Research Article

Evaluation of Different Viscosity Grades of *Guar gum* as Hydrophilic Matrix for Oral Controlled Drug Delivery

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ABSTRACT

Guar gum, in various viscosity grades, was evaluated as a carrier in the form of hydrophilic matrix for oral controlled drug delivery. Slightly soluble theophylline was chosen as a model drug. Theophylline hydrophilic matrix tablets using different proportions of various viscosity grades of guar gum were prepared by wet granulation method and subjected to in vitro drug release studies. Matrix tablets of theophylline containing either 10% low viscosity (TLV-10), 20% medium viscosity (TMV-20) or 20% high viscosity guar gum (THV-20) were found to provide a controlled delivery when compared with that of commercial SR theophylline tablets. High correlation coefficients were obtained for first order kinetics when compared to those of zero order kinetics indicating that theophylline release from all the formulations followed first order kinetics. The diffusional exponent values (n=0.63 to 0.68) indicate that the release of theophylline from guar gum matrix tablets and commercial SR tablets followed non-Fickian diffusion (diffusion and erosion). Theophylline matrix tablets were also subjected to in vitro drug release studies in rat caecal contents (simulated colonic conditions). The low viscosity guar gum appears to be superior to medium and high viscosity grades of guar gum in providing a controlled delivery of theophylline along the GI tract.

Keywords: Controlled release, Theophylline, Low-viscosity guar gum, Medium-viscosity guar gum, High-viscosity guar gum, Matrix tablets.

INTRODUCTION

Theophylline, a widely used anti-asthmatic drug, has a narrow therapeutic window. It has been reported that the effective concentration of theophylline in the serum ranges between 5 to 15 µg/mL[1]. Adverse effects like hypotension, nausea and vomiting are observed above 15 µg/mL. 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 controlled release oral dosage form.

Number of hydrophilic polymers are being used in the design of sustained release dosage forms[3,4]. Guar gum is a non-ionic polysaccharide derived from the seeds of Cyamopsis tetragonolobus, family Leguminosae. This nonionic hydrophilic polymer is unaffected by the changes in pH of the GI tract and is expected to provide sustained drug delivery irrespective of the variation in gastric emptying time of the patients.

Guar gum is an approved pharmaceutical[5,6] used in solid dosage forms as a binder and disintegrant[7], in liquid oral and topical products as a suspending, thickening and stabilizing agent. 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[8,9,10]. Hence, various viscosity grades of guar gum were used for the oral controlled drug release of theophylline in the form of a matrix.

MATERIALS AND METHODS

Materials

Theophylline was obtained from M/s Astra-IDL Limited, Bangalore, India. Low-viscosity guar gum (The viscosity of 1% aqueous solution in cP at 25°C is 125 at 2 hours and 130 at 24 hours), Medium-viscosity guar gum (The viscosity of 1% aqueous solution in cP at 25°C is 3725 at 2 hours and 4200 at 24 hours) and High-viscosity guar gum (The Viscosity of 1% aqueous solution in cP at 25°C is 5400 at 2 hours and 5650 at 24 hours) were obtained from M/s. Dabur India Limited, India. Microcrystalline Cellulose (Avicel, FMC Type pH-105), Starch, Talc and Magnesium Stearate were of US/NF grade.

Methods

Preparation of theophylline matrix tablets

Matrix tablets of theophylline were prepared by wet granulation method. Microcrystalline cellulose (MCC) was used as diluent and a mixture of talc and magnesium stearate (2:1 ratio) was used as lubricant. Different viscosity grades of guar gum were included in the formulations in various proportions. Table 1 show the composition of different formulations used in the

study containing 200 mg of theophylline in each tablet. In all the formulations, guar gum was sieved (#60 mesh) separately and mixed with theophylline (#100 mesh) and MCC (#60 mesh). The powders were blended and granulated with 5% starch paste. The wet mass was passed through a #16 mesh sieve and the granules were dried at 50°C for 2 hours. The dried granules were passéd through #18 mesh sieve and these granules were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed using 11 mm round, flat and plain punches on a single station tableting machine (M/s Cadmach Machinery Co. Pvt. Ltd., India). Matrix tablets of each composition were compressed and tested for their hardness, content uniformity and in vitro drug release characteristics.

