Formulation of Extended Release Theophylline Tablets Experimental, Modelling and Bioequivalence Studies

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Abstract

Extended release drugs formulations are intended to continuously release medication over a prolonged period, after a single dose. Drugs which have a narrow therapeutic window and a moderate half life are good candidates for such formulations. One approach to such formulations is to embed the drug in a matrix which would act as a release retardant. We describe here our studies on the formulations of an extended release theophylline tablet using polymer matrices.

Different acrylate copolymers sold in the market under the "Eudragit" label were subjected to experiment. Microcrystalline cellulose and calcium sulphate dihydrate were used as filler excepients. The theophylline release patterns of the different formulations were studied, at 37°C in phosplate buffers. The theophylline concentration were measured by UV absorption spectroscopy. A careful study of the release patterns of different formulations let to a formulation using Eudragit ® RSPO, a trimenthylammonioethyl methacrylate copolymer and calcium sulphate dihydrate, which conformed with the following release pattern in accordance with USP 25.

Time (hours)	% Drug Released
1	10 - 30
2	30 - 55
4	55 - 80
8	>80

This formulations was used to prepare tablets with two dosages, paediatric dose (125 mg) and adult dose (250 mg). The adult dose was subjected to a

bioequivalence study against an established commercially available slow release 250 mg formulation (Neulin 250 SR, 3M Pharmaceuticals, Australia) Twenty healthy male volunteers participated in the study. Theophylline concentrations in serum were determined by Fluorescence Polarization Immunoassay. There was no significant difference between the two formulations in basic bio availability and pharmacokinetic parameters (AUC C_{max} and T_{max}).

The new Theophylline ER 125 mg formulation developed is now being manufactured by the State Pharmaceutical Manufacturing Corporation (SPMC).

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Introduction

Asthma is the commonest cause of hospital admissions in Sri Lanka, which has resulted in 894.8 hospitalization and attributed to 4.4 deaths per 100,000 population[1] in 2000. Theophylline has been demonstrated to be useful in the treatment of bronchospasm associated with asthma and chronic bronchitis[2,3].

Theophylline is used in conjunction with ß agonists routinely, in the treatment of asthma. The conventional theophylline tablet or capsule formulations release theophylline drug immediately after administration orally and they are not extended release products. Patients on conventional preparations of theophylline have sub therapeutic plasma levels due to poor compliance, as shown by a study done on asthmatics attending a medical clinic at the NHSL[4]. The introduction of sustained (SR) / extended release (ER) preparations has encouraged the use of this drug and optimized it's performance in clinical practice, by reducing adverse effects caused by fluctuation in plasma levels, which often occur with conventional tablets. Extended release preparations that are administered once or twice daily also improve patient compliance compared to conventional products, which need more frequent dosing. The drug's action, kinetics and toxicity have been reviewed[5]. A plasma concentration of 10-20 µg/ml is associated with optimal bronchodilating activity where as levels above 20 µg/ml are associated with toxicity[6,7,8,9]

The objective of this study was to develop a formulation to manufacture low priced generic extended released (ER) theophylline formulation by the State Pharmaceutical Manufacturing Corporation (SPMC). It is apparent that the use of a locally formulated quality assured generic product would lead to a substantial saving of foreign exchange.

There are several methods used for manufacturing extended release devices, the mixture of beads with varying thickness of outer coat (beads coated to have a dissolution controlled drug delivery system) filled into a capsule, reservoir devices (core of drug, the reservoir, surrounded by a polymeric membrane) and Osmotic Control devices. These however, involved the use of tedious and complicated manufacturing processes such as polymer coating. The inability to restrain and confine these dosage forms to selecte regions of the gastro intestinal tract has been a major obstacle to the development of oral extended-release dosage forms. Various approaches have been tried to overcome this obstacle. They included the development type of swelling and expanding system[10] and floating system, by using shells of polymer with lower density than that of the gastrointestinal fluid[11]. Some of the polymers used have bio-adhesive system, where the system adds to the mucus and extended release for 24 hours[12]. Unfortunately, most of these systems have drawbacks. For instance, floating system require the presence of food to

delay their gastric emptying. They also do not always deliver at the intended site[13,14]. In other bio-adhesive systems the delivery system adhesion is a result of electrostatic forces and hydrogen bond formation at the mucus-polymer boundary. The binding is inhibited by an acidic environment and thick mucus present in the stomach[13]. To overcome the above problems the Matrix Embedded Drug Delivery System was selected as the method of choice in this research.

