

IN VITRO DISSOLUTION KINETIC STUDY OF THEOPHYLLINE FROM HYDROPHILIC AND HYDROPHOBIC MATRICES

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Abstract: Oral dosage forms containing 300 mg theophylline in matrix type tablets, were prepared by direct compression method using two kinds of matrices, glycerylbehenate (hydrophobic), and (hydroxypropyl)methyl cellulose (hydrophilic). The *in vitro* release kinetics of these formulations were studied at pH 6.8 using the USP dissolution apparatus with the paddle assemble. The kinetics of the dissolution process were studied by analyzing the dissolution data using four kinetic equations, the zero-order equation, the first-order equation, the Higuchi square root equation and the Hixson-Crowell cube root law. The analysis of the dissolution kinetic data for the theophylline preparations in this study shows that it follows the first order kinetics and the release process involves erosion / diffusion and an alteration in the surface area and diameter of the matrix system, as well as in the diffusion path length from the matrix drug load during the dissolution process. This relation is best described by the use of both the first-order equation and the Hixson-Crowell cube root law.

Keywords: Theophylline, glycerylbehenate, (hydroxypropyl)methyl cellulose, dissolution kinetic.

A number of methods and techniques have been used in the manufacturing of oral extended-release dosage forms. Probably the simplest and least expensive way to control the release of an active agent, is to disperse it in an inert polymeric matrix (1). In polymeric system, the active agent is physically blended with the polymer powder and then fused together by compression, moulding, which is a common process in the pharmaceutical industry (2-4). 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 (5, 6).

Hydrophobic material such as glycerylbehenate for an insoluble matrix carrier, and a water soluble hydrophilic material such as (hydroxypropyl)methyl cellulose have been reported as a most commonly used matrix carriers (7, 8).

Anhydrous theophylline, a xanthine bronchodilator is used in the treatment of both chronic and acute asthmatic attacks. 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 (9).

The aim of the present work was to study the utility of using glycerylbehenate and (hydroxypropyl)methyl cellulose for the formulation of an controlled-release anhydrous theophylline matrix tablets and to study the *in vitro* release characteristics and kinetics of the prepared formulations. The kinetics of the dissolution process was studied by the application of four kinetic equations to the dissolution data, namely, the zero-order, the first-order, the Higuchi square root and Hixson-Crowell cube root law equations.

EXPERIMENTAL

Materials and Methods

(Hydroxypropyl)methyl cellulose (Methocel K15 M) was obtained from Dow Chemical, USA, glycerylbehenate (Compritol 888 ATO) from Gattefosse, France, anhydrous theophylline from Sigma Chemical Co. England, microcrystalline cellulose (Avicel pH 10,2) from FMC Corporation, USA, magnesium stearate USP, was from Mallinckrodt Chesterfield, USA and fumed silicone dioxide (Aerosil 200) from Degussa, USA.

Preparation of direct compressible tablets

Table 1 shows the tablet formulations for direct compression. All the ingredients were passed

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through 125 μm sieve and retained on 90 μm sieve. The powders were mixed together for 10 min in a high-speed mixer (Erweka Turbula system S27, Germany). The tablets were prepared by direct compression using single flat-faced punch 13 mm diameter (Erweka-AR 400E, Germany). The hardness of tablets was controlled between 120-130 N.

Evaluation of the prepared tablets

Friability was determined using Erweka friabilator (TAR). The uniformity of weight and drug content were determined according to USP₂₀₀₂/NF 23 procedures. Mean values of weight variation, content uniformity and friability are shown in Table 2.

Dissolution studies

Dissolution study was carried out according to the USP paddle method (Hanson Research Co., USA) containing 1000 mL of pH 6.8 dissolution medium (phosphate buffer was used). The temperature of dissolution medium was controlled at $37^\circ\text{C} \pm 0.5^\circ$ and stirring speed was maintained at 50 rpm. Six tablets from each batch were tested for 8 h. Samples (5 mL) were withdrawn at predetermined time intervals and immediately replaced with equal volumes of dissolution medium. Samples were filtered (0.45 Millipore filter) and then their concentrations were determined using UV/Vis spectrophotometer (Varian Australia) at 272 nm.

RESULTS AND DISCUSSION

It could be observed that the tablets prepared fulfill the USP₂₀₀₂/NF 23 requirements for uniformity of weight, drug content and friability as shown in Table 2.

Figure 1 and Table 3 showed that a significant variation exists in the *in vitro* release pattern of theophylline from the tablets containing (hydroxypropyl)methyl cellulose 50 mg, 75 mg and 100 mg and those containing glycerylbehenate 50 mg, 75 mg and 100 mg, respectively. More specifically, 60%, 65% and 38% theophylline dissolved from F1, F2 and F3, while 75%, 40% and 33% theophylline dissolved from F4, F5 and F6, respectively, within 3 h. The results showed (Figure 1) that the release of drug from F4, F5 and F6 [(hydroxypropyl)methyl cellulose] was higher in the first half hour than F1, F2 and F3 (glycerylbehenate). This is attributed to the fact that (hydroxypropyl)methyl cellulose tablets show erosions on their surface early in the process, so the active agent placed in this area is immediately released to the dissolution medium. Glycerylbehenate tablets show less erosions on their surface than (hydroxypropyl)methyl cellulose tablets and there is no hydration or swelling at the first half hour, so the release remained slow.