Table 1: Composition of theophylline matrix tablets containing different viscosity grades of guar gum

Ingredients	Quantity(mg) present in Matrix formulation					
	TLV-5	TLV-10	TMV-10	TMV-20	THV-10	THV-20
Theophylline	200	200	200	200	200	200
Guar gum (Low viscosity)	22.5	45	---	---	---	---
Guar gum (Medium viscosity)	---	---	45	90	---	---
Guar gum (High viscosity)	---	---	---	---	45	90
Microcrystalline cellulose	191.5	169	169	124	169	124
Starch	22.5	22.5	22.5	22.5	22.5	22.5
Talc	9	9	9	9	9	9
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5
Total	450	450	450	450	450	450

In vitro drug release studies

The ability of the theophylline matrix tablets to provide controlled drug delivery was assessed by conducting in vitro drug release studies in simulated gastric and intestinal fluids. Drug release studies were conducted using USP dissolution rate test apparatus (Apparatus 1, 100 rpm, 37°C) for 1 hour in pH 1.2 buffer (900 mL). Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 mL) and tested for drug release for another 11 hours. One milliliter of the dissolution sample was taken with a pre-filter at different time intervals replacing with equal quantity of blank dissolution fluid. The samples were taken at 0.5, 1, 2, 4, 6, 8, 10 and 12 hours and suitably diluted. These samples were analyzed for theophylline content using UV-Visible Spectrophotometer (Shimadzu UV-1201) at 272 nm. Drug release studies were also conducted on Commercial sustained release tablets of theophylline (T-CSR) to optimize the formulation parameters in the design of guar gum matrix tablets.

Kinetics of drug release

The dissolution data of various theophylline formulations was fitted into various kinetic models such as zero order[11] {cumulative percentage of drug released Vs. time}, first order[11] {log cumulative percentage of drug remaining Vs. time} and Higuchi's[12] {cumulative percentage of drug released Vs. square root of time} models. For determination of mechanism of drug release data was fitted into Korsmeyer-Peppas[13] equation.

$$M_t / M_\infty = Kt^n$$

Where M_t / M_∞ is fraction of drug released at time `t', `K' represents a constant. The exponent `n' is calculated through the slope of the straight line which indicates mechanism of drug release.

Different mechanisms of drug release

`n' value	Type of Mechanism
less than (<) 0.5	Fickian diffusion
greater than (>) 1	Supercase II transport
between 0.5 to 1	Non-fickian diffusion

***In vitro* evaluation of guar gum matrix tablets in rat caecal content medium**

The performance of a sustained release dosage form, especially a hydrophilic matrix tablet, depends on its biodegradability in GI tract. The present study involves the preparation of matrix tablets containing various proportions of guar gum, a naturally occurring polysaccharide. Earlier reports indicate the susceptibility of guar gum to the action of colonic bacterial enzyme[14]. In this context, it is essential to study the influence of colonic bacterial enzymes on the drug release characteristics from the guar gum matrix tablets. The fate of the guar gum matrix tablets containing theophylline on reaching the colon was assessed by conducting in vitro drug release studies in rat caecal content medium[14,15] as per CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals), New Delhi guidelines.

Preparation of rat caecal contents medium

The susceptibility of formulations containing guar gum to the enzymatic activity of colonic bacteria was assessed by conducting the drug release studies in pH 6.8 phosphate buffered saline (PBS) containing rat caecal contents {because of their similarity with those of humans with respect to intestinal microflora[16]}. In order to induce enzymes specifically acting on guar gum in the caecum, male albino rats (supplied by M/s Ghosh Enterprise, Calcutta, India) weighing 150-200 g and maintained on normal diet were intubated with Teflon tubing, and 1 mL of 2%w/v dispersion of guar gum in water was administered directly into the stomach. The tubing was removed and this treatment was continued for 7 days. Thirty minutes before the commencement of the drug release studies, five rats were sacrificed by spinal traction. The abdomen was opened, the caecai were traced, ligated at both ends, dissected and immediately transferred into pH 6.8 PBS, previously bubbled with CO_2. The caecal bags were opened, their contents were individually weighed, pooled and then suspended in PBS to give required caecal dilution. As the caecum is naturally anaerobic, all these operations were carried out under CO_2.

Drug release studies in rat caecal contents medium

The drug release studies were carried out using a USP Dissolution Rate Test Apparatus (Apparatus 1, 100 rpm, 37°C) with slight modifications. A beaker (capacity 150 mL) containing 100 mL of dissolution medium was immersed in the water contained in the 1000 mL vessel, which was, in turn, in the water bath of the apparatus. The tablets were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal contents. The experiment was carried out with continuous CO_2 supply into the medium to simulate anaerobic environment of the caecum. At different time intervals, 1 mL sample was withdrawn without a pre-filter and replaced with 1 mL of fresh PBS bubbled with CO_2.

RESULTS AND DISCUSSION

Different viscosity grades (low-viscosity, medium-viscosity and high-viscosity) of guar gum were evaluated for their ability to control the drug release in the form of a matrix tablet. Since the guar gum was found to have poor flow properties, it is planned to granulate the mixture of guar gum and theophylline using starch paste as binder so as to impart both compressibility and flow properties. The angle of repose for theophylline granules ranged from 23°35' ± 49' to 26°20' ± 37' and the Carr's Index values ranged from 10.42 ± 0.59 to 11.97 ± 0.27 (Table 2) indicating good flow properties of theophylline granules. Theophylline matrix tablets containing different viscosity grades of guar gum were subjected to the quality control tests such as hardness, thickness, weight variation and drug content (Table 3). The hardness of the tablets ranged from 5 to 6 kg/cm^2. The thickness of the tablets was found to be between 3.52 mm and 3.63 mm. All the formulations contained 98 ± 5% of theophylline when assayed by UV Spectrophotometric method at 272 nm.

