Moded T-1044-20X, Van-Kel Industries, Clatham, NJ 07928

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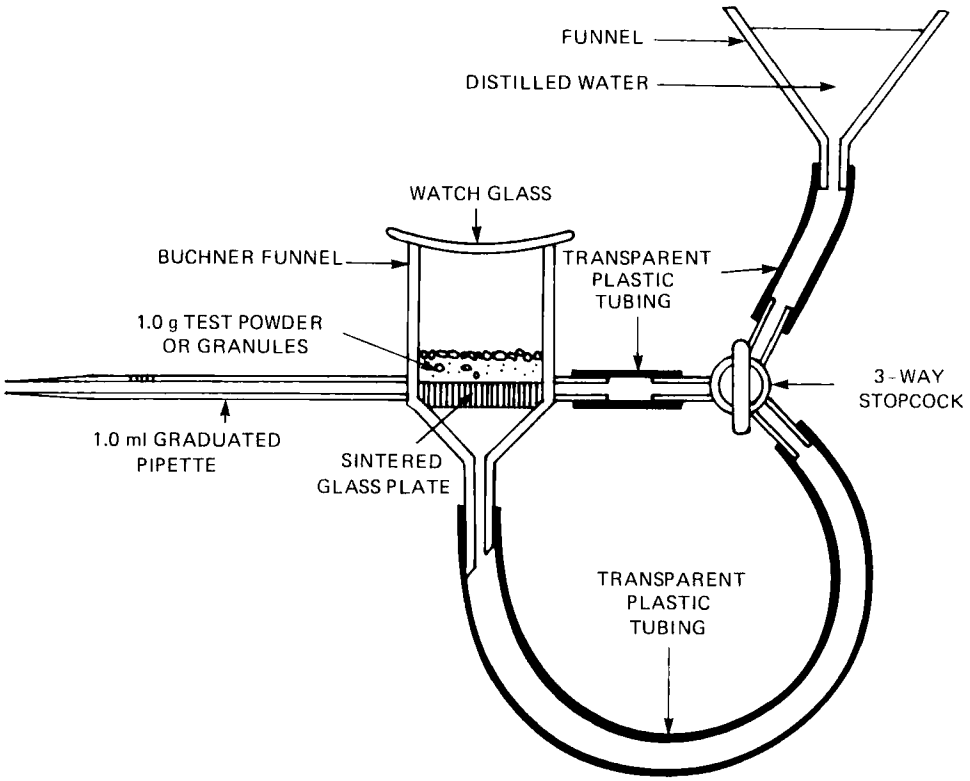

FIGURE 1

Schematic diagram of the ENSLIN apparatus

were filtered, diluted, and analyzed using a Perkin Elmer atomic absorption spectrophotometer[9] at 671 nm.

RESULTS AND DISCUSSION

The potency, water content, pH, and friability of commercial lithium carbonate products are listed in Table 1. All of the products complied with the official specification (USP XX, 1980) for potency. The water content for lithium carbonate tablets and

[9]Atomic absorption spectrophotometer, Perkin Elmer 4000, Norwalk, CT 06856

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TABLE 1

Potency, Water Content, pH and Friability of Lithium Carbonate Commercial Products

Product	Potency [%]	Water Content [%]	pH	Friability [% weight loss after rpm]			
				100	200	400	600
Lithium Carbonate Capsules USP	98.00	0.6	11.7	-	-	-	-
Eskalith® tablet	97.19	3.8	10.95	0.79	1.98	5.81	7.68
Eskalith® capsule	97.17	2.0	11.17	-	-	-	-
Lithane®	98.00	2.0	11.1	0.63	1.03	1.88	2.6
Lithonate®	98.86	0.6	11.44	-	-	-	-
Lithotabs®	99.61	2.0	11.37	0.19	0.37	0.82	1.16
Lithobid®	98.00	1.8	11.3	0.0	0.0	0.0	0.0

capsules were in the range of 1.8 to 3.8 percent, and 0.6 to 2 percent, respectively. The tablet dosage forms had a greater percentage of water compared to capsules. This may be due to the use of water in the granulation stage of tablet processing.

