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Formulation of Extended Release Theophylline Tablets – experimental, modelling and bio-equivalence studies

by

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The work described in this thesis was carried out by me under the supervision of Prof. A. M. Abeysekera (B.Sc., Ph.D.) Department of Chemistry, University of Sri Jayawardenepura

And

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And a report on this thesis has not been submitted in whole or in part to any other University for another degree / Diploma.

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We certify that the above statement made by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation.

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ABBREVIATIONS

BA	bioavailability
bd	twice daily
BE	bioequivalence
tds	three times a day
BP	British Pharmacopoeia
BNF	British National Formulary
cGMP	current Good Manufacturing Practices
CRS	chemical reference standards
Dbc/S	double convex tablet with score market embossed one side
GI	gastro intestine
GIT	gastro intestine tract
EUP	European Pharmacopoeia
Fb/S	Flat bevelled tablet with score market embossed one side
FDA	Food and Drug Administration
HPLC	high performance liquid chromatography
Hr	Hour
Hrs	Hours
IP	Indian Pharmacopoeia
JP	Japanese Pharmacopoeia
min	minute
NLT	not less than
SPC	State Pharmaceuticals Corporation
SPMC	State Pharmaceuticals Manufacturing Corporation
TER	Theophylline Extended Release
WHO	World Health Organisation
USFDA	Unites States Food and Drug Administration

Formulation of Extended Release Theophylline Tablets – experimental, modelling and bioequivalence studies

Kamal Kumara Gamini Mahendranath Parakrama Bandara Herarh

ABSTRACT

The objectives of this research project are to study the release behaviour of theophylline from the polymer matrices containing tablets, to develop an extended release theophylline formulation, to establish quality control standard specifications for the theophylline extended release tablet formulation, to scale-up the formulation for commercial manufacture, to develop a mathematical model to correlate release behaviour with the formulae, to identify the critical processes and to set manufacturing standards to ensure the reproducibility of theophylline extended release tablet formulation, to establish the bioequivalence of the formulation developed with a well prescribed preparation available in the Sri Lankan and international markets, and to market the new formulation commercially.

Extended release pharmaceutical formulations are complex, and are indicated specially in drugs having a narrow therapeutic window and a moderate half-life. The first chapter of this thesis describes studies carried out to understand the drug release behaviour of extended release formulations made from polymer matrices as applicable to theophylline, and the development of a theophylline extended release (modified or sustained release) formulation based on these studies. The selection of appropriate filler excipients was demonstrated to have a significant effect on the drug release properties of theophylline in a tablet matrices containing ammoniomethacrylate copolymer as the retarding agent. Theophylline tablets were manufactured to contain 50 to 94 percent of active ingredient, 15 to 0 percent filler excipient, and 2 to 15 percent matrices. The release rate of the drug was highest when microcrystalline cellulose was used, and slowest when calcium sulphate was used as the filler excipient, which is consistent with other reports[79a,b]. It was observed that when maize starch is incorporated, the tablets disintegrated with high variation in release rates from tablet to tablet. 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 much lower than at pH 4.5. Dissolution rates were higher in acidic media indicating that this is a factor when

calcium sulphate filler excipients are used. When no filler excipients are used dissolution rates were marginally higher or the same in near neutral pH media (pH 6.8 to 7.4 phosphate buffer) compared to the dissolution in acidic media (pH 4.5 phosphate buffer).

Ammoniomethacrylate Copolymer (Eudragit® RS-PO) was selected as the retardant, and three strengths of theophylline extended release formulations were developed; namely 125 mg (paediatric strength), 250 mg and 300mg (adult strengths). The stability of the new formulations were tested under accelerated and ambient conditions for two years, and the shelf life of the packed product was confirmed for two years under ambient tropical conditions in Sri Lanka.

Quality control standards for theophylline extended release tablets were established, for appearance, identification, physical strength, uniformity of dosage form, drug release rate and potency, using the available standards for other similar formulae with slight modifications where appropriate.

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, 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

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

The bio-equivalence study with twenty healthy adult volunteers was conducted with the above-developed formulation, using a reference theophylline sustained release product (Neulin SR 250 mg, manufactured by 3M pharmaceuticals, Australia). Serum theophylline concentrations were measured by fluorescence polarization immunoassay (FPIA). The SPMC-theophylline extended release tablet formulation developed (Manufactured by the State Pharmaceuticals Manufacturing Corporation), demonstrated that there were no significant difference between regimens with respect to bio-availability and pharmacokinetics (AUC, C_{max} & T_{max}) when the test product was compared with the reference product.

The SPMC-theophylline sustained release tablet 125 mg tablet was registered with the Drug Regulatory Authority of Sri Lanka and the first commercial order worth Rs. 50 million received from the Department of Health Supplies, Sri Lanka by winning a World Wide Open competitive tender. This amply demonstrated the commercial viability and marketability of the new product.

In conclusion all the above mentioned objectives were achieved successfully.