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Dissolution kinetics of commercially available controlled-release theophylline preparations

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Summary

The in vitro release kinetics of 8 commercially available controlled-release theophylline preparations were studied at pH 1.0 and pH 7.5 using the USP dissolution apparatus with the basket and paddle assemblies. The kinetics of the dissolution process were determined by analyzing the dissolution data using 4 kinetic equations, namely, the zero-order equation, the first-order equation, the Higuchi square root equation and the Hixson–Crowell cube root law. The results obtained at all the dissolution conditions obey both the first order and the Higuchi square root equations showing that the dissolution process is diffusion- and dissolution-controlled. The dissolution process is accompanied by a change in the diffusion pathlength and surface area of the dissolving tablets or beads as indicated from its fitness to the Hixson–Crowell cube root law. This was further substantiated by plotting the values of the first-order dissolution rate constant vs the values of the Hixson–Crowell cube root dissolution rate constants where a straight line was obtained with a slope of approximately one. The results obtained in this work show that the dissolution kinetics of the tested products are independent of the pH of the dissolution medium or the dissolution method employed.

Introduction

A number of methods and techniques have been used in the manufacture of oral controlled-release (CR) dosage forms. These dosage forms are designed to deliver the drug at a controlled and predetermined rate thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time and therefore reducing the frequency of dosing and improving patient compliance (Robinson, 1980a).

Theophylline, a xanthine bronchodilator, is used in the treatment of both chronic and acute asthmatic attacks (Buckton et al., 1988). Due to its low therapeutic index, careful control of its release from dosage forms has to be ensured. Faulty formulation may result in the release of large amounts of theophylline, i.e. dose dumping, and hence could produce toxic effects (Welling, 1983). In order to improve patient compliance, several CR theophylline preparations are available on the market. These preparations range from eroded matrix tablets, encapsulated coated beads to compressed coated beads. These forms rely on diffusion and dissolution as the principal mechanisms for controlling release.

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Very little work has been done on the comparative in vitro dissolution and in vivo bioavailability of different theophylline preparations. Simons et al. (1982) studied the dissolution and bioavailability of whole and halved sustained release theophylline tablets. They noted that in the dissolution studies of whole and halved 100 mg tablets, drug release from the halved tablet was significantly higher. These differences, however, were not reflected in the in vivo bioavailability studies. Similar results were reported by Shah et al. (1987). Buckton et al. (1988) have showed that the diverse manufacturing techniques employed in the manufacture of CR dosage forms give very different release patterns. They, however, noted that the release process shows apparent first-order kinetics.

In this work an attempt is made to study the in vitro release characteristics and kinetics of 8 commercially available CR theophylline preparations. The kinetics of the dissolution process were studied by the application of 4 kinetic equations to the dissolution data, namely, the zero-order, the first-order, the Higuchi square root and Hixson–Crowell cube root law equations.

Materials and Methods

Materials

The products tested vary from tablets to capsules, and from pH-dependent to pH-independent formulations; they are listed in Table 1. All the products were analyzed spectrophotometrically at 270 nm and were found to contain their corresponding label claim.

Methods

Dissolution studies were performed at pH 1.0 (0.1 N HCl) for 4 h and at pH 7.5 (phosphate buffer) for 7 h or until complete dissolution. Studies were performed at 50 rpm using 900 ml of the dissolution medium in a 37 °C thermostated water bath. The USP dissolution apparatus I (basket) and II (paddle) were used.

Studies were performed in an automated dissolution apparatus by placing 6 tablets (or capsules) each in a basket in the dissolution assembly (QC 72 RB, Hanson Research, Northridge, CA, U.S.A.). In the paddle assembly, the capsules were surrounded by a stainless-steel spiral to prevent their floating. In the studies of halved tablets, the tablets were carefully cut at the middle score mark and their weights were checked prior to use.

Automatic sampling was performed at 15 min intervals where filtered portions from each of the 6 vessels were pumped simultaneously (DN6EB Dissoscan, Hanson Research, Northridge, CA, U.S.A.) to a spectrophotometer containing 7 flow cells (1 mm path length) (Du 57 Uv-Vis spectrophotometer, Beckman Inst., Fullerton, CA, U.S.A.). Measurements were performed at 270 nm vs a standard solution. After the measurements were performed, the cells were automatically emptied and samples were returned to their respective vessels. This guaranteed constant volume and constant drug content throughout the dissolution test.