A dissolution profile comparison was done using the similarity factor f_2 to compare the dissolution profile of theophylline from prepared tablets

Table 1. The composition of 6 tablet formulations containing glycerylbehenate and (hydroxypropyl)methyl cellulose prepared by direct compression as described in Materials and Methods.

Formula	Glycerylbehenate (mg)	(Hydroxypropyl) methyl cellulose (mg)	Theophylline (mg)	Avicel (mg)	Aerosil (mg)	Magnesium stearate (mg)
F1	50	—	300	340	3	7
F2	75	—	300	315	3	7
F3	100	—	300	290	3	7
F4	—	50	300	340	3	7
F5	—	75	300	315	3	7
F6	—	100	300	290	3	7

Table 2. Mean values and coefficient of variation of the pharmacotechnical tablets parameters

Formula	Uniformity of weight (mg) (C.V. %)	% Friability	Drug content (mg) (C.V. %)
F1	698.67 \pm 1.3	0.378	299.5 \pm 0.7
F2	698.12 \pm 1.6	0.226	298.8 \pm 1.3
F3	699.89 \pm 1.3	0.306	298.6 \pm 1.4
F4	701.13 \pm 0.9	0.405	299.4 \pm 1.2
F5	701.02 \pm 0.7	0.337	300.2 \pm 1.2
F6	698.77 \pm 1.4	0.502	297.1 \pm 1.5

Table 3. Dissolution rate constants and r values for all formulations obtained from the application of the zero-order, first-order, Higuchi square root and Hixson-Crowell cube root equations.

Formula No.	Zero order rate constant (K_0)	First order rate constant (K_1)	Higuchi square root rate constant (K_2)	Hixson-Crowell rate constant (K_3)
1	10.255 r = 0.941	0.332 r = 0.994	38.014 r = 0.983	0.356 r = 0.997
2	9.858 r = 0.914	0.280 r = 0.973	37.010 r = 0.968	0.321 r = 0.982
3	5.349 r = 0.955	0.086 r = 0.976	19.667 r = 0.990	0.121 r = 0.989
4	6.836 r = 0.917	0.300 r = 0.994	25.686 r = 0.972	0.290 r = 0.990
5	4.248 r = 0.962	0.074 r = 0.980	15.555 r = 0.993	0.102 r = 0.992
6	3.550 r = 0.948	0.053 r = 0.965	13.110 r = 0.983	0.077 r = 0.979
7*	6.154 r = 0.980	0.091 r = 0.991	22.094 r = 0.992	0.130 r = 0.9967*
8**	3.950 r = 0.990	0.050 r = 0.995	14.073 r = 0.995	0.075 r = 0.998

*Theophylline capsules (THEOLIN SR 300 mg).** Theophylline tablets (UNIPHYLLIN SR 300 mg). r = correlation coefficient. Number of data points was 8 for all formulations.

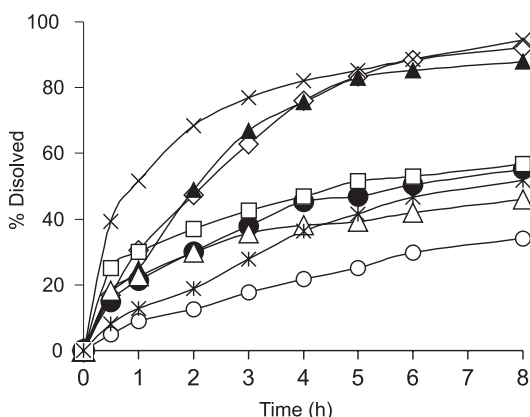


Figure 1. A plot of % dissolved versus time for the dissolution data in accordance with the zero-order equation. F1 (◊), F2 (▲), F3 (●), F4 (x), F5 (◻), F6 (Δ), F7 (○) and F8 (Ж).

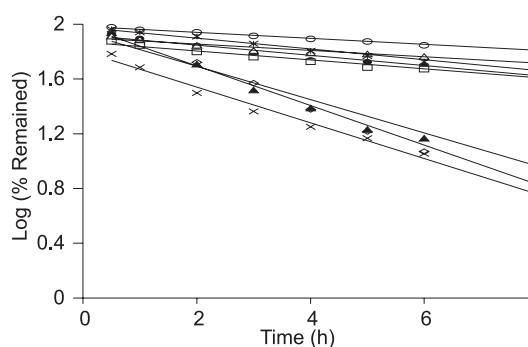


Figure 2. A linear plot of log (% remaining) versus time for the dissolution data accordance with the first-order equation. F1 (◊), F2 (▲), F3 (●), F4 (x), F5 (◻), F6 (Δ), F7 (○) and F8 (Ж).

with those of commercial SR tablets of theophylline used in this study. Similarity factor was calculated from the following equation:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n W_i (R_i - T_i)^2 \right]^{0.5} \times 100 \right\}$$

where:

R_i = reference assay at time point t.

