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Sustained Release of Theophylline from Eudragit RLPO and RSPO Tablets

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ABSTRACT

Newer polymeric grades of Eudragit, RLPO and RSPO, were explored for their utilities by formulating a sustained-release tablet of theophylline as a model drug. Formulations selected on the basis of their lower polymer content and drug release content, over the period of 12 hr, were compared with the marketed formulation. These were evaluated for dissolution characteristics. In vitro release showed zero-order kinetics ($r = 0.9879$–0.9945; $p < 0.001$). In vivo evaluations were carried out on healthy human volunteers (23 ± 2.68 years old; 48.64 ± 6.31 kg). Dissolution rate constant (k), C_{max}, T_{max}, AUC_{0-12}, AUC_{0-24}, and $t_{1/2}$ were evaluated statistically by two-way ANOVA. Upon t test, a highly significant difference between test products and the marketed product was observed. Wagner–Nelson analysis of the in vivo data revealed controlled-release absorption profiles for selected formulations. Linear regression analysis of the mean % of dose absorbed versus mean in vitro release, resulted in statistically significant correlation. Coefficient of correlation values between AUC_{0-12} and k, and AUC_{0-24} and k were found to be 0.991 ($p < 0.01$) and 0.984 ($0.01 < p < 0.05$), respectively. These data support a level-A correlation between in vitro release rate profiles and the in vivo absorptions for theophylline.

INTRODUCTION

Theophylline is widely used as a bronchodialator for the treatment of asthma or obstructive pulmonary diseases. This effect of theophylline increases with serum concentration levels over a range of 5–20 μg/ml, but at levels of 20 μg/ml there is increased risk of serious toxicity. Maximum bronchodialation with minimum toxicity occurs at levels between 10 and 20 μg/ml (1–3). A sustained-release form is desirable because of its narrow range of effective blood concentration and short elimination half-life in human (4). In the present study, in

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order to control the release of theophylline from a controlled-release tablet, the newer polymeric grades of Eudragit—RLPO and RSPO—were explored by changing their contents in the tablets. To evaluate body fluid level profiles of theophylline in volunteers, saliva levels were measured (5).

EXPERIMENTAL

Materials

Theophylline I.P (Warner-Hindustan, Hyderabed; Nicholas Laboratories, Bombay)
Eudragit RLPO and Eudragit RSPO (Rohm Pharma, Germany)

All solvents and reagents used were of AnalaR grade.

Methods

Preparation of Matrices and Tablets

Theophylline (321 mg/tablet), polymer, and diluents were blended in dry form and granulated using acetone. Eudragit RLPO and RSPO (8–10% w/w) along with dicalcium phosphate/polyvinyl pyrrolidone (when required) were used in the formulations. A 20/40 fraction of granules was lubricated using 2% w/w talc and 1% w/w magnesium stearate, and compressed on a Cadmach single-stroke, single-punch machine at a constant pressure. Tablets thus prepared were subjected to the tests for weight variation, hardness, friability, drug content, and drug content uniformity, by standard methods.

Evaluation of Tablets

In Vitro Dissolution Studies

The in vitro dissolution profile of each prepared formulation and the marketed formulation taken was determined on a USP XIX dissolution apparatus. The dissolution media consisted of 1000 ml of standard buffer of pH 1.2 for the first 2 hr, followed by pH 4.6 for the next 2 hr, and pH 7.2 for the remaining period of time. The temperature of the medium was maintained at 37 ± 1°C. The speed of rotation of basket was 100 rpm. Aliquots were withdrawn at 1-hr intervals, for a total of 12 hr and analyzed on Beckman UV-Vis spectrophotometer, model 34, at 274 nm. The amount of drug released was calculated using standard curve (r = 0.9929–0.9989; $p < 0.001$). The sample so withdrawn was replenished with fresh medium maintained at the same temperature. The dissolution characteristics of each formulation were studied, after accounting for the loss in the initial concentration of theophylline, while changing the buffer. The dissolution characteristics, namely dissolution rate constant and coefficient of correlation, of selected formulations were determined and were also evaluated statistically.