Automatic calculation and plotting of percent dissolved (M_t) versus time (t) were carried out using built-in software (Dissolution Soft pack module, Beckman Inst., Fullerton, CA, U.S.A.). Percent remaining (M_r) was calculated by subtracting M_t from the label claim (100%). Each data point is the average of 6 individual measurements. In all cases, the relative S.D. was less than 3%.

Results and Discussion

In order to describe the kinetics of the release process of drugs formulated in CR preparations, various equations are normally used such as the zero-order rate equation which describes the systems where the release rate is independent of the concentration of the dissolving species (Najib and Suleiman, 1985). The first-order equation (Schwartz et al., 1968; Singh et al., 1967; Desai et al., 1966; Buckton et al., 1988) describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. The Higuchi square root equation (Higuchi 1963) describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion (Baveja et al., 1988; Chemtob et al., 1986). The Hixson–Crowell cube root law de-

TABLE 1

Types of controlled-release preparations

No.	Name	Theo-phylline content (mg)	Manufacturer	Form
A	Broncho-Retard	500	Klinge Pharma, F.R.G.	Capsules containing coated beads.
B	Broncho-Retard	200	Klinge Pharma, F.R.G.	Capsules containing coated beads.
C	Theodur	300	Key Pharmaceuticals, U.S.A.	Tablets containing coated beads.
D	Lasma	300	Pharmax Ltd., U.K.	Tablets containing coated beads.
E	Slo-Phyllin Gyrocaps	250	W.H. Rorer, U.S.A.	Capsules containing coated beads.
F *	Theo-SR	300	Al-Hikma Pharmaceuticals, Jordan.	Round bisect nondisintegrating eroding tablet.
G *	Theo-SR	150	Al-Hikma Pharmaceuticals, Jordan.	Half of tablet F
H *	Theo-SR	500	Al-Hikma Pharmaceuticals, Jordan.	Capsule-shaped nondisintegrating eroding tablet.
I *	Theo-SR	250	Al-Hikma Pharmaceuticals, Jordan.	Half of tablet H
J	Nuelin	250	Riker Labs., U.K.	Round Convex nondisintegrating eroding tablet.

* The same formulation.

scribes the release from systems where there is a change in surface area and diameter of the particles or tablets. Such a change in area and diameter is reflected by a change in the weight of the particles. The applicability of all of these equations is tested in this work.

The dissolution data obtained for all brands at pH 7.5 are plotted in accordance with the zero-order equation i.e. percent dissolved as a function of time (Fig. 1). It is evident from the figure that the plots are curvilinear suggesting that the release process is not zero-order in nature. This indicates that the dissolution rate of the drug is dependent