T_i = test assay at time point t.

n = is the number of pull points

W_i = optional weight factor.

The results obtained from the calculation of f_2 factor showed that there is a similarity of dissolution profiles between F6 and Uniphylin SR tablets, as well as between F3 and Uniphylin SR tablets, with f_2 values 55 and 56, respectively ($f_2 > 50$, dissolution profiles are defined as similar) (10, 11).

In order to describe the kinetics of the release process of drug in the 6 formulations as well as in the 2 standard commercial formulations, various equations were used such as the zero-order rate equation, which describes the systems where the

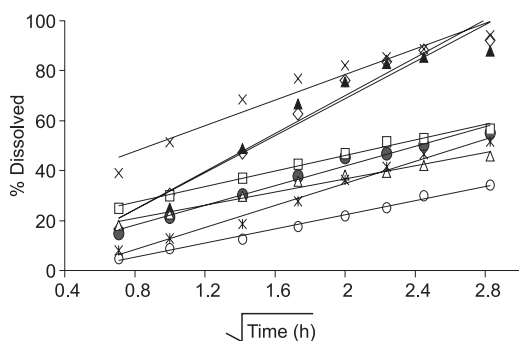


Figure 3. A linear plot of % dissolved versus square root of time for the dissolution data in accordance with the Higuchi square root equation. F1 (◇), F2 (▲), F3 (●), F4 (x), F5 (□), F6 (Δ), F7 (o) and F8 (Ж).

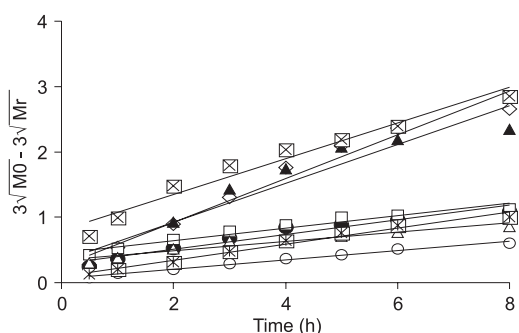


Figure 4. A linear plot of the cube root of the initial concentration minus the cube root of percent remaining versus time for the dissolution data in accordance with the Hixson-Crowell cube root law. F1 (◇), F2 (▲), F3 (●), F4 (x), F5 (□), F6 (Δ), F7 (o) and F8 (Ж).

release rate is independent of the concentration of the dissolved species (12). The first-order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species (13). The Higuchi square root equation 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 (14, 15). The Hixson-Crowell cube root law describes the release from system where there is a change in surface area and diameter of the particles or tablets (16, 17). The applicability of all of these equations was tested in this work.

The dissolution data obtained for all formulations at pH 6.8 were plotted in accordance with the zero-order equation i.e. percent dissolved as a function of time (Figure 1). It is evident from the figure that the plots are curvilinear suggesting that the release process is not zero-order in nature.

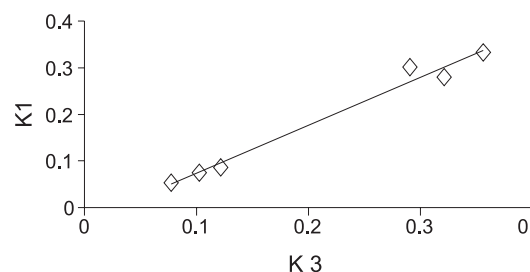


Figure 5. A linear plot for the relationship between the first-order dissolution rate constant (K_1) and the Hixson-Crowell cube root dissolution rate constant (K_3).

The dissolution data of all formulations at pH 6.8 were plotted in accordance with the first order equation, i.e. the logarithm of the percent remaining as a function of time (Figure 2). It is evident from Figure 2 and Table 3 that a linear relationship was obtained with r value close to unity for all formulations 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 6.8 were plotted in accordance with the Higuchi square root equation, i.e. percent dissolved as a function of the square root of time (Figure 3). A linear relationship is obtained after an initial lag time has lapsed in all cases. The linearity of the plots indicates that the release process is diffusion-controlled.

The dissolution data were 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 remaining, as a function of time (Figure 4). Figure 4 indicates that a linear relationship was obtained in all cases.

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 K_1 vs K_3 for all the formulations (Figure 5). A linear relationship was obtained according to the following equation:

$$K_1 = -0.029 + 1.028 K_3 \quad (r = 0.991)$$

This equation suggests that the slope of the $K_1 - K_3$ plot is approximately one, r is very close to unity and the intercept, 0.029 is near zero. This shows that the change in surface area, diameter of the dissolved particles or tablets and the change in diffusion path length during the dissolution process follow the cube root law.

CONCLUSION

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 formulations. The use of (hydroxypropyl)methyl cellulose (hydrophilic polymer) and glyceryl behenate (waxy material) with different amounts can result in preparation of controlled release tablets with different release rates.

The analysis of the dissolution kinetic data for the theophylline preparations in this study shows that it follows the first order kinetics and the release process involves erosion / diffusion and an alteration in the surface area and diameter of the matrix system as well as in the diffusion path length from the matrix drug load during the dissolution process. 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 formulations.

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