The pH of a 10 percent solution was in the range of 10.95 to 11.7. The tablet formulations complied for friability to accepted

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TABLE 2

Weight Variation and Hardness of Lithium Carbonate Commercial Products

Product	Mean Weight [mg]	Standard deviation [mg]	Relative Standard deviation [mg]	Hardness [kg]	Standard deviation [kg]
Lithium Carbonate Capsules USP	376.01	8.10	2.15	-	-
Eskalith® tablet	490.14	12.39	2.52	8.20	1.11
Eskalith® capsule	467.85	6.43	1.37	-	-
Lithane®	499.94	5.92	1.18	8.72	0.59
Lithonate®	375.78	12.27	3.25	-	-
Lithotabs®	377.67	2.45	0.65	7.05	0.42
Lithobid®	421.59	7.60	1.80	>13	

standards as the weight loss after 100 rmp was less then 0.8 percent. The Lithobid® tablets showed zero percent weight loss after 100 rpm. This may be due to the hardness (>13 kg) and film coating of the product.

Weight variation and hardness of lithium carbonate tablets are given in Table 2. The sustained release tablet (Lithobid®) had a hardness greater than 13 kg whereas the other products had a hardness in the range of 7 to 8.7 kg.

The dissolution data of nonsustained release products are summarized in Tables 3 and 4, and Fig. 2. The dissolution data for the sustained release tablet is summarized in Table 5 and Fig. 3.

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TABLE 3

Dissolution Data of Lithium Carbonate Commercial Products (mean ± S.D.; n = 3)

Product	Percent dissolved at time t [min]				
	1.5	3	5	8	15
Lithium Carbonate Capsule USP	7.23±12.5	44.31±17.42	83.6±0.17	91.99±3.33	99.64±3.91
Eskalith® tablet	81.59±1.83	91.51±2.2	95.85±5.46	100	
Eskalith® capsule	6.0±0.5	25.52±25.7	63.09±2.2	87.17±6.51	92.46±6.62
Lithane®	17.21±1.46	33.26±2.03	51.01±4.17	70.76±3.43	74.02±6.4
Lithonate®	2.76±2.38	57.79±24.4	92.19±2.38	94.49±6.35	95.99±5.12
Lithotabs®	73.05±3.33	87.62±6.3	88.96±7.09	91.02±5.34	92.06±4.83

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TABLE 4

Dissolution Data of Lithium Carbonate Commercial Products

Product	Percent remaining to be dissolved at time t [min]				
	1.5	3	5	8	15
Lithium Carbonate Capsules USP	92.77	55.69	16.40	8.01	0.0
Eskalith® tablet	18.41	8.41	4.15	0.0	
Eskalith® capsule	94.00	74.48	36.91	12.83	7.54
Lithane®	82.79	66.74	48.99	29.24	26.00
Lithonate®	97.24	42.21	7.81	5.51	4.01
Lithotabs®	26.95	12.38	11.04	8.98	7.94

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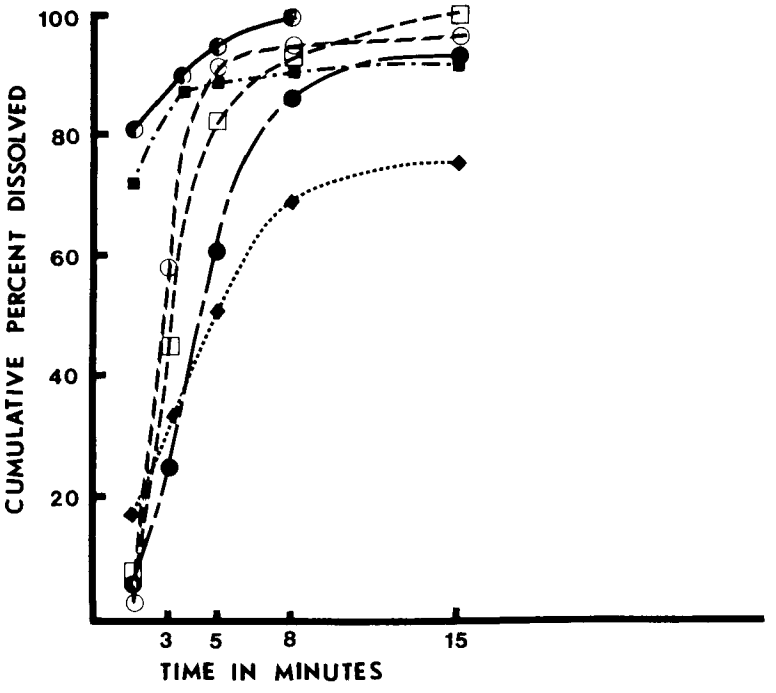

