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A STUDY ON IN VITRO RELEASE OF FIVE BRANDS OF PHENYTOIN CAPSULES, MARKETED IN IRAN

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ABSTRACT

In relation to the new pharmaceutical system in Iran, the in vitro release of five brands of 100 mg phenytoin sodium capsules , namely A,B,C,D & E were determined in distilled water, using three dissolution methods, i.e. Rotating basket, Magnetic basket and Levy beaker method. Also the average amount of phenytoin content of each brand was measured.

The results showed that although the dissolution rate of each product is different by each method, but the pattern of drug release is more or less similar.

The dissolution time for products C and D is much longer than those of products A,B & C with all methods, but the dissolution behaviour of capsules C & D is not equivalent to those of standard "slow release" phenytoin

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capsules. The release pattern of products A & E are similar to those of standard "fast release" phenytoin capsules. The dissolution of product B is poor and not acceptable.

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INTRODUCTION

Phenytoin,formerly named diphenylhydantoin, has been used for decades in the control of grand-mal type of epileptic seizures. It is chemically analogous to the barbiturates, with little or no sedative effect (1). In addition its clinical use is in the treatment of digitalis-induced arrhythmias(2).

Phenytoin has been classified as a drug with high risk potential with respect to bioavailability problems(3). Because of its physicochemical properties , narrow therapeutic range, and dose-dependent kinetics, phenytoin has been identified as a critical drug with a potental bioavailability-bioequivalence problem(4-8). Various formulations of phenytoin are manufactured by different companies which exhibited problems in their bioavailability(3,5,8).

In recent years, considerable interest has been focused on the development of a reliable *in vitro* dissolution test method which can truely minic *in vivo* dissolution rate-controlled absorption of drugs administered in solid dosage forms(9).

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In vitro testing, as a valid predictor of bioequivalence,can greatly reduce human subject risk and cost involved with in vivo testing (4). Reports of good correlations between in vitro dissolution and in vivo parameters for this drug have been published (10-11).

In relation to the new pharmaceutical system in Iran, and changes in formulations so obtained, the aim of present work is to determine the in vitro dissolution profiles for various brands of phenytoin capsules distributed in Iran.

EXPERIMENTAL

Materials

Five commercially available products of 100mg phenytoin sodium capsules, identified as products A,B, C,D and E were used. Ethyl alcohol, sodium hydroxide, hydrochloric acid, diethyl ether, chloroform all from E merck Darmstadt (West Germany) were used.

Methods

a) Assay: The average weight of phenytoin content per capsule in all brands were determined according to USP_{XX}(12). The content of 20 capsules were dissolved, completely in alcohol, the solution was filtered and then evaporated to dryness.The residue was dissolved in a mixture of 1N NAOH and water.An aliquot of the

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solution was diluted, acidified with 3N HCl, then extracted 3 times with a mixture of ether-chloroform (1:2).

The combined extracts was dried at 105 C for 4 hrs. The weight of the residue of phenytoin so obtained, multiplied by 1.087, represents the corresponding weight of phenytoin sodium in the aliquat taken.

The above experiment was repeated 5 times and the standard deviation was calculated.

b) Calibration curve:A calibration curve for phenytoin sodium was constructed over the range between 10-100 ug/ml of water. The data were subjected to linear regression analysis to give the appropriate calibration factor.

c) Dissolution rate study : Three methods were used to determine the dissolution of the various phenytoin capsules, namely; the official U.S.P(xx) Rotating basket(12): Magnetic basket(13) : Levy beaker method (14) All dissolution studies were carried out at 37±0.5 C in 900 ml water.

At zero time , one capsule (100mg) was placed in the apparatus. A 2ml sample was withdrown at various time intervals, using a filter-holder syring(equiped with cellulose acetate filter). To compensate the sample withdrawn , volumes of 2ml water at 37 ± 0.5 C were immediately added to the medium.

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TABLE 1

The Mean Weight of Phenytoin Sodium Content in Various Capsule products.

Products	W.t.(mean)	S.D.
A	108.70	± 4.40
B	80.79	± 2.30
C	98.79	± 0.74
D	90.95	± 2.13
E	97.81	± 1.90

d) Analysis; The absorbance of all samples were measured by a UV spectrophotometer (Perkin-Elmer , 550S) at 258 nm(12).

