Research Article

In vivo Evaluation of Theophylline Sustained Release Matrix Tablets containing Low Viscosity Guar Gum

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ABSTRACT

The present investigation was carried out to evaluate the utility of guar gum as a hydrophilic matrix carrier in the design of oral controlled drug delivery. Based on the earlier reports, the low viscosity guar gum appears to be superior to medium and high viscosity grades of guar gum in providing a sustained delivery of theophylline along the GI tract. Conducting *in vivo* studies on theophylline matrix tablets containing 10% of low viscosity guar gum as a representative formulation assessed the *in vivo* performance of the guar gum matrix tablets. The *in vivo* studies were carried out in dogs. The effective concentration of theophylline was sustained for a period of 16 hours. The extended tmax, reduced absorption rate constant, prolonged MRT, unchanged Cmax and unchanged bioavailability indicate a controlled release of theophylline from the guar gum matrix tablets resulting in a sustained absorption and prolonged blood levels of theophylline. The theophylline matrix tablets showed blood levels well below 15 µg/mL indicating freedom from adverse effects. Based on the studies, guar gum appears to be a potential carrier in the design of oral controlled drug delivery systems.

Keywords: *In Vivo* Studies, Sustained release, Hydrophilic matrix tablets, Theophylline, Low Viscosity Guar gum, Dog model.

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INTRODUCTION

Theophylline is used in the treatment of asthma. The bronchodilator effect of theophylline increases in the concentration range of 5 to 20 µg/mL. Adverse effects like hypotension, nausea and vomiting are observed above 15 µg/mL. Hence the effective concentration is optimized in the range of 5 to 15 µg/mL[1]. Between 20 and 40 µg/mL, cardiac arrhythmia and seizures are seen, while theophylline concentrations above 40 µg/mL can produce cardiorespiratory arrest[2]. The drug therefore shows a well-defined "therapeutic window". The biological half-life of theophylline ranges from 6.9 to 11.1 h[1]. These features make theophylline a popular model drug to be formulated into sustained release oral dosage form.

Number of hydrophilic polymers are being used in the design of sustained release dosage forms[3,4]. The efficiency of the hydrophilic matrix in controlling the drug release in addition to other factors, is dependent on the viscosity of such hydrophilic polymers incorporated in the formulation[5,6,7]. Hence, various viscosity grades of guar gum were evaluated for the oral controlled drug release from the theophylline matrix tablets using in vitro dissolution studies. The results indicated that a minimum of either 10% low-viscosity (TLV-10), 20% medium-viscosity (TMV-20) or 20% high-viscosity (THV-20) guar gum provided better controlled drug release rates compared with commercial sustained release theophylline tablets[8]. Since guar gum is a colon-specific drug carrier[9], the influence of colonic bacterial enzymes on guar gum matrix tablets TLV-10, TMV-20 and THV-20 was studied by carrying out in vitro drug release studies in simulated colonic conditions (rat caecal content medium).

The matrix formulation TLV-10 was found intact up to 8 hours and released about 50% of the drug. At the end of 12 hours of testing, TLV-10 was acted upon by the colonic bacterial enzymes, and was broken into four pieces releasing another 37% of the drug. Between 12 to 24 hours, the matrix formulation TLV-10 released the remaining drug in simulated colonic conditions. The other formulations TMV-20 and THV-20 were broken down quickly by the action of colonic bacterial enzymes, thereby releasing about 90% of the drug within 12 hours giving little scope for sustained absorption. However, the relative performance of the guar gum matrix formulation, would be known when subjected to in vivo performance in either human volunteers or animal models.

The present study is carried out to find the in vivo performance of theophylline matrix tablets containing 10% of low-viscosity guar gum (TLV-10 formulation) in dogs. An immediate release theophylline tablet (CT) was formulated and used as a control to compare the pharmacokinetic behavior of theophylline from immediate release formulation with that of the guar gum matrix tablets (TLV-

10). Pharmacokinetic evaluation was carried out on (1) theophylline matrix tablets containing 200 mg of theophylline and 10% w/w low-viscosity guar gum (TLV-10) and (2) conventional immediate release theophylline tablets containing 100 mg of theophylline (CT) in dogs (n=5) as per the following methodology.