Squillante and Mehta had demonstrated sustained release property of chlophenirmine maleate (CPM) from Eudragit RSPO in soild dispersions method[15]. Acrylic polymer Eudragit® S100, was incorporated into theophylline with various filler excipients and the release rates were studies by Cameron and McGinity[16]. Mainly the incorporation of acrylic polymer Eudragit® S100 and L100 into theophylline and other active ingredients were done using a manufacturing process known as film coating. Here the polymer is dissolved in an organic or aqueous solution with other excipients and sprayed on to the prepared tablets or granule particles of the active drug[17,18].

This paper describe the release behaviour of theophylline from the polymer matrices containing tablets, developing an extented release theophylline formulation, manufacturing and testing the extended release theophylline formulation chemically and clinically (bioequivalence study) The purpose of the bioequivalence study was to compare the bio-availability of extended release theophylline manufactured by SPMC with Neulin SR (3M pharmaceuticals), well prescribed brand.

Experiments

All the materials were used after analysing these for their quality according to the specification of each material. Preparation of the blends was done by simple mixing as per the different experimental tablet formulations that are tabled (table 1). Compression of the tablets was done using selected 8 mm die set (Hata Iron Works, Japan) 42 station tableting machine (Hata Iron Works, Japan) The main pressures, filling depth, machine speed, and feed control adjustments of the machine were adjusted to obtain tablets with the required hardness and other properties[19]. Tablet analysis and the raw material analysis done as per the USP[19,20].

Bioequivalence study. The 20 volunteer subjects, in the study were, healthy males with an average age of 32 years [range 20-51] and an average body mass of 57.9 kg (range 44 to 93 kg). Their blood counts, liver function tests, creatinine and electrolytes were all normal. All subject were not taking any other medication. For 12 hours before the administration theophylline they did not consume xanthenes containing beverages or alcohol and they were fasting. The subjects were allocated randomly into 2 groupd of 10 persons and each group was given 500 mg of either Neulin SR or theophylline ER [SPMC] with 100 water. Breakfast was given 30 minutes after ingestion of the durg to minimize the effect of food on bio-availablity[21]. Blood samples were drawn immediately before and 2,4,6,8,11 and 24 hours after administration of the drug. The samples were centrifuged immediately and the plasma separated and stored at -20^0C till analysis. After a washout period of one week the subjects in the groups were crossed over, and the experiment was repeated.

The concentration of theophylline in serum was determinded by Fluorescence Polarization Immunoassay [FPIA] using a rapid automated Abbot TD_x FL_x analyzer, which had been validated against a high pressure liquid chromatography[19,22].

Results and Discussion

The challenge in developing a theophylline extended release formula is to maintain the therapeutic plasma level of theophylline for over 12 hours. Studying the 'drug release pattern' (dissolution rate) of a tablet by testing enables one to predict the therapeutic effect of the tablet, with relation to time. Different acrylate copolymers sold in the market under the "Eudragit" lable were subjected to experiment. Microcrystalline cellulose and calcium sulphate dihydrate were used as filler excepients. The theophylline release patterns of the different formulations were studies, at 37^0C in phosphate buffers. The theophylline concentration were measured by UV absorption spectroscopy. A careful study of the release patterns of different formulations using Eudragit ® RSPO, a trimenthylammonioethyl methacrylate copolymer and calcium sulphate dehydrate are given bellow, out of which formula FD00M01 conformed with USP 27 dissolution test[20] (Table 1).

Table 1: *The formulations with varied amount of resin and filler excipients per Theophylline Extended Release tablet and their Drug release profiles.*

Name of the Material	Lot No and Amount of Material Per Tablet (%)			
	FD01E01	FD01E04	FD00M01	FD00M02
Theophylline Anhydrous	60.14	60.14	60.14	60.14 ·
Amino Methacrylate copolymer (Eudragit ® RSPO)	0.00	5.00	10.00	15.00
Calciumsulphate Dihydrate (Compacted)	0.00	32.61	27.61	22.61
Micro crystalline cellulose	37.61	0.00	0.00	0.00
Lubricants Mix SPMC 1	2.25	2.250	2.25	2.25
Total Traget weight/Compression wt.	100	100	100	100
Dissolution rates [20]	**Percentage of above tablets dissolved under test (media : Phosphate buffer of pH 4.5)**			
Time and standard % dissolved	FD01E01	FD01E04	FD00M01	FD00M02
1 Hrs (10 - 30%)	100%	32.36%	23.92%	20.53%
2 Hrs (30 - 55%)	-	48%	38.00%	30.93%
4 Hrs (55 - 80%)	-	85%	57.33%	51.00%
8 Hrs (NLT 80%)	-	100%	84.33%	72.66%