RESULTS AND DISCUSSION

The average amount of phenytoin content per capsule measured by USP_{XX} method, for five brands(all labelled 100 mg) are presented in table 1. Comparison between the results show that the phenytoin content of products C and E apply the amount indicated on their labelling. The amount of phenytoin measured in products A,B and D varied significantly from those labelled on them. These variations could make difficulties in investigating the In-vivo and In-vitro parameters of phenytoin. In this relation it is worthnothing that , the

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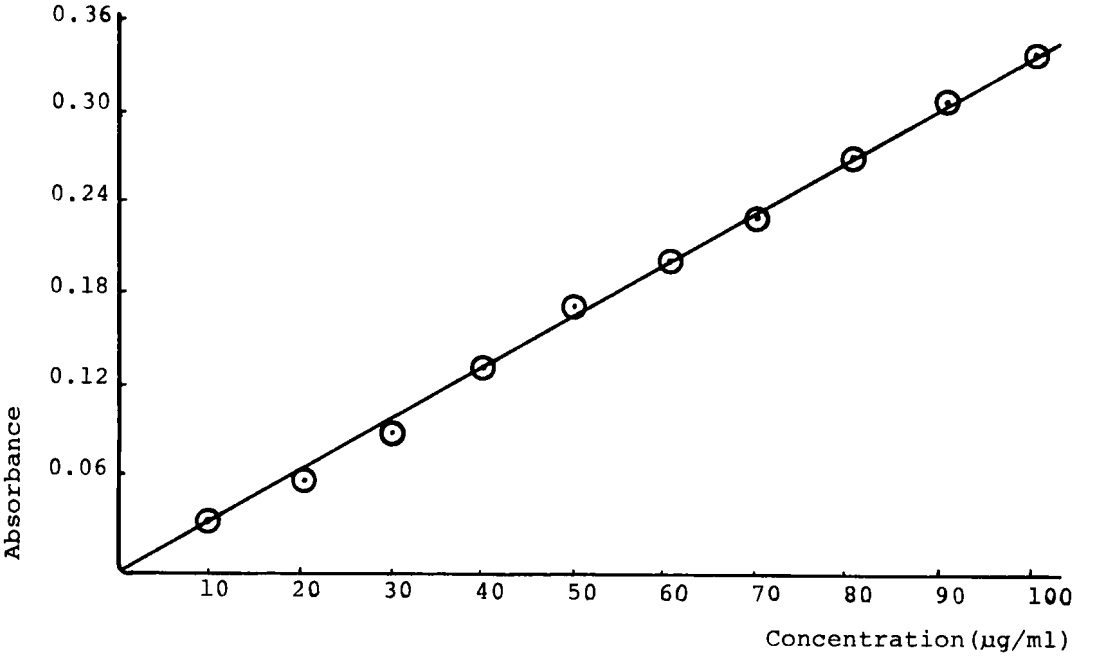

FIGURE 1

The calibration curve of phenytoin sodium solution in water.

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therapeutic range of phenytoin is narrow and its kinetic of absorption, distribution and excretion is dose dependent(10).

The calibration curve of phenytoin sodium in the ranges stated followed a linear line (Fig. 1). The correlation coefficient of replicate curves showed to be about 0.999 .

Comparison between brands

The dissolution rate patterns for the different phenytoin capsules using the three dissolution methods are shown in Figs. 2,3 & 4.

