
Guar Gum as a Hydrophilic Matrix for Preparation of Theophylline Controlled-Release Dosage Form

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Compressed tablets were prepared from theophylline and guar gum. Effect of the viscosity grade of the polymer and polymer content in the tablets on release pattern of theophylline was examined *in vitro*. Release rate was retarded with increase in polymer content as well as the viscosity grade of polymer. Dissolution profile was independent of pH, while the compression pressure had only marginal effect on release pattern. *In vivo* crossover study with twelve human volunteers following oral administration, shown that guar gum formulation of theophylline is bioequivalent with the marketed product Theodur.

Commercially available water soluble cellulose derivatives¹ are generally considered to be stable and safe for development of sustained release tablets. These cellulose derivatives (methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose and sodium carboxymethylcellulose) are quite expensive as compared to noncellulose derivatives such as glactomannans, for example guar gum, alginates and agar. An attempt has been made to evaluate guar gum for sustained release tablet preparation. Guar gum is stable over a wide pH range and the non-ionic nature of the molecule is responsible for the almost constant viscosity of its solutions in the pH range 1-10.5². Nakano *et al.*³ evaluated different viscosity grades of guar gum for screening and optimising various physical parameters for development of sustained release tablets of theophylline.

In the present study, guar gum was used to prepare sustained release formulations of theophylline, which has a short elimination half-life and variable bioavailability and is a suitable candidate for sustained release.

MATERIALS AND METHODS

Three viscosity grades of guar gum (1500 cps LV/2500 cps MV/4000 cps HV viscosity of Dabur, India) were

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used. Theophylline I.P. was procured from Bakul Chem. India. The excipient materials like, starch, lactose, talc and magnesium stearate of USP grade were used. All other chemicals were of I.P. grade.

Preparation of Tablets

Appropriate quantities of theophylline, starch and guar gum were weighed and sifted through # 60 mesh. These were mixed using a laboratory model planetary mixer. The blend was granulated with guar gum paste (2 %) and dried in a fluid bed dryer (FBD) at 50-60° for 20-25 min. The semi-dried granules were passed through # 16 mesh using an oscillating granulator. These granules were further dried to have loss on drying in the range of 4-5% w/w. The dried granules were sifted through # 20 mesh. Talc (2 %) and magnesium stearate (1 %) were sifted through # 60 mesh and mixed with dried granules. The lubricated granules were then compressed to 13.0 mm flat faced tablets using single station tablet press (Allied Engg. India) by applying different compression pressure.

Drug Release Studies

Six tablets from each batch were taken for evaluating dissolution rate in three different dissolution media at

100 rpm using 900 ml of medium at $37 \pm 1^\circ$. Dissolution test apparatus (Vanderkamp 600, USA) was used for these studies using basket (type 1). At predetermined intervals, 2 ml portion of the medium was pipetted out for HPLC (Shimadzu, Japan) with 2 nm x 30 cm column containing packing L1 for determination of theophylline concentration at 254 nm after diluting with buffer solution. Mobile phase consisted of acetonitrile.

The following dissolution media were used to study the effect of pH of medium on drug release.

- A. Potassium chloride-hydrochloric acid buffer having pH 2.0 ± 0.05 .
- B. Acetate buffer having pH 4.0 ± 0.05 .
- C. Phosphate buffer having pH 7.0 ± 0.05 , 7.40 ± 0.05 .

Measurement of Plasma Level in Human Volunteers

Twelve healthy volunteers (25-35 years of age) were chosen for this study. The subjects were asked to abstain from any drinks containing caffeine in order to eliminate possible formation of theophylline *in vivo*. Blank blood sample was collected a few minutes before administering the preparation. After overnight fasting, a single dose of 200 mg of theophylline (as a fast dissolving preparation), Theodur-SR-200 tablets (as reference sustained release tablets of M/s. Astra, England) and guar gum based SR tablet (as test sample) containing the same amount of drug was administered, with 150 ml water. Plasma samples were collected at pre-determined intervals up to 24 h and kept frozen until analysis. No food was taken for 4 h post dose. A crossover design was used and a minimum washout period of 7 days was allowed between trials.

Analysis of Theophylline Levels in Plasma

A high-performance liquid delivery system equipped with an automatic sample injection was used in conjunction with photodiode UV visible detector set at 274 nm. A reverse phase C18 Nova pac analytical column (3.6 x 180 mm) was used for achieving separation and quantification⁴.