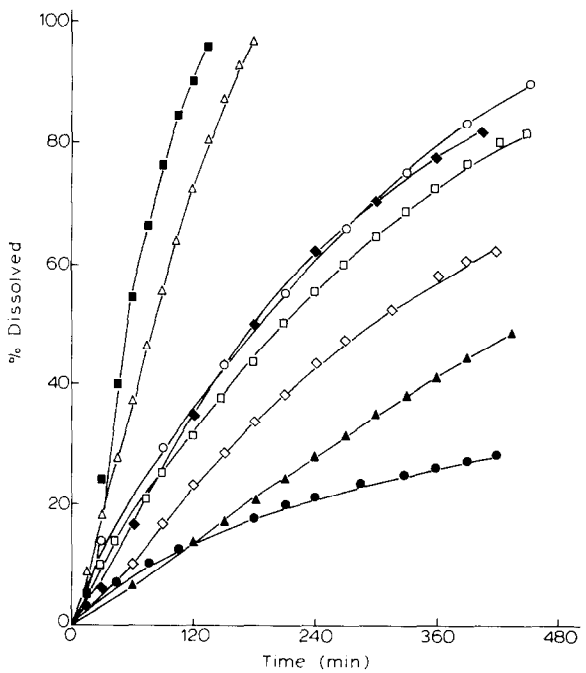
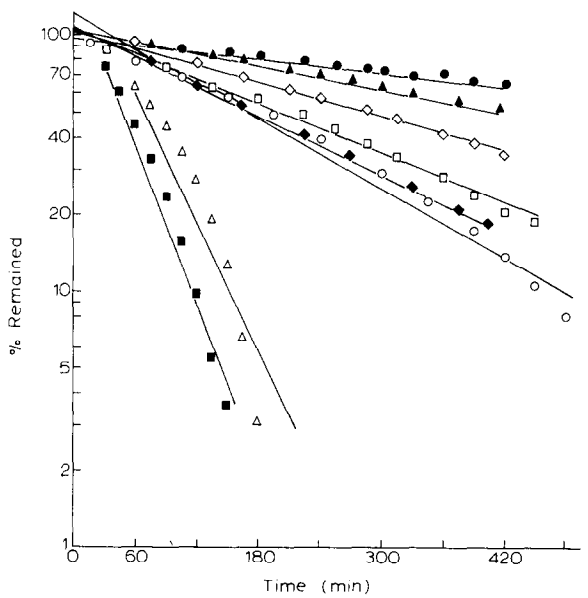


Fig. 1. Dissolution profiles of theophylline products. A (◆); B (◇); C (●); D (▲); E (■); F (○); H (□); J (△).



Semilogarithmic plot of percent remained vs time. A (◆); B (◇); C (●); D (▲); E (■); F (○); H (□); J (△).

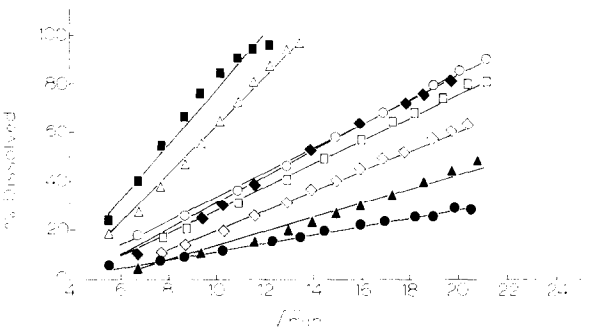


Fig. 3. Percent dissolved vs square root of time. A (◆); B (◇); C (●); D (▲); E (■); F (○); H (□); J (△).

on the amount of drug available for dissolution and diffusion from the matrix. The plot also exhibits a large degree of brand-to-brand variation ranging from product E which release almost 100% of its contents in 2 h to product C which release only 20% of its contents in 5 h. This difference in the release characteristics is due to formulation differences between the tested products. In the case of preparations of the same brand but different drug load, e.g. products A and B, the release was greater in the case of product A showing the dependency of the release rate on the matrix drug load.

The dissolution data of all brands at pH 7.5 are plotted in accordance with the first order equation, i.e. the logarithm of the percent remained as a function of time (Fig. 2). It is evident from the figure that a linear relationship was obtained for all brands showing that the release is an apparent first-order process. This indicates that the amount of drug released is dependent on the matrix drug load.

The dissolution results at pH 7.5 (Fig. 3) are plotted in accordance with the Higuchi square root equation, i.e., percent dissolved as a function of the square root of time. A linear relationship is obtained after an initial lag time has lapsed in all cases. This lag time is a measure of the time needed by the drug to diffuse from the matrix interior through the boundary layer and then to the dissolution medium. The linearity of the plots indicates that the release process is diffusion-controlled.