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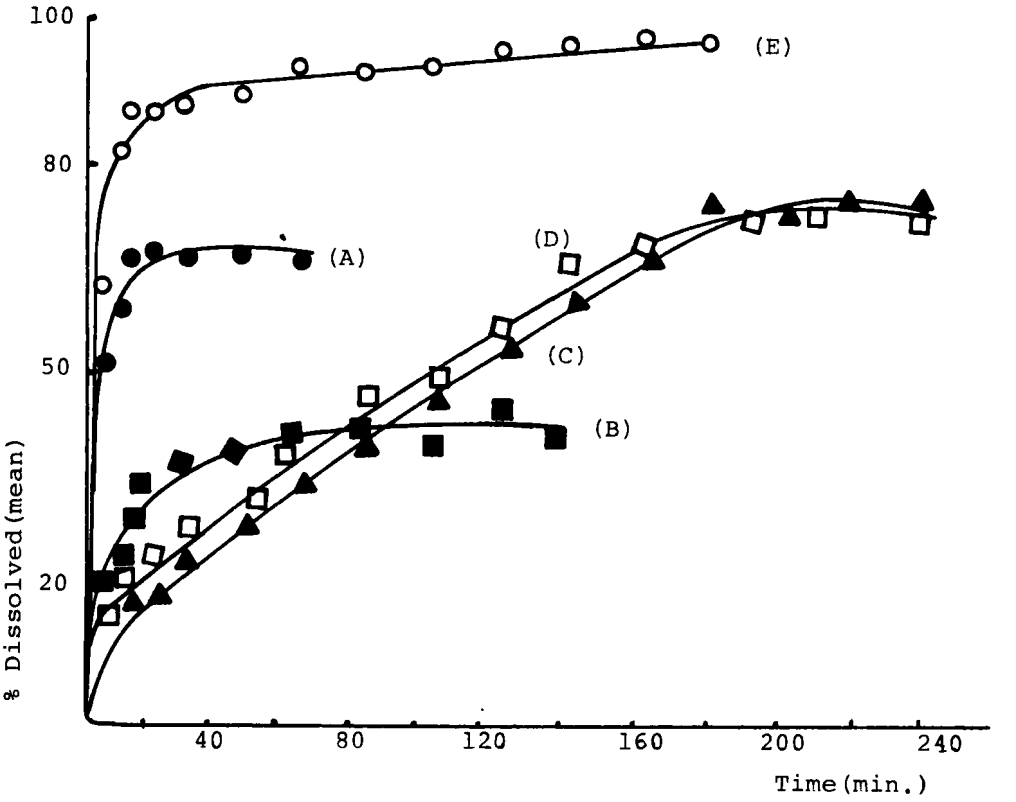

FIGURE 2

Dissolution rate profiles of 5 brands of phenytoin sodium in water, at 37 C, using the Rotating basket method (50 r.p.m.).

The results showed that although the dissolution rate of each product is different by each method, but the pattern of drug release is more or less similar. In all methods the dissolution time for products C and D is longer than those of products A,B and C.

Product B showed a higher dissolution rate , in first hour, than products C and D, but thereafter it

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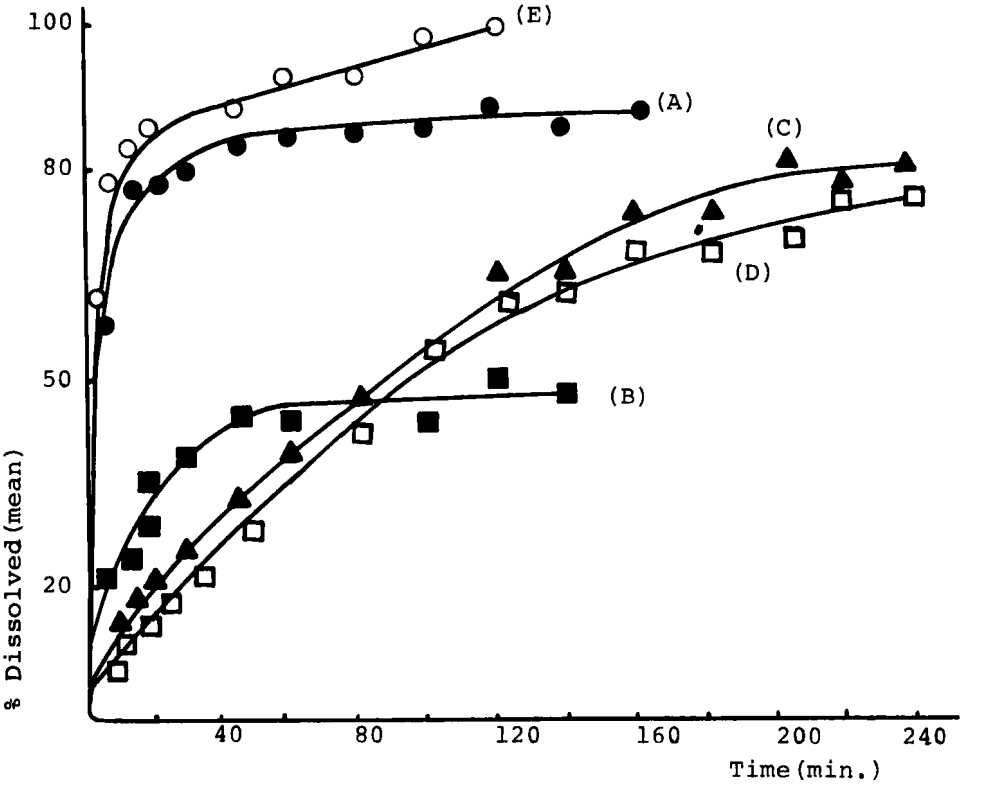

FIGURE 3

Dissolution rate profiles of 5 brands of phenytoin sodium in water, at 37 C, using the Magnetic basket method (50 r.p.m.).

appeared to be the slowest dissolving brand on using any dissolution method. The time necessary for 50% dissolution (t 50%) with Rotating and Magnetic methods (Figs. 2 and 3 respectively) is much longer than with Levy method (Fig. 4).