METHODOLOGY

A cross-over design was followed in which dogs (n=5) received conventional immediate release theophylline tablets (CT) and theophylline guar gum matrix tablets (TLV-10) at different occasions with a wash out period of 14 days. The dogs were divided into two groups, one containing three and the other containing two. On day 1, three dogs were administered orally the conventional immediate release theophylline tablets (CT) and remaining two were administered TLV-10 tablets. After a washout period of 14 days, the dogs received conventional tablets (CT) were administered with TLV-10 and those that received TLV-10 were administered with conventional theophylline tablets (CT).

Protocol of the Study

The dogs weighing between 8.25 to 12 kg of either sex were used. They were fed on uniform diet. During the experiments, dogs were fasted overnight. Fasting was continued until 4 h post oral dose, but water intake was not restricted. The procedure of the Institutional Animal Ethics committee was strictly followed on the care and use of the animals in the present study as per the guidelines of CPCSEA, New Delhi.

After collecting the zero hour blood sample (blank), the product involved in the study was administered orally. Blood samples (2 mL) were withdrawn from the cephalin or femoral vein at different time intervals and were collected in sample tubes containing trisodium citrate. The blood samples were thoroughly mixed, centrifuged at 3,000 rpm and the plasma was separated. The plasma samples were transferred into dry screw capped tubes and stored at -20˚C until analysis. Theophylline content of the plasma samples was determined by HPLC method as described below.

HPLC Method for the estimation of Theophylline in Plasma

A UV Spectrophotometric method[10,11,12] was more frequently used for the determination of theophylline in plasma. The sensitivity of this method is good but is subjected to interference with theophylline metabolites. GC methods may require derivatization of theophylline prior to analysis[13]. For this reason, a high pressure liquid chromatography method was selected owing to its attributes like accuracy, simplicity, specificity, sensitivity, reliability and reproducibility. It also provides rapid analysis with minimum amount of sample. Various HPLC methods for estimating theophylline were reported[14,15,16]. The method reported by Iwase[17] was used in the present study with a slight modification.

Construction of standard graph for the estimation of Theophylline by HPLC in plasma

Materials: Theophylline was obtained from M/s. Astra-IDL Limited, Bangalore, India; Etophylline was obtained from M/s. ICI Pharmaceuticals, Chennai, India. HPLC grade Acetonitrile, Triple Distilled Water were obtained from Qualigen fine Chemicals, Mumbai, India.

Apparatus: A gradient High Pressure Liquid Chromatograph (Shimadzu HPLC Class VP series) with two LC-10AT VP pumps, variable wave length programmable UV/VIS detector SPD-10A VP and RP C-18 column (250 mm × 4.6 mm I.D.) packed with 5 µm was used.

Preparation of stock solution of Internal standard: Etophylline was used as internal standard for the estimation of theophylline by HPLC. About 125 mg of Etophylline was accurately weighed, transferred to 25 mL volumetric flask, dissolved in triple distilled water (TD water) and made upto volume with TD water to give a stock solution of 5000 µg/mL (Stock-I). One milliliter of this stock solution was diluted to 100 mL with TD water to give 50 µg/mL solution (Stock-II). One hundred microliters of Stock-II solution representing 5 µg is added to either blank plasma or the plasma sample obtained in the *in vivo* study.

Preparation of stock solutions of theophylline: About 125 mg of theophylline was accurately weighed and transferred to 50 mL volumetric flask. It was dissolved in TD water on slight warming and the solution was made upto volume with TD water. Each milliliter of this stock solution (Stock-I) contained 2500 µg. One milliliter of stock-I solution (2500 µg) was diluted to 100 mL with TD water to give a stock solution containing 25 µg/mL (Stock-II). From Stock-II, 0.02, 0.04, 0.08, 0.16, 0.4 or 0.8 mL of solution representing 0.5, 1, 2, 4, 10 and 20 µg of theophylline respectively were added to 0.3 mL of plasma containing 5 µg of internal standard (Etophylline).