In Vivo Studies

In vivo evaluations of the successful formulations and the marketed formulation were carried out by estimating the saliva theophylline level for a period of 12 hr and 24 hr, following a latin square design. Eight healthy human volunteers with a mean age of 23 ± 2.68 years and a mean weight of 48.64 ± 6.31 kg were selected. None of the subjects had GIT disorders, viz. ulceration, diarrhea, anorexia, etc. Use of other drugs, alcoholic beverages, caffeine-containing beverages, and smoking were not allowed for 48 hr prior to and during the period of study.

Before administration of the tablet 250 ml of water was given to each volunteer. Saliva secretion was induced by placing a few crystals of citric acid in the mouth. After administration of tablet, minimum 2 ml of saliva was collected predose and at 1-hr intervals for a period of 12 hr postdosing and at the end of 24 hr. The withdrawn samples were stored in well-closed test tubes under refrigeration. Salivary theophylline level was measured by the method suggested by Shah and Riegelman (5). The standard curve (r = 0.9976; $p < 0.001$) for theophylline was plotted with the same method. The plasma concentration of theophylline was calculated from the saliva theophylline concentration by the method of Koysooko et al. (6).

The pharmacokinetic parameters, namely, area under the plasma concentration curve (AUC), maximum plasma concentration (C_{max}), time taken to reach the peak plasma concentration (T_{max}), and elimination half-life ($t_{1/2}$) were calculated for test products A–D and tabulated. AUC was computed using the trapezoidal rule.

Statistical Analysis

Pharmacokinetic parameters were analyzed using two-way ANOVA (analysis of variance). The differences between the plasma theophylline concentrations for test products A–D were examined for their significance using the t test (7).

In Vitro/In Vivo Data Analysis

In vitro/in vivo correlation is a functional or qualitative relationship between in vitro dissolution and in vivo bioavailability parameters. In vitro dissolution is used as a quality control tool and a surrogate for bioavailability, bioequivalence. In vitro/in vivo correlation for the selected data was established by utilizing the plasma level profile and the dissolution profile level-A correlation (8–10).

In vitro dissolution rate constant data were correlated with in vivo parameters, namely C_{max}, T_{max}, AUC, and $t_{1/2}$. Further, in vitro percent dose released was correlated with in vivo percent dose absorbed. Absorption profiles of drug were evaluated for each subject using the Wagner-Nelson function.

$$\% \text{ dose absored} = \frac{C_{(t)} + K_e \cdot AUC_{(t)}}{K_e \cdot AUC_{(I)}}$$

$$AUC_{(I)} = AUC_{(t)} + C_{(t)}/K_e$$

where K_e is the elimination rate constant calculated as the negative slope of the log-linear terminal phase of the plasma concentration–time curve; $AUC_{(t)}$ and $AUC_{(I)}$ are cumulative area under the plasma concentration–time curves from zero to time t and zero to infinity, respectively, and C_t denotes the concentration of drug at time t.

RESULTS AND DISCUSSION

Among the various Eudragit-based theophylline formulations tried, those prepared with 9% w/w Eudragit RLPO, 9% w/w Eudragit RSPO, and 8% w/w Eudragit RLPO + 5% w/w PVP could satisfactorily retard the release to give the desired drug release pattern (Fig. 1).

From the in vitro dissolution profile data, kinetics of drug release was found for zero-order, first-order, and Higuchi matrix type release. The coefficient of correlation of each of these release kinetics was calculated and compared (Table 1). Data revealed that the release patterns of test products (A–D) are best fitted for zero-order release kinetics as their coefficient of correlation values predominate over first-order and Higuchi matrix type release kinetics. A significant linear correlation (r = 0.9879–0.9945; $p < 0.001$) is found for zero-order release kinetics.

