
Formulation and Evaluation of Sustained Release Dosage Form of Theophylline Using a Combined Hydrophobic and Hydrophilic Matrix

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Combination of aliphatic alcohol (cetyl alcohol) and partially hydrated methylcellulose was investigated as a sustained release matrix. Theophylline is used as a model drug for evaluating the matrix system. Cetyl alcohol and methyl cellulose were used in different proportions i.e., 2:1, 3:1, and 4:1 along with usual tablet additives, lactose and talc. The matrix component was varied from 20, 25 and 30 % w/w of total tablet weight. The *in vitro* release data showed that 30% w/w total matrix component gave extended release of theophylline for more than 8 h. Analysis of drug release rate from the matrix system indicated that the drug was released by anomalous diffusion obeying first order rate kinetics.

Because of reduced frequency of administration, sustained release dosage forms enjoy convenience and ambulatory patient compliance, which is a problem normally associated with some classes of drugs such as NSAID'S, antihypertensive agents, antiasthmatic drugs and antipsychotic drugs. In recent past, several sustained delivery compositions and methods have been developed. Nath and Satish Reddy¹ have reported a method for preparing wax/fat microspherules containing ibuprofen for controlled release using bees wax, sugarcane wax and paraffin wax as matrices by emulsification and phase separation process. The use of inert wax matrix for sustained release and the effect of surfactant and povidone on the release of triprolidine hydrochloride has been reported in a series of papers.²⁻⁴ Vast literature is accumulated showing the use of hydrophilic matrices to formulate controlled release dosage forms of different drugs⁵⁻⁸. Normally the formulations using hydrophobic fatty substances such as cetyl alcohol will retard the release of the embedded drug and only a small portion of the drug will be made available to the system if they are

used exclusively. To enhance drug release, a surfactant or a hydrophilic substance like poly ethylene glycol is required. Semi-synthetic cellulose derivatives represent a vast group of hydrophilic polymers, which can also be expected to enhance the release of the embedded drug from the hydrophobic matrix. So in the present investigation, an attempt has been made to fabricate a controlled-release dosage form of theophylline using a unique process in which a combination of cetyl alcohol and partially hydrated methyl cellulose was used as matrix material with other commonly used tablet excipients. The *in vitro* release studies were conducted for all the formulations and an attempt has been made to study the drug release kinetics from the formulations.

MATERIALS AND METHODS

Theophylline IP was a gift sample from Remidex Pharma Pvt. Ltd., Bangalore. Cetyl alcohol and lactose were procured from S.D. Fine Chemicals, Mumbai. Methyl cellulose was purchased from Loba Chemie, Mumbai. All other chemicals and reagents used were of analytical grade and were used as procured.

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TABLE 1: TABLET INGREDIENTS (% w/w OF TOTAL WEIGHT)

Ingredients	20% w/w Combined matrix material				25% w/w Combined matrix material				30% w/w Combined matrix material			
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cetyl alcohol (CA)	20.00	13.40	15.00	16.00	25.00	16.70	18.75	20.00	30.00	20.00	22.50	24.00
				0								
Methyl cellulose (MC)	-	6.60	5.00	4.00	-	8.30	6.25	5.00	-	10.00	7.50	6.00
Theophylline	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
				0								
Lactose	37.00	37.00	37.00	37.00	32.00	32.00	32.00	32.00	27.00	27.00	27.00	27.00
				0								
Talc	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
				0								
Talc and Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00

Method of preparation of matrix tablets:

Tablets were prepared by congealing method. Briefly, cetyl alcohol was melted at 60° by heating over a water bath to which known amounts of lactose and theophylline were added and stirred until the drug was uniformly dispersed. The congealed mass was then passed through a # 16 stainless steel mesh and dried at room temperature. Simultaneously, methyl cellulose was partially hydrated using 3 parts of water for each part of methyl cellulose along with talc. The cetyl alcohol embedded granules of theophylline were then mixed with the paste of methyl cellulose and again passed through a # 16 stainless steel mesh and dried. The granules were lubricated with additional talc and magnesium stearate and compressed into tablets, each weighing 400 mg to a hardness of 5-6 kg/sq.cm using a single punch tablet press (Cadmach, Ahmedabad). In total, twelve formulations were prepared with 20%, 25% and 30% w/w matrix component consisting of cetyl alcohol and methyl cellulose in three ratios 2:1, 3:1 and 4:1 (Table 1). Tablets with only cetyl alcohol (20%, 25% and 30% w/w) as matrix material were also prepared.