Procedure: The blank plasma was taken in a series of test tubes. Theophylline solutions representing 0.5 to 20 µg were added to the above series of test tubes along with 100 µL (5 µg) of Internal Standard (Etophylline) using Hamilton syringes. These plasma samples containing varying amount of theophylline and a fixed amount of internal standard (5 µg) were treated for their extraction as per the method described by Leonard[18]. The procedure involved the addition of 4 mL of a mixture of chloroform and isopropanol (1:1) to each of the plasma sample. These samples were vortexed and allowed to stand for the separation of organic and aqueous layers. Then 2 mL of the organic phase from each sample were transferred into clean test tubes and evaporated to dryness. These dried samples were reconstituted with 1 mL of mobile phase (10% of Acetonitrile and 90% of TD water) and filtered through 0.2 µ membrane filter medium using syringe filter (diameter 10 mm). Twenty microliters of each of the filtered solution were injected in duplicate into the column under the following chromatographic conditions.

HPLC conditions:

Column : C-18 RP (ODS-A) 250 × 4.6 mm I.D. packed with 5 µm

Mobile Phase : Acetonitrile : TD water (10:90)

Flow rate : 1.4 mL/min

Injection volume : 20 µL

Detector : UV–VIS spectrophotometer detector at 280 nm

The column pressure varied from 220 to 225 kgf. The retention times for theophylline and internal standard were 6.91 and 8.55 min respectively. The retention times of both theophylline and internal standard were almost uniform and the coefficient of variation was less than 0.2%. A model chromatogram is shown in Fig. 1. The ratio of peak area of theophylline to peak area of internal standard for different concentrations set up as above were calculated and the average values for 6 such determinations are shown in Fig. 2. The coefficient of variation within the 6 replicates of samples, interday and intraday determinations were found less than 1% indicating the reproducibility of the method.

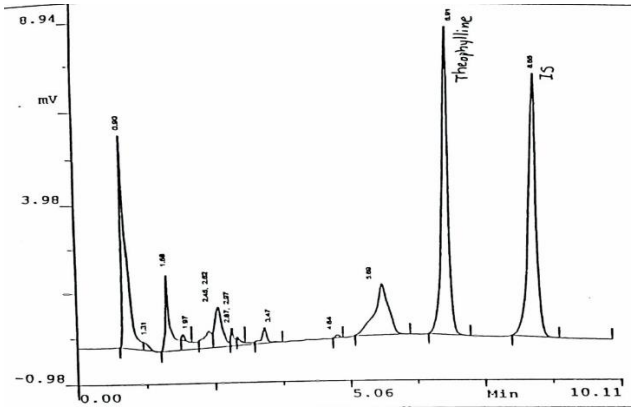

Figure 1: A Model chromatogram for the HPLC estimation of theophylline using etophylline as internal standard (IS)