Brands E and A both showed to have similar dissolution pattern ; having the fastest release property,

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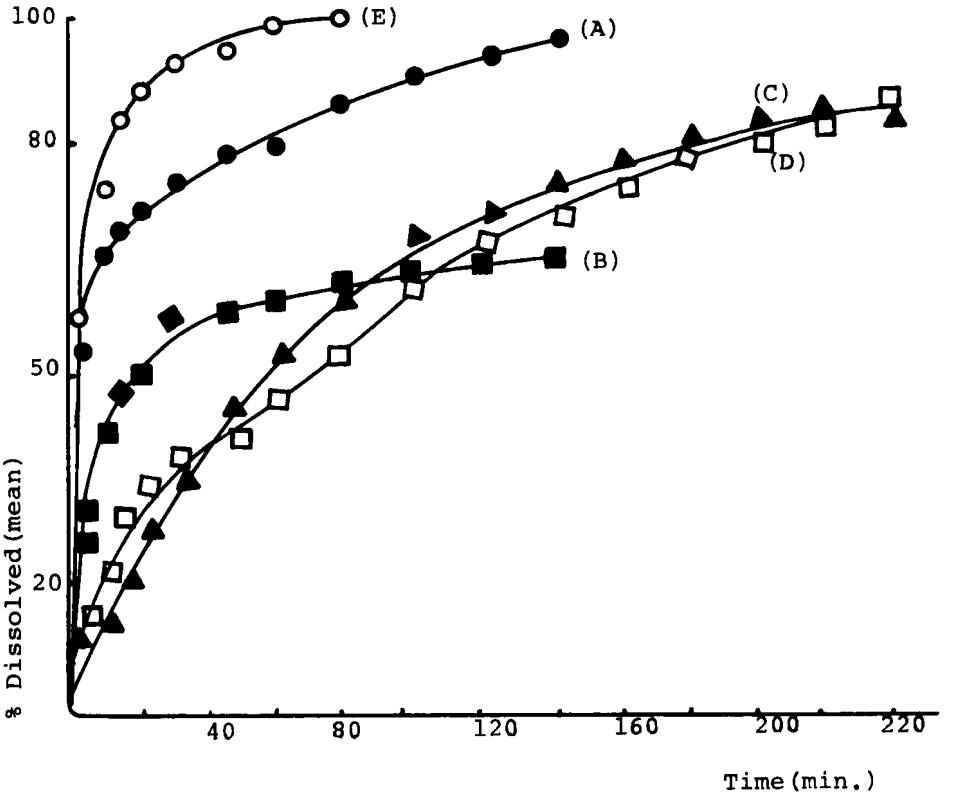

FIGURE 4

Dissolution rate profiles of 5 brands of phenytoin sodium in water, at 37 C. using the Levy beaker method (50 r.p.m.).

but the rate and extend dissolution pattern of capsule E showed to be higher than that of brand A.

It is evident from Figs. 2,3 and 4 that after 60 mins. in all the dissolution methods tested, there was about twofold increase in drug release from capsule E compared to B.