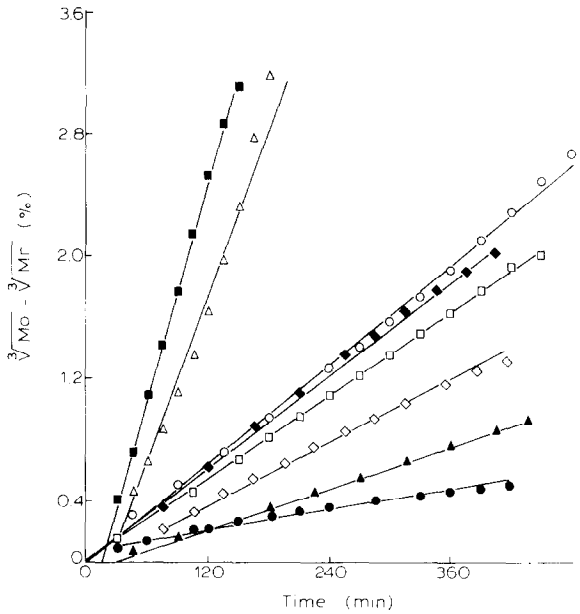


Fig. 4. A plot of cube root of initial concentration (M_b) minus cube root of concentration remained (M_r) vs time. A (◆); B (◇); C (●); D (▲); E (■); F (○); H (□); J (△).

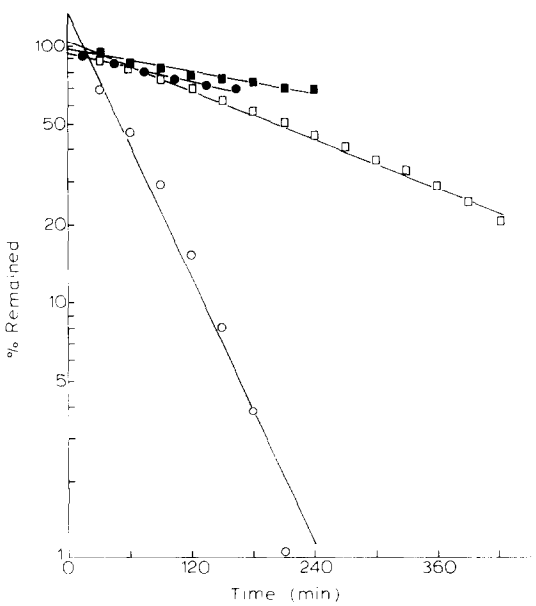


Fig. 5. Semilogarithmic plot of percent remained vs time for product H under different dissolution conditions. Basket, pH 1 (■); paddle, pH 1 (●); basket, pH 7.5 (□); paddle, pH 7.5 (○).