RESULTS AND DISCUSSION

Effect of Viscosity Grade and Polymer content:

Figure 1 shows the release patterns of theophylline from tablets prepared using 40% guar gum of different viscosity grades. The drug release was fast from tablets

RELEASE PATTERN OF THEOPHYLLINE FROM GUAR GUM TABLETS

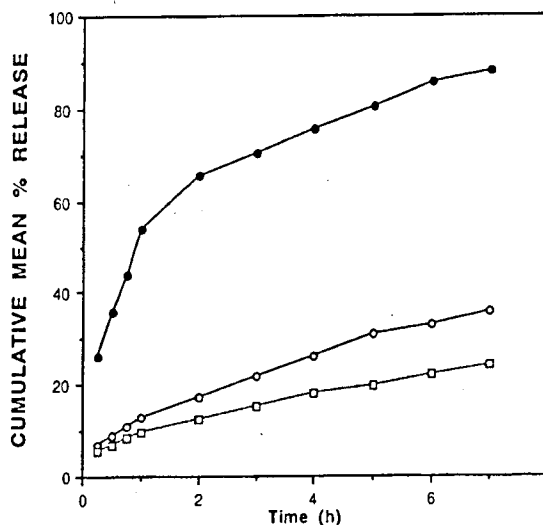


Figure 1: Theophylline release was studied using basket type dissolution apparatus from tablets made of 40% guar gum of low viscosity (●-●), medium viscosity (○-○) and high viscosity (□-□)

RELEASE PATTERN OF THEOPHYLLINE FROM GUAR GUM TABLETS

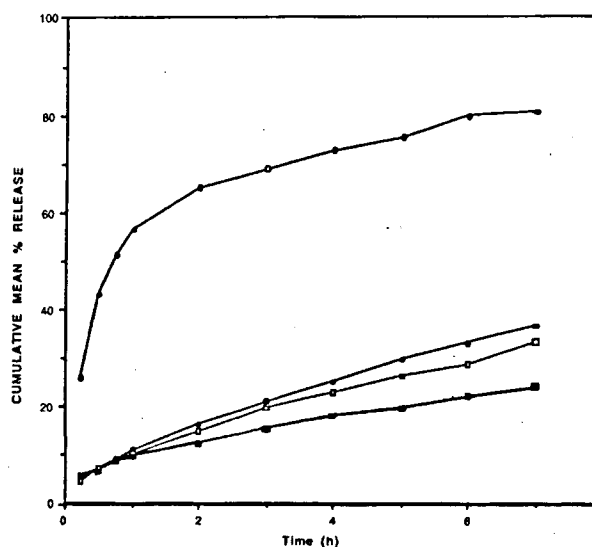


Figure 2: Theophylline release was studied using basket type dissolution apparatus from tablets made with 10% (○-○), 20% (●-●), 30% (□-□), 40% (■-■) of high viscosity guar gum

made of low viscosity grade polymer, while it was slow from tablets made of the polymer of medium and high

COMPARATIVE RELEASE PATTERN OF THEOPHYLLINE FROM TABLETS MADE WITH GUAR GUM Vs MARKETED PRODUCT

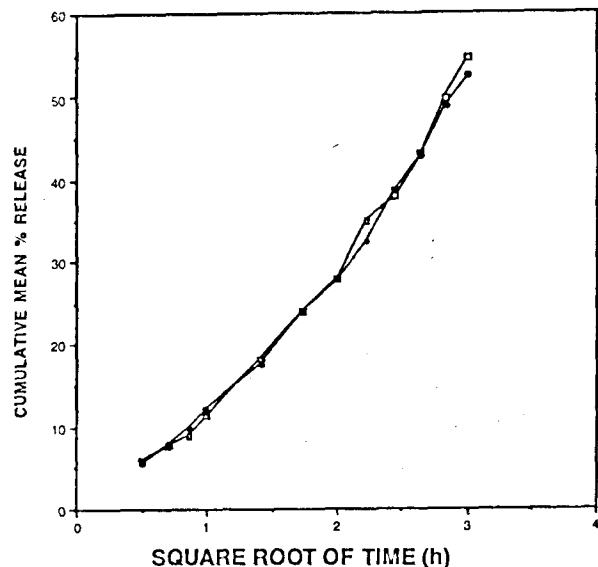


Figure 3: Comparative theophylline release was studied using basket type dissolution apparatus from tablets made with guar gum (o-o) and marketed sample, THEODUR (□-□)

viscosity grades. Figure 2 shows the drug release from tablets made with 10, 20, 30 and 40% of high viscosity guar gum. Apparently tablets having low concentration of guar gum exhibited faster drug release compared to tablets with higher concentrations of guar gum. Therefore, drug release could be modified by changing the viscosity grade⁵ and content of guar gum in the tablets.

Figure 3 shows a plot of the amount of drug released against square root of time for the developed formulation and for a marketed product. The straight lines obtained indicated a release mechanism as expected from the Higuchi equation for release of drug from solid matrices. It was observed that penetration of water into the guar gum based sustained release tablets resulted into formation of a gel layer on the tablet surface that swelled up initially and controlled the release thereafter.

Effect of Compression Pressure on Drug Release:

The effect of compression force was looked for, by applying 1000, 2000 and 3000 kg/cm² pressure for 30 seconds. These tablets were evaluated for dissolution rate results shown in Table 1 indicate that mean cumulative percentage of drug release from batch 12A and 12B at 1st, 3rd, 6th and 9th h have no significant difference.