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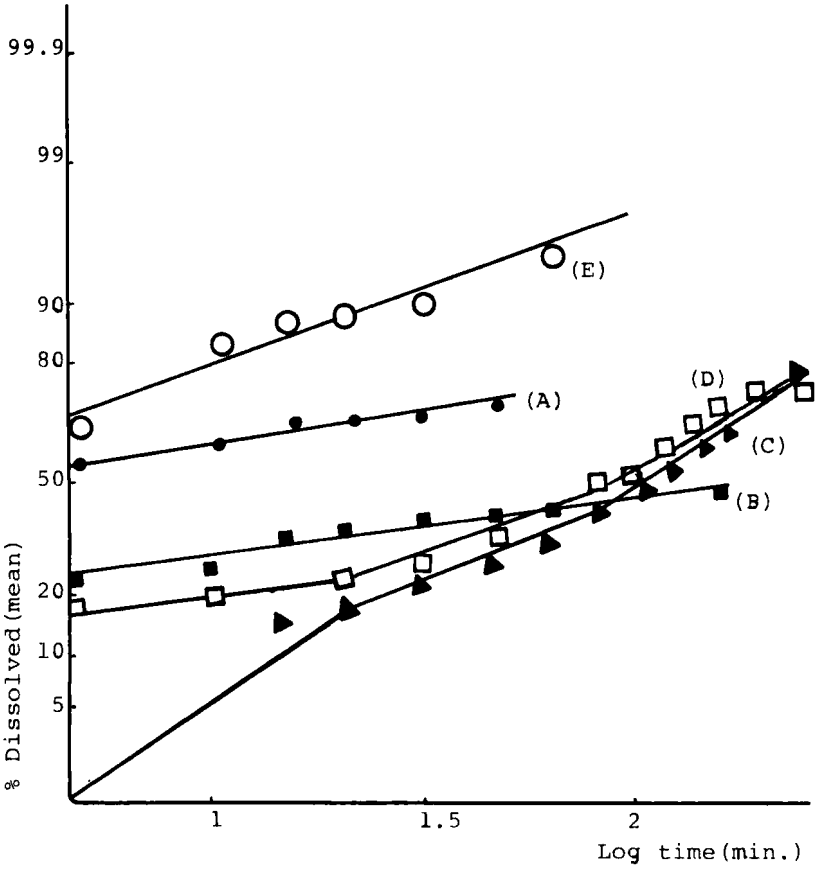

FIGURE 5

Log-probability plot of percent drug dissolved against time of 5 brands of phenytoin sodium capsules in water, at 37 C, using the Rotating basket method (50 r.p.m.).

The observed reduction in drug release from capsule B may be attributed to type and concentration of the additives (9), manufacturing procedures, and storage conditions. On the other hand, rapid deaggregation of capsule E content, after the dissolution of its gelatin shell, resulted in a rapid disintegration and

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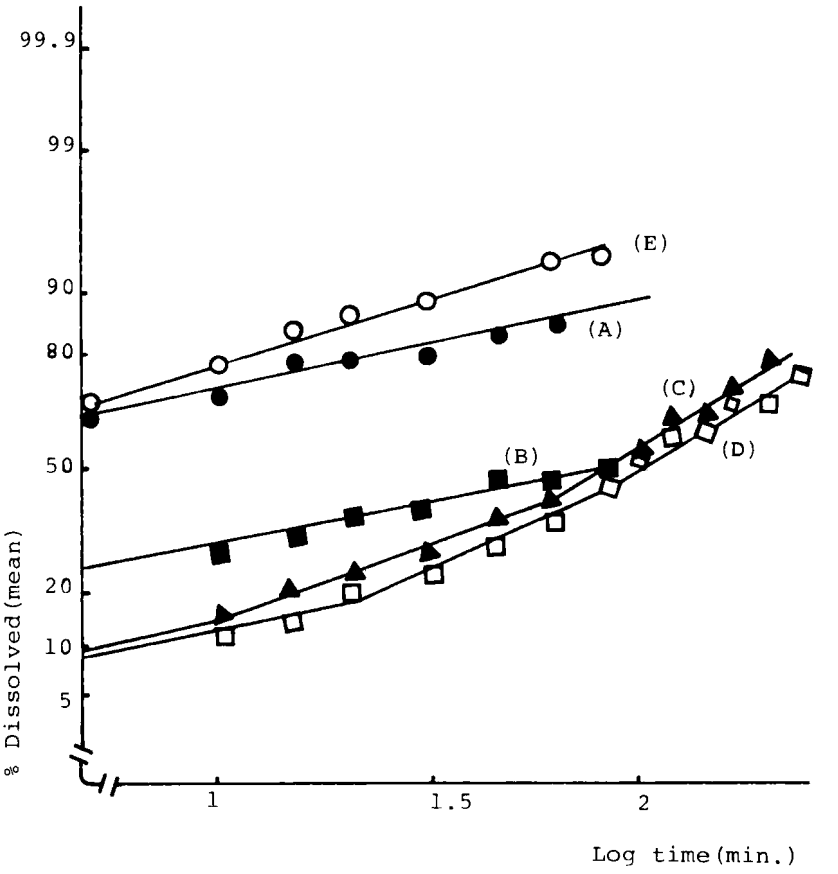

FIGURE 6

Log-probability plot of percent drug dissolved against time of 5 brands of phenytoin sodium capsules in water, at 37 C, using the Magnetic basket method (50 r.p.m.).

large exposed surface of particles and caused it to dissolve faster than product B. This may be due to the presence of diluents or additives such as lactose.