FIGURE 2

Cumulative percent dissolved versus time plot of lithium carbonate products (Escalith® tablet ——●——, Lithotabs® - - - ■ - - -, Lithonate - - - ○ - - -, Lithium carbonate capsules USP - - - □ - - -, Escalith® capsule — — ● — — and Lithane® ·····◆·····)

TABLE 5

Dissolution Data of Sustained Release Lithium Carbonate Tablets (Lithobid®) (mean±S.D., n = 3)

Time [hours]	Percent dissolved
0.5	13.71±0.09
1.0	24.56±0.21
2.0	75.52±7.28
3.0	100.00

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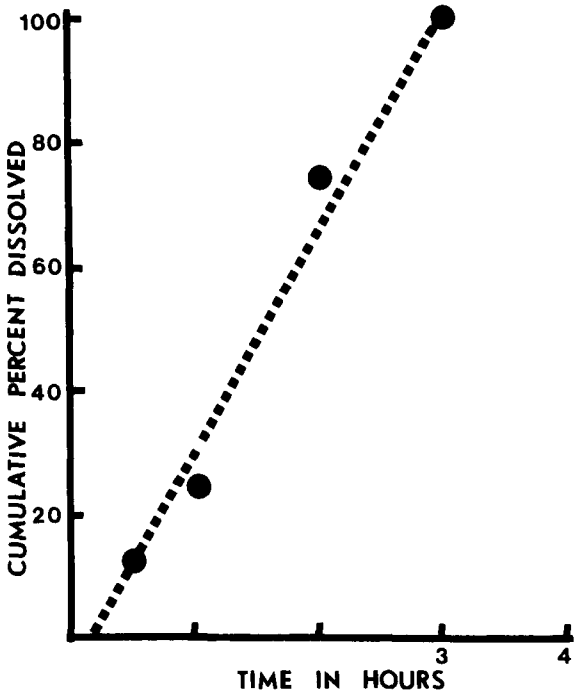

FIGURE 3

Cumulative percent dissolved versus time plot of sustained release lithium carbonate tablet.

The data in Table 3 show that more than 90 percent of lithium carbonate goes into solution from all products within 15 minutes, except in Lithane® tablets where only 74 percent of the lithium carbonte is released. The sustained release product released all its lithium carbonate within 3 hours.

In order to gain additional insight into dissolution data, further parameters were evaluated like mean residence time (MRT), dissolution rate constants, and percent dissolved at 5 and 10 minutes (Tables 6 and 7). The MRT was determined from RRSBW plots[16]. It was not possible to evaluate the MRT for

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TABLE 6

ENSLIN Number, Mean Residence Time, Disintegration Time and Dissolution Rate Constant of Lithium Carbonate Commercial Products

Product	ENSLIN number [ml/10 min]	Mean residence time [min]	Disintegration time [min]	Dissolution rate constant [min^{-1}]	
				k_1	k_2
Lithium Carbonate Capsules USP	0.87	4.2	3.25	0.349467	-
Eskalith® Tablet	0.67	-	0.32	1.1281841	0.421734
Eskalith® Capsule	0.56	4.8	6.05	0.2683125	0.0759377
Lithane®	0.14	6.8	0.23	0.15445	0.0617773
Lithonate®	0.86	3.4	6.65	0.526591	0.0628929
Lithotabs®	0.79	-	1.19	0.696362	0.030265
Lithobid®	0.09	90	86.45	36.62*	

*Zero-order release rate in mg/h

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TABLE 7

ENSLIN Numnber, and Percent Dissolved at
5 and 10 Minutes of Lithium Carbonate Commercial Products