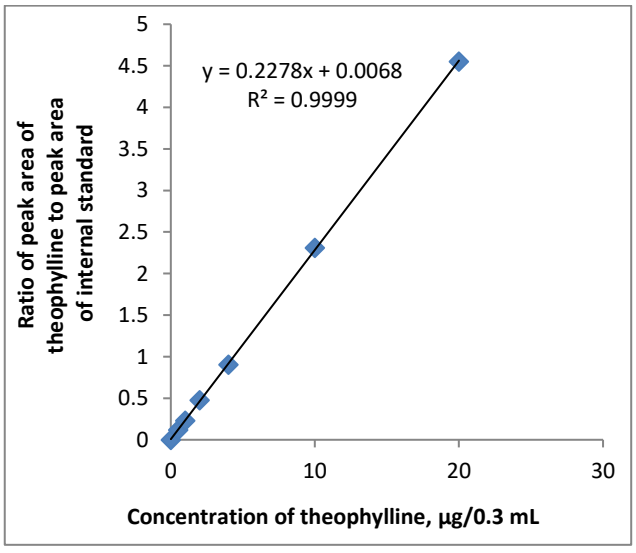

Figure 2: Standard graph for the HPLC estimation of theophylline in plasma

A perfect linear relationship (r = 0.9999) was observed when a graph was plotted between the plasma concentration of theophylline and the ratio of peak areas (Fig. 2). The detection limit was found to be 0.5 µg and the linearity was observed in the concentration range of 0.5 to 20 µg/0.3 mL.

Pharmacokinetic Analysis: The peak serum theophylline concentration (C_{max}) and the time to reach peak levels (t_{max}) were obtained from the experimental data. The other pharmacokinetic parameters were calculated using a computer program based on the following equations[19].

1. Absorption rate constant(k_a): Assuming first order kinetics, k_a was obtained using the equation:

$$k_a = 4.61/t_a$$

Where t_a is the absorption time obtained from a semi-logarithmic plot of concentration versus time data. This equation is based on the assumption that at time zero upon extravascular administration 100% is unabsorbed, and that at the time that the actual blood level time curve after the peak is just distinguishable before entering the distribution phase or the terminal phase, only 1% is unabsorbed[20].

2. Half-life ($t_{1/2}$): The overall elimination rate constant (k_e) was calculated from the slope of the terminal elimination phase of a semi-logarithmic plot of concentration versus time, after subjecting it to linear regression analysis. Assuming the elimination to be a first-order process:

$$t_{1/2} = 0.693/k_e \text{ where } k_e = \text{-slope}$$

3. Area under the concentration versus time curve (AUC): The AUC extended to infinity, which represents the extent of bioavailability of a drug, was calculated by means of the trapezoidal rule:

$AUC_{0-\infty} = AUC_{0-t} + c/k_e$, where c is the serum theophylline concentration at the last time point 't'.

4. Area under the first moment curve (AUMC) was also computed by the trapezoidal rule, and was the area under the curve resulting from plotting the product of serum concentration and time versus time:

$$AUMC_{0-\infty} = AUMC_{0-t} + [c_t/k_e + C/k_e^2] \text{ µg.h}^2\text{/mL}$$

5. Mean residence time (MRT) which represents the time for 63.2% of the administered dose to be eliminated was the statistical moment analog of $t_{1/2}$

$$MRT = AUMC/AUC$$

6. Apparent volume of distribution (V_d) was calculated using the equation

$$V_d = (f \times dose)/[(K_e \times AUC_{0-\infty}) \times body\ weight] \text{ mL/kg}$$

where f is the fraction of dose absorbed, which is taken as 0.8 for theophylline in dogs[21].

7. Systemic clearance (CL) was obtained using the relation

$$CL = (f \times dose)/(AUC_{0-\infty} \times body\ weight) \text{ mL/h/kg}$$

Statistical Analysis

Since the same group of dogs received both the immediate release form (CT) and sustained release matrix tablet (TLV-10) of theophylline, a paired t-test is used to test the significance of difference in pharmacokinetic parameters. A value of $p<0.05$ is considered statistically significant in the pharmacokinetic parameters.

RESULTS AND DISCUSSION

Theophylline was administered at a dose of 100 mg only as immediate release tablet to avoid the possible adverse effects. The average plasma levels of theophylline following oral administration of sustained release theophylline matrix tablets (dose 200 mg) containing 10% low-viscosity guar gum (TLV-10) and conventional immediate release (IR) tablets (dose 100 mg) of theophylline (CT) are shown in Fig. 3. With the conventional IR tablets of theophylline, the minimum effective plasma theophylline levels (5.0 µg/mL) were attained within half an hour, and were maintained for a period of 6.5 h. In case of guar gum matrix tablets (TLV-10), the effective therapeutic plasma theophylline levels were attained after an initial lag period of 2 to 4 h and were sustained for a period of 16 h. Time to reach maximum drug concentration (t_{max}) for theophylline matrix tablets (TLV-10) was 6.24 ± 1.28 h and the peak concentration (C_{max}) at that time was 11.54 ± 1.21 µg/mL.