TABLE 2

Dissolution rate constants obtained under all test conditions

No.	Name	First order rate constant (K_1)				Higuchi square root rate constant (K_2)				Hixson–Crowell rate constant (K_3)			
		pH 1.0		pH 7.5		pH 1.0		pH 7.5		pH 1.0		pH 7.5	
		Basket	Paddle	Basket	Paddle	Basket	Paddle	Basket	Paddle	Basket	Paddle	Basket	Paddle
A	Broncho-Retard 500	0.004 $r = 0.999$ $n = 12$	0.005 $r = 0.999$ $n = 12$	0.004 $r = 0.999$ $n = 27$	0.005 $r = 0.999$ $n = 24$	5.441 $r = 0.998$ $n = 12$	5.941 $r = 0.998$ $n = 12$	5.310 $r = 0.998$ $n = 27$	5.590 $r = 0.996$ $n = 24$	0.006 $r = 0.981$ $n = 12$	0.007 $r = 0.999$ $n = 12$	0.005 $r = 0.998$ $n = 27$	0.006 $r = 0.996$ $n = 24$
B	Broncho-Retard 200	0.002 $r = 0.999$ $n = 12$	0.003 $r = 0.999$ $n = 12$	0.003 $r = 0.999$ $n = 28$	0.005 $r = 0.999$ $n = 28$	3.330 $r = 0.995$ $n = 12$	4.551 $r = 0.997$ $n = 12$	3.989 $r = 0.996$ $n = 28$	5.251 $r = 0.996$ $n = 28$	0.003 $r = 0.998$ $n = 12$	0.005 $r = 0.999$ $n = 12$	0.003 $r = 0.999$ $n = 28$	0.005 $r = 0.997$ $n = 28$
C	Theodur 300	0.001 $r = 0.985$ $n = 11$	0.001 $r = 0.993$ $n = 12$	0.001 $r = 0.992$ $n = 28$	0.002 $r = 0.992$ $n = 26$	1.313 $r = 0.999$ $n = 11$	1.692 $r = 0.999$ $n = 12$	1.548 $r = 0.999$ $n = 28$	3.303 $r = 0.980$ $n = 26$	0.001 $r = 0.984$ $n = 11$	0.002 $r = 0.991$ $n = 12$	0.001 $r = 0.991$ $n = 28$	0.003 $r = 0.995$ $n = 26$
D	Lasma 300	0.002 $r = 0.997$ $n = 12$	0.002 $r = 0.998$ $n = 12$	0.002 $r = 0.999$ $n = 29$	0.002 $r = 0.999$ $n = 25$	2.681 $r = 0.981$ $n = 12$	3.330 $r = 0.986$ $n = 12$	3.021 $r = 0.986$ $n = 29$	3.572 $r = 0.987$ $n = 25$	0.003 $r = 0.998$ $n = 12$	0.003 $r = 0.998$ $n = 12$	0.002 $r = 0.999$ $n = 29$	0.003 $r = 0.996$ $n = 25$
E	Slo-phyllin 250	0.004 $r = 0.998$ $n = 12$	0.005 $r = 0.999$ $n = 11$	0.024 $r = 0.989$ $n = 10$	0.023 $r = 0.994$ $n = 10$	4.620 $r = 0.999$ $n = 12$	5.631 $r = 0.999$ $n = 11$	11.402 $r = 0.993$ $n = 10$	10.302 $r = 0.988$ $n = 10$	0.005 $r = 0.997$ $n = 12$	0.006 $r = 0.998$ $n = 11$	0.023 $r = 0.999$ $n = 10$	0.022 $r = 0.998$ $n = 10$
F	Theo-SR 300	0.002 $r = 0.996$ $n = 16$	0.002 $r = 0.996$ $n = 12$	0.005 $r = 0.984$ $n = 34$	0.014 $r = 0.969$ $n = 18$	2.331 $r = 0.999$ $n = 16$	2.502 $r = 0.999$ $n = 12$	4.931 $r = 0.998$ $n = 34$	7.301 $r = 0.998$ $n = 18$	0.002 $r = 0.989$ $n = 16$	0.003 $r = 0.994$ $n = 12$	0.005 $r = 0.998$ $n = 34$	0.012 $r = 0.997$ $n = 18$
G	Theo-SR 150	0.002 $r = 0.991$ $n = 12$	0.002 $r = 0.993$ $n = 12$	0.008 $r = 0.987$ $n = 24$	0.019 $r = 0.984$ $n = 15$	2.682 $r = 0.999$ $n = 12$	2.891 $r = 0.999$ $n = 12$	5.891 $r = 0.999$ $n = 24$	7.660 $r = 0.992$ $n = 15$	0.003 $r = 0.989$ $n = 12$	0.003 $r = 0.990$ $n = 12$	0.008 $r = 0.999$ $n = 24$	0.016 $r = 0.999$ $n = 15$
H	Theo-SR 500	0.002 $r = 0.997$ $n = 16$	0.002 $r = 0.996$ $n = 12$	0.004 $r = 0.996$ $n = 30$	0.020 $r = 0.990$ $n = 16$	2.341 $r = 0.999$ $n = 16$	2.751 $r = 0.999$ $n = 12$	4.751 $r = 0.997$ $n = 30$	8.110 $r = 0.987$ $n = 14$	0.002 $r = 0.992$ $n = 16$	0.003 $r = 0.995$ $n = 12$	0.005 $r = 0.999$ $n = 30$	0.017 $r = 0.999$ $n = 16$
I	Theo-SR 250	0.002 $r = 0.994$ $n = 12$	0.002 $r = 0.991$ $n = 11$	0.004 $r = 0.996$ $n = 30$	0.016 $r = 0.986$ $n = 18$	2.291 $r = 0.999$ $n = 12$	2.442 $r = 0.999$ $n = 11$	5.032 $r = 0.999$ $n = 30$	6.862 $r = 0.988$ $n = 18$	0.002 $r = 0.994$ $n = 12$	0.002 $r = 0.990$ $n = 11$	0.005 $r = 0.999$ $n = 30$	0.013 $r = 0.999$ $n = 18$
J	Nuelin	0.002 $r = 0.998$ $n = 12$	0.002 $r = 0.988$ $n = 12$	0.019 $r = 0.950$ $n = 12$	0.029 $r = 0.988$ $n = 7$	2.362 $r = 0.999$ $n = 12$	2.563 $r = 0.999$ $n = 12$	9.861 $r = 0.995$ $n = 12$	12.670 $r = 0.998$ $n = 7$	0.002 $r = 0.994$ $n = 12$	0.003 $r = 0.985$ $n = 12$	0.018 $r = 0.986$ $n = 12$	0.033 $r = 0.996$ $n = 7$