Product	ENSLIN Number [ml/10 min]	Percent dissolve at 5 minutes	Percent dissolve at 10 minutes
Lithium Carbonate Capsules USP	0.87	83.6	96
Eskalith® tablet	0.67	95.85	100
Eskalith® capsule	0.56	63.09	90
Lithane®	0.14	51.01	73.5
Lithonate®	0.86	92.19	96
Lithotabs®	0.79	88.96	92

Eskalith® tablets and Lithotabs® as both these products released more than 70 percent of drug within 1.5 minutes. Thus, sufficient data points were not available to generate RRSBW plots for these two products. The sustained release product (Lithobid®) had a MRT of 90 minutes, whereas the other products had a MRT in the range of 3.4 to 4.8 minutes.

The dissolution rate constants were determined from sigma-minus plots[17] (Fig. 4). It was observed that except for Lithium carbonate capsules USP, all other products had two disso-

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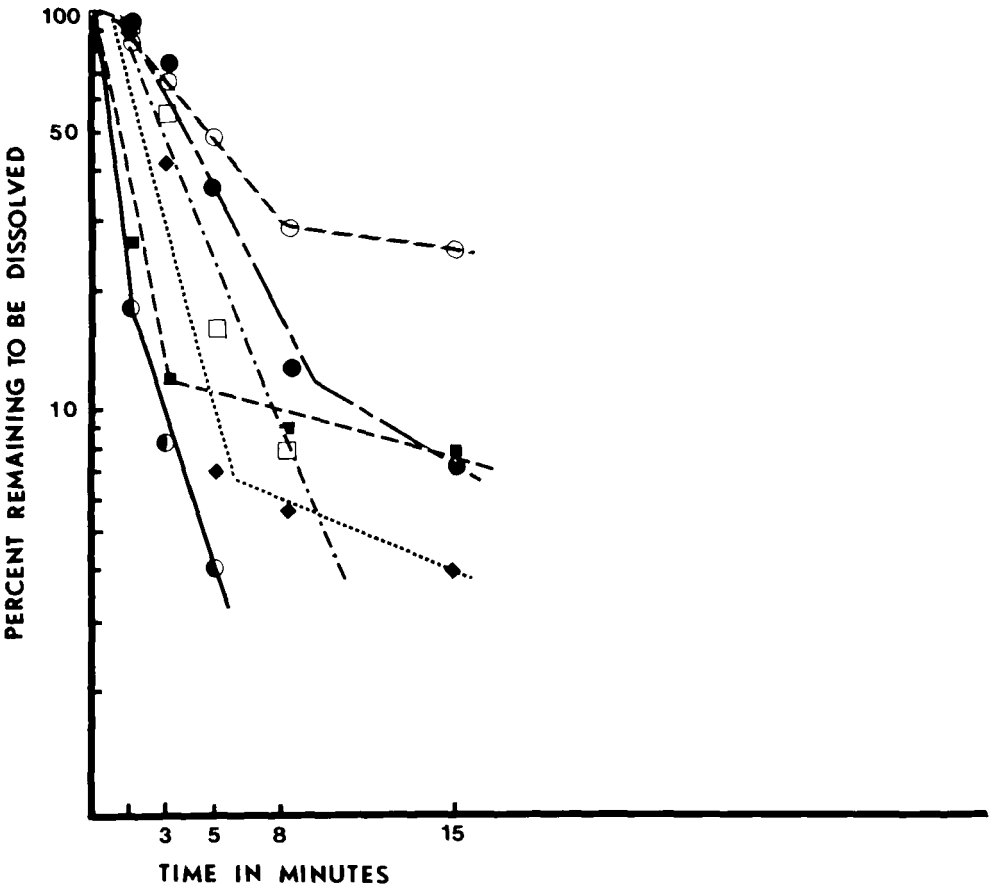

FIGURE 4

Sigma-minus plot of percent remaining to be dissolved versus time of lithium carbonate products (Lithane® ——○——, Eskalith® capsule ——●——, Lithotabs® ——■——, Lithium carbonate capsules USP -·-·-□-·-·-, Lithonate® ····◆····, and Eskalith® tablet ——◐——).

lution rate constants. The initial fast dissolution rate is due to the dissolution of finer particles of lithium carbonate followed by a slower dissolution rate due to the dissolution of coarser particles or aggregates of lithium carbonate. However, the sustained release tablet showed zero-order release (36.62

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mg/h). The mechanism of release from this product was observed to be by surface erosion and diffusion. Among the non-sustained release products, Eskalith® tablets had the fastest dissolution rate (1.28 min^{-1}).