The mean C_{max} values obtained following ingestion of conventional IR theophylline tablets and guar gum matrix tablets of theophylline were not significantly different ($p>0.05$) in spite of the larger dose of theophylline present in the guar gum matrix tablets (Table 1). The mean t_{max} value after administration of conventional tablets was 1.16 ± 0.22 h which was significantly different ($p<0.05$) from the t_{max} of 6.24 ± 1.28 h for guar gum matrix tablets of theophylline. Thus, the results of the *in vivo* study in the dog model indicate that the drug release from the matrix tablets is slow, providing a prolonged delivery of the drug. The lag time in t_{max} might be due to the low amount of drug released from the surface of the matrix tablets in the initial periods. This is not a serious concern on the benefit of the guar gum matrix formulation in providing quick therapeutic response. The administration of the subsequent doses of the guar gum matrix tablets provides quick response and prolonged therapeutic drug concentrations. However, *in vivo* studies involving multiple doses of guar gum matrix tablets would reveal a better information.

The area under the plasma theophylline concentration versus time curves ($AUC_{0-\infty}$) for the conventional and guar gum matrix tablets of theophylline were 94.90 ± 27.12 and 213.34 ± 57.13 µg/mL/h respectively and were significantly different ($p<0.05$) from each other. The dose contained in matrix formulation is twice that contained in conventional IR tablet and hence the AUC obtained from matrix formulation is significantly different from conventional tablet.

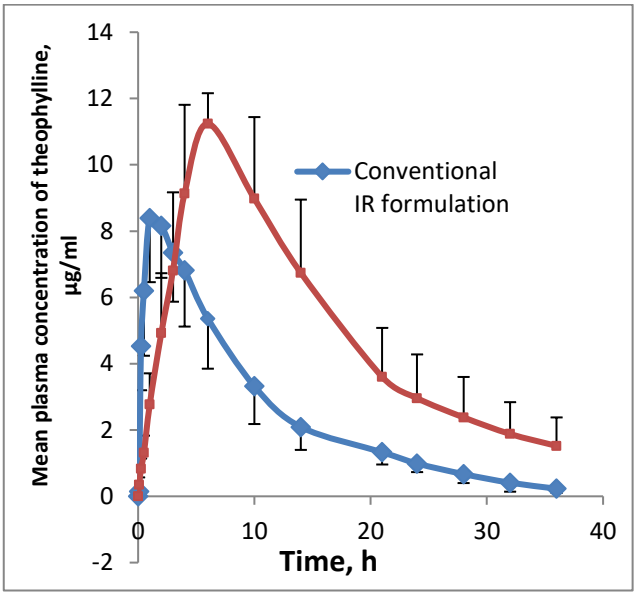

Figure 3: Mean theophylline concentrations (±S.D.) as a function of time in plasma obtained in dogs (n=5) following oral administration of conventional tablets(CT) and guar gum matrix tablets (TLV-10)

The mean relative bioavailability of theophylline from guar gum matrix tablets when compared to conventional tablets is 113.45 ± 7.53% (corrected to dose administered). This indicates that theophylline on being slowly released from the formulation might be completely absorbed resulting in a slightly higher extent of bioavailability. The conventional formulation, on fast disintegration followed by fast dissolution might be passing quickly along the GI tract giving absorption of drug which maintained therapeutic level for 6.5 h.

The mean elimination half-life for theophylline following oral ingestion of conventional and guar gum matrix tablets were 7.16 ± 2.33 and 12.28 ± 4.09 h respectively which are significantly different ($p<0.05$). Thus, the prolonged $t_{1/2}$ is another important indication on the in vivo performance of the guar gum matrix tablets. The slow and prolonged release of the drug from the matrix tablets might have resulted in slow and prolonged absorption of theophylline. This, in turn, resulted in controlled and prolonged drug concentration in the blood. Thus, the elimination half-life after oral administration is prolonged (Table 1).