Dissolution rate constant was calculated for all the four test products and compared (Table 1). In order to determine whether the four sets of in vitro dissolution profile data of test products are same or they differ from each other, two-way ANOVA was employed. Dissolution rate constant data showed a significant difference (Table 1) between test products ($p < 0.01$), but within test products, no significant difference was observed ($p > 0.05$), indicating that the four sets of data differ significantly. Hence, it may be inferred that the test products are not same but are different in their formulations.

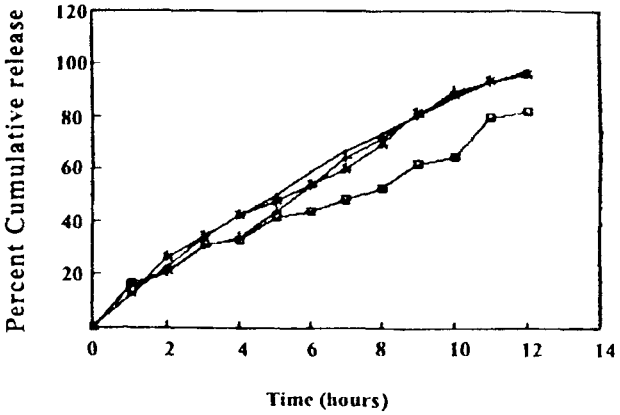

Figure 1. Dissolution profiles of thephylline sustained-release formulations (-●-, A; -+-, B; -*-, C; -□-, D).

The in vivo studies in human volunteers revealed that the prepared formulations exhibited an extended release pattern for a period of 12 hr. The data revealed that the formulations made were better than the marketed product (D) of theophylline with respect to their T_{max}, AUC_{0-12}, AUC_{0-24} (Table 2), and their period of sustaining the plasma concentration of drug. The mean plasma concentration versus time profiles of the four test products (A–D) are depicted in Fig. 2. The prepared formulations (A–C) and the marketed formulation (D) showed sustained plasma drug concentration level for 19 hr and 10.5 hr, respectively at the therapeutic range (5 μg/ml). The desired concentration of plasma level (10 μg/ml) was attained in the test products A, B, C, and D at 4.4, 4.0, 3.5, and 4.7 hr, respectively. Comparing with the marketed formulation, the data revealed that the values for T_{max}, AUC_{0-12}, and AUC_{0-24} were less in case of the marketed formulation. On the basis of AUC_{0-12} and AUC_{0-24} (Table 2), the four test products could be rated as B > A > C > D. C_{max} and $t_{1/2}$ values of these test products were found more or less the same, with a small

Table 1

Dissolution Characteristics of Selected Formulations

Test Products[a]	Coefficient of Correlation: First-Order	Higuchi Matrix Type	Zero-Order	Dissolution Rate Constant (k)[b]
A	0.9816	0.9802	0.9932	0.1217 (1.13%)
B	0.9728	0.9668	0.9945	0.1204 (1.11%)
C	0.9773	0.9829	0.9890	0.1231 (1.94%)
D	0.9568	0.9698	0.9879	0.1573 (0.36%)
Level of significance[c]			$p < 0.001$ HS	
ANOVA, two way[c]				$p < 0.01$ HS

[a]A: 9% w/w Eudragit RLPO; B: 9% w/w Eudragit RSPO; C: 8% w/w Eudragit RLPO + 5% w/w PVP; D: Marketed.
[b]Values in parentheses indicate % CV.
[c]HS = highly significant.

difference (Table 2). The mean values of half-life obtained after administration of these test products was found to be 10.05–10.84 hr ($n = 8$), which is in agreement with several reports given in the literature (11,12).

Upon statistical evaluation (two-way ANOVA), C_{max} data did not show a significant difference within and between test products ($p > 0.05$). The T_{max} data showed a significant difference between test products ($p < 0.01$) but not within test product ($p > 0.05$). AUC_{0-12} and AUC_{0-24} data showed a significant difference ($p < 0.01$) between test products but not within test products ($p > 0.05$). Also, $t_{1/2}$ data did not show a significant difference ($p > 0.05$) between and within test products (Table 2). The t-test data revealed that the formulations made with the different grades and concentrations of Eudragit differ significantly, when compared with the marketed product (D) (Table 2).