The percentages of lithium carbonate dissolved after 5 and 10 minutes were determined from a plot of cumulative percent dissolved versus time (Table 7 and Fig. 2). Except for Lithane® tablets, from all the other products more than 60 percent of the lithium carbonate was dissolved after 5 minutes and 90 percent within 10 minutes. However, all the products, except the sustained release product complied with the USP specification[2] that more than 60 percent of the lithium carbonate should dissolve in 30 minutes.

It is well known that the dissolution test is a very important biopharmaceutic parameter as absorption and availability of a sparingly soluble drug depends upon how much of the drug has gone into solution. Thus an attempt was made to correlate various other biopharmaceutic parameters, such as ENSLIN number, disintegration time, hardness, etc. with the dissolution parameters such as MRT, t(5), t(10), and dissolution rate constants. The various correlations obtained are listed in Table 8. It was observed that the ENSLIN number which is the amount of water in ml absorbed by 1 gram of powdered substance in 10 minutes, showed high correlation with MRT, t(5) and t(10) (Fig. 5 to 7). These high correlations were obtained by comparing the ENSLIN number of nonsustained release products. But when the biopharmaceutic parameters of the

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TABLE 8

Correlation of ENSLIN Number and Disintegration Time with Various Dissolution Test Parameters

ENSLIN number versus mean residence time	0.96745
ENSLIN number versus percent dissolved at 5 minutes	0.8559
ENSLIN number versus percent dissolved at 10 minutes	0.88873
ENSLIN number versus dissolution rate constant k_1	0.613564
Disintegration time versus mean residence time	0.84261

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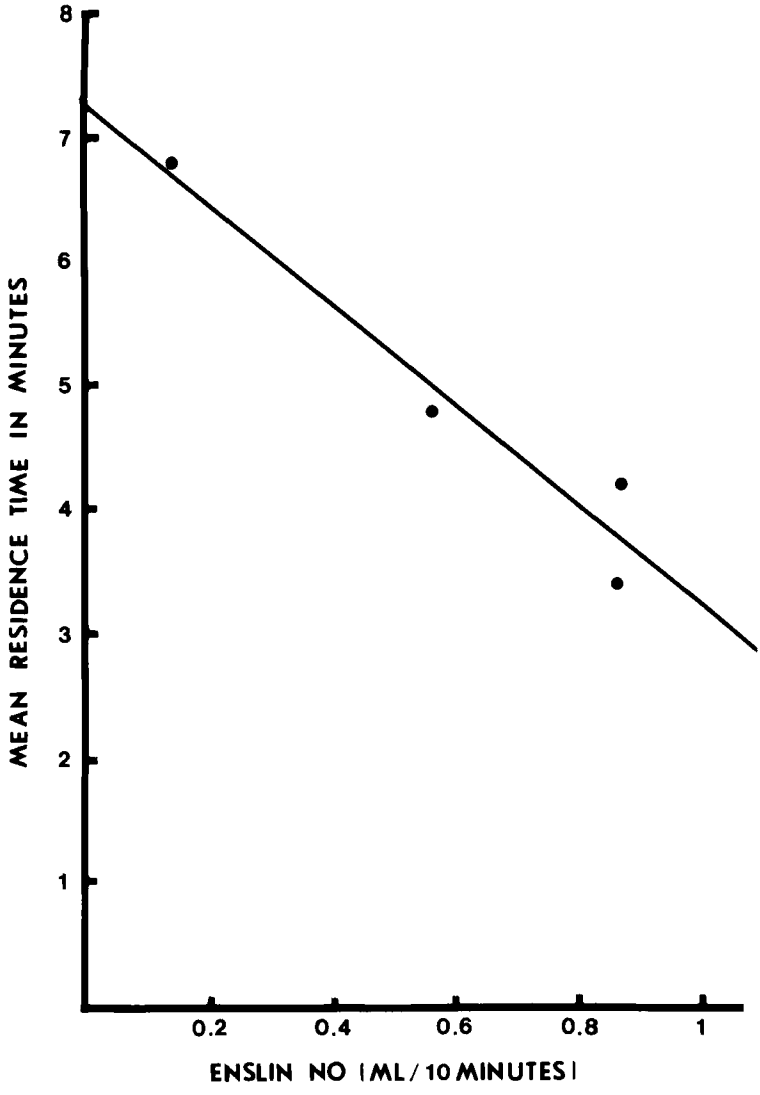