The log-probability plots of percent drug dissolved against time, based on Noyes & Whithney equation (15), indicated a one phasic dissolution profile,for

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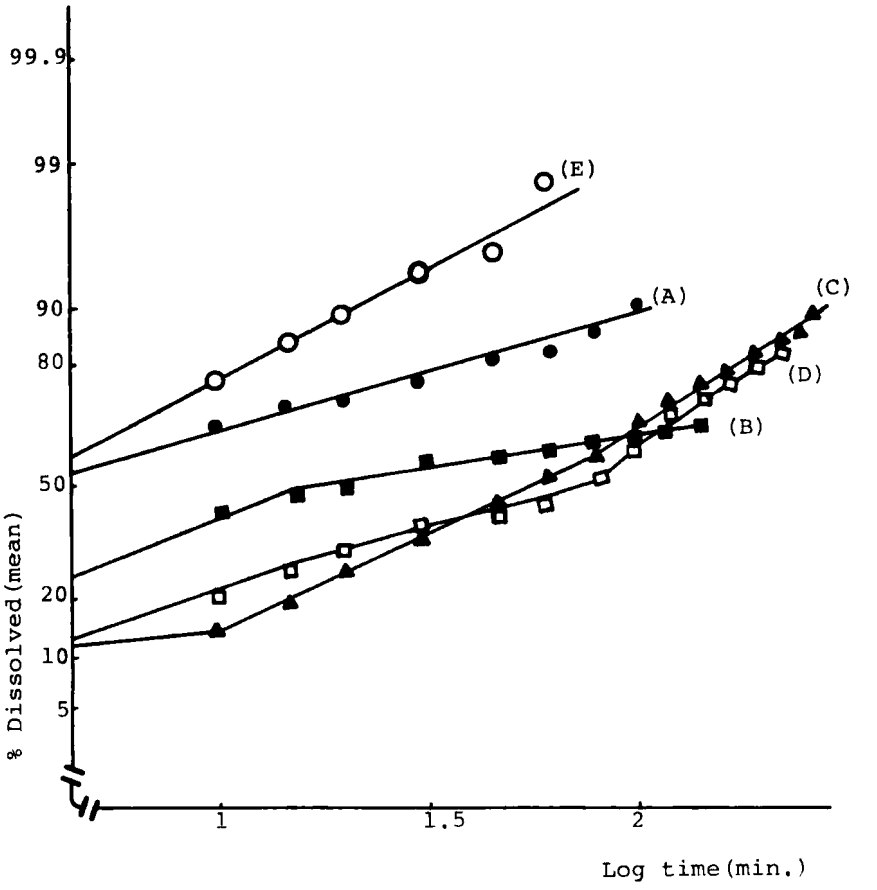

FIGURE 7

Log-probability plot of percent drug dissolved against time of 5 brands of phenytoin sodium capsules in water, at 37 C , using the Levy beaker method (50 r.p.m.).

product A,E, but a three phasic profile for product C and D in all the methods. Product B showed a one phasic profile with Rotating and Magnetic method, but a two phasic profile with Levy method (Figs. 5,6 and 7).

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Capsules A & E are filled with powder, and their dissolution pattern are similar to those of standard " fast release " phenytoin capsules; these capsules should release 85% of the drug in first 30 mins. (11 , 16,17). Capsules C and D are filled with granules , although the dissolution behaviour of these products is not equivalent to those of standard "slow released" phenytoin capsules; these capsules should release 15-35% of drug in first 30 mins., 45-60% in 60 mins.,and 85% in 2h(11,16,17).

The slow release of these capsules could be due to the effect of factors such as slow dissolution of shells (18,19) and deaggregation time of granule content of the capsules.

The dissolution time for capsules shell were , 1.5-3 minutes for product A and E, 3-5 minutes for product B and about 10 minutes for products C and D.

A comparison between the methods showed that the Levy method gave the highest, and the Magnetic method gave the lowest release of products A,B,C. The rate and dissolution of product D or E did not differ significantly by using either Rotating or Magnetic method, however these products showed a higher release pattern by Levy method, same as other products; A,B and C.

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