Estimation of drug content in different batches of tablets:

Ten tablets from each formulation were powdered. To 400 mg of the powder, 100 ml of 0.1N hydrochloric acid was added and digested for 15 min at 60° and filtered. The filtrate was then suitably diluted with 0.1N hydrochloric acid and analyzed against a blank reagent spectrophotometrically⁹ at 270 nm using a Hitachi U-2000 double beam spectrophotometer.

In vitro release studies:

The *in vitro* release of theophylline was studied for the first 2 h in 0.1N hydrochloric acid (pH 1.2) and for subsequent 6 h in isotonic phosphate buffer of pH 6.8 using a USP XXI Dissolution Apparatus 1. An amount of 900 ml of the respective dissolution fluids were used at 37 ± 1° with a stirring speed of 70 ± 2 rpm. The dissolution studies were carried in triplicates. The *in vitro* release data obtained in the present work has been treated according to first order rate equation, Higuchi's diffusion equation ($Q = Kt^{1/2}$) and exponential equation ($Q = Kt^n$)¹⁰ to know precisely the mechanism of drug release from the matrix tablet.

RESULTS AND DISCUSSION

The drug content in all the formulations was found to be fairly uniform. Initially 20% w/w combined matrix material was selected to keep the amount of the matrix to a minimum. Theophylline was used as a model drug. Tablets containing cetyl alcohol and methyl cellulose in the ratio 2:1, 3:1 and 4:1 (F2, F3 and F4) were prepared. A tablet containing only cetyl alcohol (20% w/w) was also prepared (F1). The *in vitro* release studies revealed that the drug was completely released within 2-3 h. from the tablets containing cetyl alcohol and methyl cellulose in the ratio 2:1, 3:1 and 4:1 (F2, F3 and F4). While the tablet containing 20% w/w cetyl alcohol alone as the matrix component (F1) released only 49.0% of the drug at the end of 8 h of dissolution. The fast release of the drug in the formulations containing methyl cellulose may be attributed to the hydrophilicity of methyl cellulose, which facilitates the dissolution fluid to penetrate the cetyl alcohol matrix containing the drug. In this batch of tablets, none of the formulations are suitable for sustained release system.

In the next batch of tablets, the matrix material was increased to 25% w/w of total tablet weight. The same three proportions of cetyl alcohol and methyl cellulose i.e., 2:1, 3:1 and 4:1 (F6, F7 and F8) were used. In addition, a tablet with only cetyl alcohol (25 %w/w) as matrix material was also prepared (F5). The *in vitro* release studies indicated that the release of the drug was extended up to a period of 6-8 h for the formulations containing cetyl alcohol and methyl cellulose as combined matrix material. However 50-70% of the drug was released in the first 2 h of dissolution, while the tablet with only cetyl alcohol (25% w/w) as matrix material released only 48.9% of the drug at the end of 8 h of dissolution. Since the rate of drug release was extended up to 6-8 h compared to only 2-3 h in the batch of formulations containing 20% w/w matrix material, it indicates that the total amount of combined matrix component is significantly affecting the release rate of drug.