n, Number of data points; r, correlation coefficient.

The dissolution data are also plotted in accordance with the Hixson-Crowell cube root law, i.e. the cube root of the initial concentration minus the cube root of percent remained, as a function of time. Fig. 4 indicates that a linear relationship was obtained in all cases. A small non-zero intercept was noticed in most of the plots. This is not, however, unexpected since the particles are not isometric. Such a non-zero intercept was reported earlier (Carstensen and Patel, 1975).

The dissolution kinetics of whole vs halved tablets (Table 2; products F–I) were almost similar regardless of the pH or the dissolution conditions. This is not surprising since they all have the same basic formulation as mentioned in Materials and Methods. On the other hand, the dissolution kinetics of products A and B are not similar which reflects a difference in the basic formulation.

The dissolution data at pH 1.0 behave in a similar fashion as those at pH 7.5. As shown in Table 2, the data at pH 1.0 are linear when plotted according to the first-order, the Higuchi square root and the Hixson–Crowell Cube root equations (Figs. 5–7). It is interesting to note that at pH 7.5, larger differences are noticed between products than at pH 1.0. For example, the ratio of the first order dissolution rate constant of product E to product C is 24 at pH 7.5 (basket) and 4 at pH 1.0 (basket). This is due to the large increase in the dissolution rate of the pH-dependent product E at pH 7.5.

The dissolution of all the tested brands was also performed in the paddle assembly and results

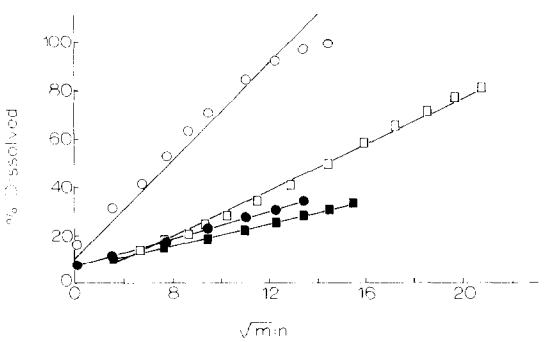


Fig. 6. Percent dissolved vs square root of time for product H under different dissolution conditions. Basket, pH 1 (■); paddle, pH 1 (●); basket, pH 7.5 (□); paddle, pH 7.5 (○).

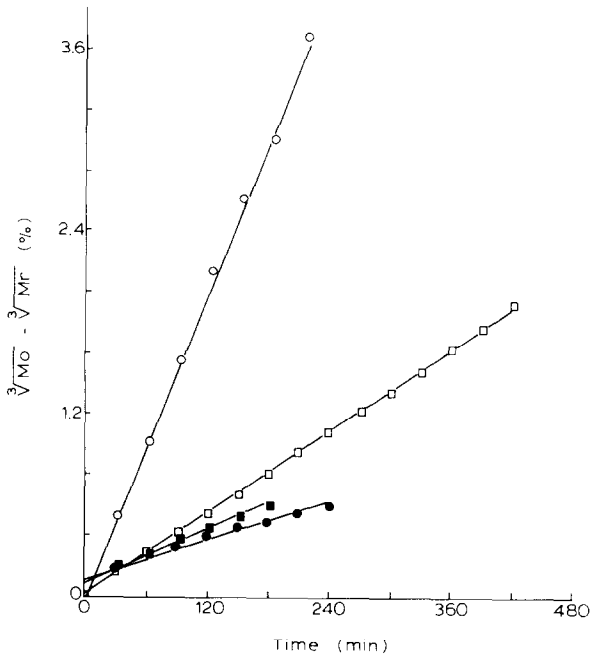


Fig. 7. A plot of cube root of initial concentration (M_o) minus cube root of concentration remained (M_r) vs time for product H under different dissolution conditions. Basket, pH 1 (●); paddle, pH 1 (■); basket, pH 7.5 (□); paddle, pH 7.5 (○).