Theophylline clearance was found to be 85.86 ± 28.55 and 75.07 ± 21.40 mL/h/kg following ingestion of conventional and guar gum matrix tablets respectively. These clearance values were significantly different ($p<0.05$) from each other. The mean MRT values obtained for immediate release and guar gum matrix tablets were 10.48 ± 1.71 and 18.29 ± 5.94 h respectively. A statistically significant difference ($p<0.05$) was obtained between the MRT values of the two formulations. Both $t_{1/2}$ and MRT are independent of the dose administered. The apparent volume of distribution for theophylline following ingestion of conventional tablets of theophylline was 814.66 ± 130.81 mL/kg. This was not significantly different ($p>0.05$) from 1256.33 ± 270.20 mL/kg obtained from the guar gum

matrix tablets. This indicates that prolonged blood levels are not due to difference in distribution of the drug in the body. Theophylline produces adverse effects like nausea and vomiting when the blood levels are above 15 µg/mL. All guar gum matrix tablets showed blood levels well below 15 µg/mL indicating freedom from adverse effects.

Table 1: Mean (± S.D.) Pharmacokinetic parameters of Theophylline in dogs (n=5) administered with conventional IR tablets containing 100 mg of theophylline (CT) and theophylline matrix tablets containing 200 mg of theophylline and 10% low-viscosity guar gum (TLV-10)

Pharmacokinetic parameters	In dogs orally administered with		P
	Immediate Release Formulation (CT) (100 mg)	Matrix Formulation (TLV-10) (200 mg)	
$AUC_{0-\infty}$ (µg/mL/h)	94.90 ± 27.12	213.34 ± 57.13	0.001
$AUMC_{0-\infty}$ (µg/mL/h)	1020.05 ± 388.37	4133.14 ± 2199.73	0.0197
Relative Bioavailability (%)	----	113.45 ± 7.53	----
Terminal Half-life (h)	7.16 ± 2.33	12.28 ± 4.09	0.041
MAT (h)	1.36 ± 0.48	6.22 ± 1.79	0.0048
Absorption rate constant (1/h)	3.84 ± 1.61	0.80 ± 0.27	0.0165
Clearance (mL/h/kg)	85.86 ± 28.55	75.07 ± 21.40	0.0492
Vol (area) (mL/kg)	814.66 ± 130.81	1256.33 ± 270.20	0.0615
MRT (h)	10.48 ± 1.71	18.29 ± 5.94	0.0218
T_{max} (h)	1.16 ± 0.22	6.24 ± 1.28	0.00134
C_{max} (µg/mL)	8.53 ± 1.71	11.54 ± 1.21	0.0522

The duration of therapeutic action as per the blood levels of theophylline (Fig. 3) from matrix tablets is 16 h and from conventional tablets, it is 6.5 h indicating that the guar gum matrix tablets are more effective than conventional tablets. One possible argument for such difference is that theophylline dose contained in matrix tablet. In spite of the higher dose, it appears that matrix tablets released the drug slowly for prolonged time providing prolonged therapeutic action for 16 hours.

The in vivo evaluation of guar gum theophylline matrix tablets in dog model showed delayed t_{max}, unaltered C_{max} and bioavailability, and prolonged $t_{1/2}$, MRT and MAT indicating a slow and prolonged release of theophylline from guar gum matrix tablets.

CONCLUSION

The results of the investigation indicated that guar gum may be useful in the form of hydrophilic matrix carrier for the design of oral controlled drug delivery systems. The in vivo performance of guar gum matrix tablets of theophylline is to be studied in human volunteers/patients by pharmaco-scintigraphy to get more information on the clinical utility of guar gum as a hydrophilic matrix carrier.

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