The effect of the pH in drug release was tested, and dissolution rates in phosphate buffer media at pH 6.8 and 7.4 were found to be 50% lower than at pH 4.5. When calcium sulphate filler excipients were used dissolution rates were sensitive to the pH of the dissolution media, as mentioned above, showing that there may be additional binding mechanisms, such as pielectron of theophylline to metal cation interactions (ion dipole interaction), as discussed in our previous study[23,24], involved in addition to simple permeability control or hydrophobic charater of polymer. Excellent content uniformity was seen in tablets for all excipients studied. Variation of tablet hardness was minimal and the friability of the tablets was within 0% to 0.2%, which is well within the acceptable range (friability standard to be less than 1%).

The drug release mechanism of the tablet developed, in this study can be described as mainly dissolution rate controlling mechanism though diffusion controlled mechanism could be expected. Recognizing that both mechanisms co-exist in practice, a formula was developed that encompass both of these

mechanisms. In the general dissolution model given in equation (1) diffusivity is expressed by two constants, **a** and **c**, as well as the amount of the retarding agent **x**, that can be used to adjust the dissolution rate.

$$\frac{dQ}{dt} = - A \; \alpha \; D_c$$

Where, Q = amount of the durg involved

dQ/dt = dissolution (drug release) rate of the drug

A = surface area of the tablet

αD_c = diffusion coefficient, described by three parameters where α is a constant and Dc is a function of retarding agent 'X' that expressed percentage and constant 'C'

First, the theoretical formula for dissolution is derived for a spherical tablet and using a set of experimental date. the appropriate from of the exponential decay factor of the diffusivity is examined. Considering the necessity to have suficient sensitivity to the amount of retarding agent present in the tablet the form of the exponential decay factor of the diffusivity coefficient is selected as is given in equation (2).

$$D_c(X, C) = e^{-cx} \qquad\qquad (2)$$

Next, the theoretical formula for a cylindrical tablet is derived and verified by applying a number of experimental data. In order to simplify the model used in the predicted dissolution, an 'equivalent radius', *Er0* concept is employed where the initial volume of a given tablet is represented by a spherical tablet of radius *Er0*. Using cylindrical tablet experiment results, it is shown that a common formula can be used to predict the dissolution rates of both cylindrical and spherical tablets. Finally, it is shown that for a given composition, common constant parameters **C** and **a** can be estimated, for the proposed dissolution rate required from the formula, so that it can adequately describe the dissolution rates of tablets with various amounts of retarding agent as well as the different shapes and initial dimensions.

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The extended release theophylline tablets formulated using formula no. FD00M01 manufacture in the SPMC was tested with innovator brand and a mean peak concentration of 11.5 µg/ml [S.E.M. 2.8] at 6.5 hours and 10.8 µg/ml [S.E.M. 2.3] at 7 hours respectively were obtained for theophylline SR [SPMC] and Neulin SR and. The area under the "plasma concentration verses time curve" [AUC $_{(0-24)}$] were 162.29 µg/ml/h and 150.44 µg/ml/h for theophylline ER [SPMC] and Neulin SR respectively. Graph no. 1 Bioequivalence study of theophaylline of SPMC Manufactured Vs. Neulin SR. Manufactured by 3M, Australia. These values are comparable to those published in the literature[1]. Comparison of peak concentrations and the AUC was carried out using the students paired t - test. The differences were not statistically significant within 90% confidence interval suggesting they are biologically equivalent. The extended release theophylline 125 mg tablets are being manufactured by SPMC and sold to the government.

Graph No: Bioequivalence study of Theophaylline of SPMC Manufactured Vs. Neulin SR, Manufactured by 3M, Australia.

BIO-EQUIVALENCE STUDY OF THEOPHYLLINE
SPMC [T] Vs 3M (Neulin,Australia) [N]
- AVERAGE OF 20 SUBJECTS

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Acknowledgement

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