COMPARATIVE PLASMA LEVEL PROFILES OF THEOPHYLLINE FROM TABLETS MADE WITH GUAR GUM AND MARKETED PRODUCT THEODUR

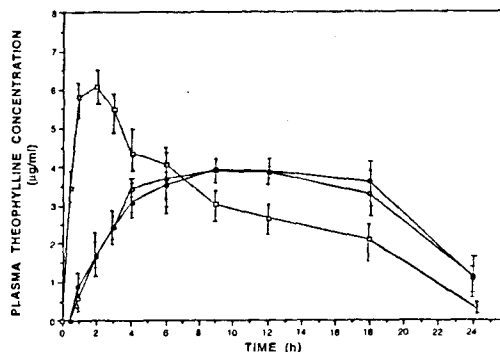


Figure 4: *In vivo* theophylline release was studied after administration of tablets made with guar gum (o-o), marketed sample, THEODUR (o-o) and regular formulation (□-□) to healthy volunteers

The values obtained from batch No. 12C show marginally significant difference in release profile at 3rd, 6th and 9th h when compared to batch 12A and 12B. From this data, it is concluded that compression pressure of 1000 kg/cm² and 2000 kg/cm² yielded tablets with similar dissolution profiles whereas on increasing compression pressure to 3000 kg/cm² will yield slightly decreased drug release.

Effect of pH of Dissolution Medium:

The drug release from the theophylline tablets made with guar gum, in buffers having four different pH values exhibited similar release pattern. This reveals that drug release pattern of theophylline is independent of the pH of dissolution medium used in this study. The pH independent release demonstrated in this study may be explained by recognising that the pH inside the matrix controls the solubility of the drug and therefore, the release rate is constant.

Effect of Ionic Strength of Dissolution Medium:

Ions reduce the activity of water, reduce hydration of the matrix, resulting in decrease of drug release rate but the drug release profile of theophylline in dissolution media having different ionic strengths was more or less similar. The dissolution rate of theophylline SR tablets is slightly higher in case of 0.1 N hydrochloric acid buffer (ionic strength of 0.10) as compared to its dissolution in other two buffer systems with higher ionic strengths. The drug release in 0.1 N Hydrochloric acid was comparable with drug releases in buffers with lower ionic strengths. Hence

TABLE 1: DETAILS OF MANUFACTURING PROCEDURE OF TABLETS MADE WITH GUAR GUM

Composition of tablets	Quantity in each tablet type (mg)				
	1	2	3	4	5, 6, 7*
Theophylline	200	200	200	200	200
Guar gum (GHK-250)	50	100	150	200	200
Starch	235	185	135	85	85
Talc	10	10	10	10	10
Magnesium stearate	5	5	5	5	5

Tablet type 5 prepared with low viscosity, tablet type 6 prepared using medium viscosity and tablet type 7 prepared using high viscosity.

TABLE 2: EFFECT OF COMPRESSION PRESSURE ON DISSOLUTION OF TABLETS MADE WITH GUAR GUM

B.No.	Compression Pressure (Kg/cm ²)	Percentage cumulative drug release* in phosphate buffer (pH 7.0) at different times			
		1 h	3 h	6 h	9 h
12A	1000	13.84 ± 1.48	23.19 ± 1.58	39.46 ± 1.30	58.33 ± 1.08
12B	2000	13.73 ± 1.12	22.81 ± 1.10	38.90 ± 1.62	57.99 ± 1.33
12C	3000	13.04 ± 1.25	20.78 ± 1.04	36.86 ± 0.97	55.70 ± 0.85

*Each value is the mean ± standard deviation of six determinations.

it could be concluded that drug release is independent of ionic strength of the dissolution media.

Plasma Levels Following Oral Administration:

In Figure 4 the average plasma levels of theophylline following oral administration of two kinds of sustained release tablets are compared⁶ with those of plain drug. As evident, lower and plasma superimposable levels were observed after administration of sustained release tablets prepared using guar gum and the standard Theodur preparation. After an initial lag period the drug concentration increased and was sustained over a period of 18-20 h and then declined gradually till the end of 24 h. Time to reach maximum drug concentration in plasma (T_{max}) was 8-9 h and drug concentration (C_{max}) at that time was 3.95 µg/ml. The $AUC_{(0)}$ for the test and reference sample are 78.21 and 80.02 g.h/ml respectively. These results of *in vivo* study imply that the plasma levels of theophylline following the administration of reference sample (Theodur-200) are the same as obtained with that of test sample (guar gum based tablets).

From this *in vitro* and *in vivo* study, it is possible to conclude that guar gum can be used with equal success to synthetic celluloses like HPMC for sustaining drug

release from tablets. The release depends upon the polymer content and viscosity grades that can be adjusted to get the desired rate and profile. No effect is seen of the compression force. The *in vitro* dissolution of theophylline from guar gum is found to be pH independent and dependent upon ionic strength. Hence dissolution studies may be carried out at any pH but with ionic strength adjusted to a fixed value.

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