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Formulation of extended release theophylline tablets – experimental, modelling and bioequivalence studies

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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, and the mathematically modeling of its release.

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 concentrations 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	25-55
4	45-80
8	>75

The drug release mechanism of the tablet developed in this study can be described as mainly a dissolution rate controlling mechanism although a 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, α and C, as well as the amount of the retarding agent X, that can be used to adjust the dissolution rate.

$$\frac{dQ}{dt} = -A\,\alpha\,D_c \qquad (1)$$

Where,

Q = amount of the drug involved

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

A = surface area of the tablet

á Dc = diffusion coefficient, described by three parameters where

á is a constant and Dc is a function of retarding agent 'X' that is expressed as a percentage and a constant 'C'

First, the theoretical formula for dissolution is derived for a spherical tablet and using a set of experimental data, the appropriate form of the exponential decay factor of the diffusivity is examined. Considering the necessity to have sufficient 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).

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

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 the 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 α 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.

This formulation was used to prepare tablets with two different 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.