obtained are shown in Table 2. It is evident from the Table that the same profiles of dissolution kinetics exist. Furthermore, the dissolution rates obtained at pH 1.0 in the paddle assembly are similar to those obtained in the basket assembly. However, at pH 7.5 and in the pH-dependent products, the paddle dissolution rates are larger than their corresponding basket dissolution rates (Table 2, products F–J). This is attributed to the fact that in the paddle assembly, the dissolution medium is more easily accessible to the drug matrix than in the basket assembly.

The effects of the dissolution conditions on the same product are better observed in Figs. 5–7, where the dissolution conditions affect the dissolution rate in the same magnitude regardless of the kinetic manipulation of the data.

It is important to mention that the slopes obtained from the Higuchi square root plots were higher than those obtained from the first-order or Hixson–Crowell plots. This is attributed to using the square root of time in the Higuchi plots. It is

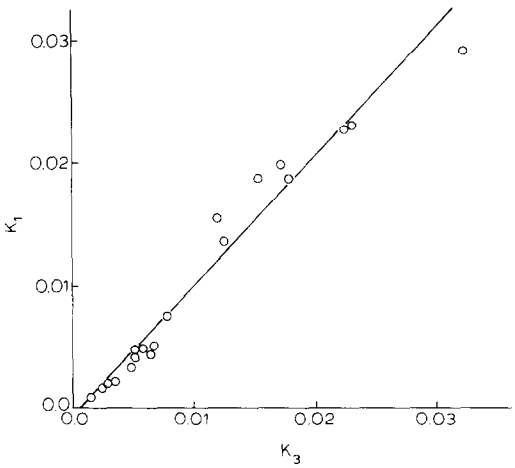


Fig. 8. A plot of first order dissolution rate constants vs cube root dissolution rate constants for all data points.

interesting to note that the dissolution rate constants obtained from the first-order plots were similar to those obtained from the Hixson-Crowell plots.

The relationship between the first-order dissolution rate constant (K_1) and the Hixson-Crowell cube root dissolution rate constant (K_3) is best illustrated by plotting K_1 vs K_3 for all the experimental conditions (Fig. 8). Needless to say that a linear relationship was obtained in the following equation:

$$K_1 = -0.0007 + 1.050\ K_3\ (r = 0.987;\ n = 40)$$

This equation suggests that the slope of the K_1–K_3 plot is approximately one and the line passes through the origin.

From the results obtained in this work it can be concluded that a significant variation exists in the in vitro release pattern of theophylline from the tested commercially available CR formulations. The release process for all brands is dependent on pH and for any one product on the matrix drug load.

The analysis of the dissolution kinetic data was carried out by the application of the zero-order, first-order, the Higuchi square root and Hixson–Crowell cube root law equations.

The inapplicability of the zero-order equation to the dissolution data shows that the release process is dependent on the matrix drug load. The applicability of the first order and the Higuchi square root equations shows that the release process is diffusion- and dissolution-controlled. The applicability of the Hixson–Crowell cube root law to the dissolution data indicates that during the dissolution process there is an alteration in the surface area and diameter of the matrix system as well as in the diffusion pathlength from the matrix drug load.

A linear relationship with a slope of approximately 1 was obtained when the first-order dissolution rate constants were plotted against the Hixson–Crowell cube root dissolution rate constants. This shows that the change in surface area, diameter of the dissolving particles or tablets and the change in diffusion pathlength during the dissolution process follow the cube root law. It appears therefore that, in such situations, both the first-order equation and the Hixson–Crowell cube root law can best describe the kinetics of the dissolution process of theophylline from all the tested products. Such kinetic profiles are independent of the pH of the dissolution medium or the dissolution methodology.

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