Therefore, in the next batch of tablets, to control the initial burst release of the drug, the total matrix component was increased to 30% w/w of total tablet weight. Four formulations with the same ratios of cetyl alcohol and methyl cellulose i.e., 2:1, 3:1 and 4:1 (F10, F11 and F12) along with a formulation containing only cetyl alcohol (30% w/w) as matrix material (F9) were prepared. The *in vitro* data plotted as cumulative % of drug release ver-

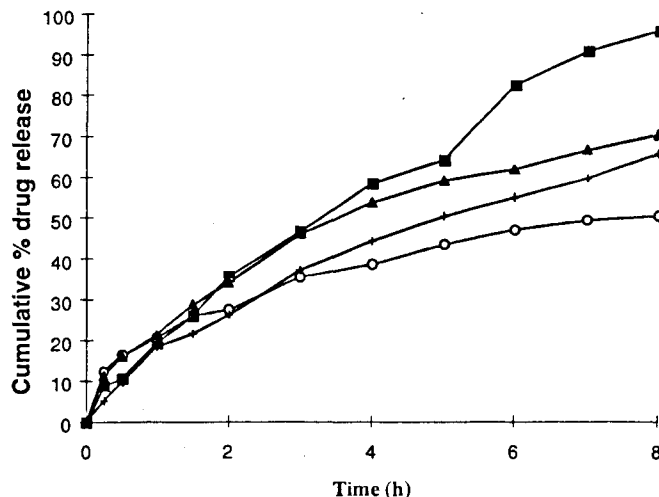


Fig. 1: *In vitro* release of theophylline from tablets containing 30% combined matrix material containing either cetyl alcohol alone (F9 —O—) or 2:1 CA and MC (F10 —■—) or 3:1 CA and MC (F11 —▲—) or 4:1 CA and MC (F12 —◻—).

sus time (h) is represented in Figure 1. The results indicate that the release rate of the drug from the formulations containing cetyl alcohol and methyl cellulose as combined matrix material was fairly uniform throughout the dissolution period of 8 h, while the tablet with only cetyl alcohol (30% w/w) as matrix material released only 50.33% of the drug at the end of 8th h of dissolution.

To know the kinetics of drug release, the data was treated according to first order rate kinetics equation, Higuchi's diffusion equation ($Q = Kt^{1/2}$) and exponential equation ($Q = Kt^n$). The formulations with 20% w/w combined matrix material released the embedded drug following first order kinetics with linear regression co-efficient values, -0.996, -0.996, -0.997 and -0.991 and first order rate constants, 0.073, 1.529, 1.411 and 1.377 for F1, F2, F3 and F4 respectively. The formulations with 25% w/w combined matrix also released the drug obeying first order kinetics as indicated by the linear regression co-efficient values, -0.985, -0.981, -0.940 and -0.895 and with first order rate constants, 0.073, 0.575, 0.405 and 0.259 for F5, F6, F7 and F8, respectively. The embedded drug was released from the formulations containing 30% w/w combined matrix material according to first order rate kinetics with linear regression co-efficient values, -0.946, -0.961, -0.988 and -0.998 and first order rate constants, 0.073, 0.348, 0.138 and 0.124 for F9, F10, F11 and F12 respectively.

The data when treated according to Higuchi's diffusion equation indicated that the formulations released the embedded drug by diffusion with linear regression co-efficient values of 0.997, 0.978, 0.959 and 0.952 for F1, F2, F3 and F4; 0.996, 0.994, 0.985 and 0.989 for F5, F6, F7 and F8; and 0.996, 0.991, 0.995 and 0.998 for F9, F10, F11 and F12, respectively.

Further to know whether there was any swelling of the tablets during dissolution, the data was treated according to exponential equation ($Q = Kt^n$), and the slope (n) were computed. All the formulations containing cetyl alcohol and methyl cellulose gave slope values of more than 0.5 (0.53 to 0.66) indicating that the tablets swelled during dissolution studies¹⁰ while the tablets with only cetyl alcohol gave slope values in the range of 0.42 to 0.44 indicating that there was no swelling of these tablets during dissolution. The swelling of the tablets with cetyl alcohol and methyl cellulose as matrix material can be attributed to the inherent swelling property of methyl cellulose when in contact with aqueous dissolution fluids.

Thus it can be concluded that the presence of methyl cellulose as well as the % of total matrix material in each ratio significantly influences the release rate of

the embedded drug, theophylline. The tablets with 30% w/w matrix component of total tablet weight with cetyl alcohol and methyl cellulose in different ratios gave satisfactory results to be formulated as sustained release dosage form of theophylline with further *in vivo* studies.

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