No significant in vitro/in vivo correlation was observed when in vitro dissolution rate constant (k) data of test products A–D were correlated with C_{max} and T_{max} data; but a good correlation was observed when k values were correlated with AUC_{0-12} ($r = 0.991$; $p < 0.01$), AUC_{0-24} ($r = 0.984$; $0.01 < p < 0.05$), and $t_{1/2}$ ($r = 0.957$; $p < 0.05$). Further, a higher correlation was observed between percentage of dose absorbed and percentage of dose released. The corresponding regression parameters are summarized in Table 3. These data indicate a good correlation for test products A–C and not for test product D. The slopes of the regression line for test products A–C were similar, with a relative stan-

Table 2

Pharmacokinetic Characteristics of Test Products of Theophylline

Test Products	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-12} (μg·hr/ml)	AUC_{0-24} μg·hr/ml)	$t_{1/2}$ (hr)
A**	11.365 (4.47%)	7.75 (5.58%)	109.288 (4.11%)	180.489 (5.93%)	10.56 (8.78%)
B**	11.178 (4.14%)	7.75 (5.58%)	109.723 (4.43%)	184.710 (5.35%)	10.84 (11.28%)
C*	11.581 (7.94%)	6.25 (6.92%)	104.590 (4.92%)	170.546 (6.45%)	10.63 (13.27%)
D	11.589 (6.61%)	5.75 (7.53%)	83.484 (5.02%)	124.790 (4.75%)	10.05 (14.61%)
ANOVA (two way)	$p > 0.05$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p > 0.05$

Note. Student's t test: **$p < 0.05$, *$p < 0.1$, two-tailed (**$p = 0.025$, *$p = 0.05$, one-tailed; statistically significantly greater) when compared to D. Values in parentheses indicate % CV.

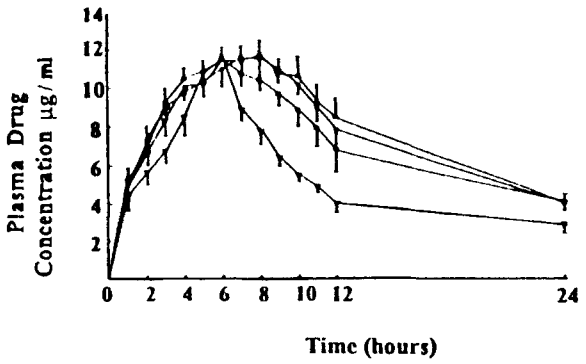

Figure 2. Plasma profiles of theophylline in 8 human volunteers following oral administration (-○-, A; -●-, B; -Δ-, C; -▲-, D).

dard deviation of 6.59% (Table 3). The slopes reported suggest that the theophylline in vivo absorption rate was slower than the observed in vitro release rate. However, high correlation coefficients indicate that in vivo absorption profiles of test products (A–C) are correlated with in vitro release profiles. The observed negative intercepts are due to the absorption lag time noted following oral administration of controlled-release dosage forms (9).

CONCLUSIONS

The test products (A–C) prepared were found better than the marketed formulation taken (D) in their in vitro dissolution and pharmacokinetic characteristics. The in vitro/in vivo correlations of these test products were also observed to be statistically significant. Further, amounts of drug released versus time data (r = 0.9879–0.9945; $p < 0.001$) were found to be linear, indicating a slow and controlled release of drug, thus supporting the finding that test products A–C are suitable for controlled-release formulations. In conclusion, our study has shown that the prepared test products are better than the marketed theophylline formulation studied, and have a sustained release profile.

Table 3

In Vivo/In Vitro *Regression Parameters for Test Products Obtained by Linear Regression Analysis*

Test Product	Slope	Intercept	r	p Value
A	1.169	-35.029	0.9296	0.001
B	1.113	-32.254	0.9119	0.001
C	1.025	29.447	0.774	0.01
D	0.416	11.474	0.494	0.1
Mean (A-C)	1.103			
% CV	6.59			

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