FIGURE 5

Plot of ENSLIN number versus mean residence time.

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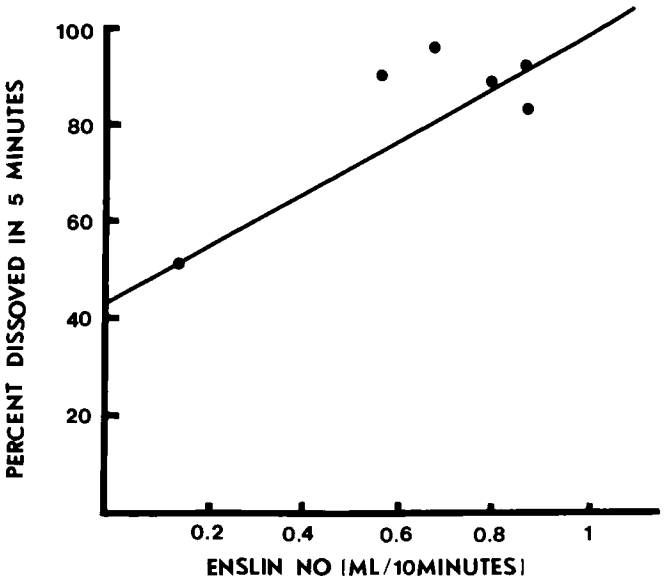

FIGURE 6

Plot of ENSLIN number versus percent dissolved in 5 minutes.

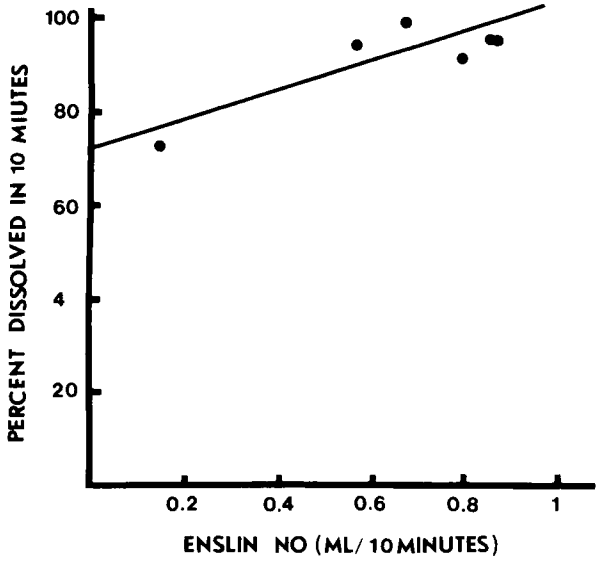

FIGURE 7

Plot of ENSLIN number versus percent dissolved in 10 minutes.

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sustained release product were included the correlation decreased (linear plot R = 0.6342, semilog plot R = 0.7360 and log-log plot R = 0.8169). Hence the nonsustained release products were considered as a separate group and data resulting from them only were correlated.

The ENSLIN number characterizes the hydrophilicity of material present in tablets or capsules. Many times surfactants or hydrophilic substances are included in a peroral formulation to increase the dissolution rate of a sparingly soluble drug. One of the mechanism by which these surfactants or hydrophilic substances act is to enhance the wetting of the drug particles and thus increase the effective surface area of drug particles available for dissolution. The good correlation of the ENSLIN number with various dissolution parameters emphasizes its inclusion as an important biopharmaceutic parameter in evaluating the dissolution characteristics of peroral solid dosage forms.

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