Table 2: Mean Angle of Repose and Carr's Index values of theophylline granules (n=3) containing various proportions of low, medium and high-viscosity guar gum

Granules of Matrix formulation	Mean Angle of Repose ± S.D.	Mean Carr's Index ± S.D.
TLV-5	23°35' ± 49'	10.42 ± 0.59
TLV-10	23°96' ± 55'	11.02 ± 0.60
TMV-10	26°20' ± 37'	10.47 ± 0.60
TMV-20	25°82' ± 38'	11.97 ± 0.27
THV-10	24°44' ± 69'	10.48 ± 0.64
THV-20	25°53' ± 37'	10.74 ± 0.55

Table 3: Characteristics of Theophylline Matrix Tablets (n=10)

Matrix Formulation	Hardness Kg/Sq. cm ± S.D.	Average Weight (mg) ± S.D.	Thickness of Tablet (mm) ± S.D.	Drug content (%) ± S.D.
TLV-5	5.5 ± 0.41	449.6 ± 6.66	3.52 ±0.06	100.81 ± 1.38
TLV-10	5.5 ± 0.41	449.95 ± 8.17	3.55 ± 0.05	100.28 ± 0.63
TMV-10	5.0 ± 0.41	449.7 ± 6.04	3.56 ± 0.07	99.6 ± 1.64
TMV-20	5.5 ± 0.24	449.3 ± 7.43	3.63 ± 0.06	97.90 ± 0.21
THV-10	5.05 ± 0.44	450.3 ± 7.12	3.55 ± 0.05	100.87 ± 1.23
THV-20	5.45 ± 0.28	448.75 ± 7.99	3.63 ± 0.03	97.49 ± 0.23

Matrix tablets containing 5%w/w (TLV-5) and 10%w/w (TLV-10) of low-viscosity guar gum and commercial theophylline SR formulation (T-CSR) were subjected to in vitro drug release studies. The matrix formulation TLV-5 was found to be disintegrated after 45 minutes of dissolution testing in 0.1 N HCl whereas the other matrix formulation TLV-10 retained its shape upto 12 hours of dissolution testing. The commercial SR formulation of theophylline has swollen and eroded slowly with time to about 80% of its initial swollen volume at the end of 12 hours of testing and remained as a mass in the basket. The mean cumulative percent of theophylline released at different time intervals from the matrix tablets (TLV-10) and commercial SR formulation (T-CSR) are shown in Fig. 1. The matrix tablets of TLV-10 are found to be controlling the drug release better than the commercial SR

theophylline tablets. Hence, the minimum amount of low-viscosity guar gum required to control the drug delivery was fixed at 10%w/w of matrix tablet.

Theophylline matrix tablets containing 10%w/w (TMV-10) and 20%w/w (TMV-20) medium-viscosity guar gum were subjected to in vitro drug release studies. Matrix tablets containing 10%w/w medium-viscosity guar gum (TMV-10) were disintegrated within half an hour whereas matrix tablets containing 20%w/w medium-viscosity guar gum retained their shape for more than 12 hours. The mean cumulative percent of theophylline released at different time intervals from the matrix formulation TMV-20 and commercial SR formulation T-CSR are given in Fig. 1. The release profile of theophylline from the matrix formulation TMV-20 is found to be better controlled when compared with commercial theophylline SR formulation. Hence, the minimum amount of medium-viscosity guar gum required providing controlled drug delivery was fixed at 20%w/w of matrix tablet.

Theophylline matrix tablets containing 10%w/w (THV-10) and 20%w/w (THV-20) high viscosity guar gum were subjected to in vitro drug release studies. Matrix tablets containing 10%w/w high-viscosity guar gum disintegrated within half an hour whereas matrix tablets containing 20%w/w high-viscosity guar gum retained their shape up to 12 hours. Fig. 1 shows the cumulative percent of theophylline released from THV-20 and T-CSR at different time intervals. The matrix formulation THV-20 also provided drug delivery at better controlled rates compared to T-CSR formulation. Hence, the minimum amount of high-viscosity guar gum required providing controlled delivery of theophylline was fixed at 20%w/w of matrix tablet.

The data obtained from in vitro dissolution studies of theophylline matrix tablets (TLV-10, TMV-20 and THV-20) and commercial SR tablets (T-CSR) were fitted to Zero order, First order, Higuchi and Korsmeyer-peppas equations and the results are shown in Table No. 4. The correlation coefficients were found to be higher for first-order kinetics (0.9935 to 0.9960) when compared to zero-order kinetics (0.9259 0.9782) indicating that theophylline release from all the matrix formulations and commercial SR formulation followed first-order kinetics. All the formulations (TLV-10, TMV-20, THV-20 and T-CSR) showed good correlation in Higuchi kinetics (0.9851 to 0.9929), clearly indicating that the drug release mechanism was predominantly diffusion controlled.

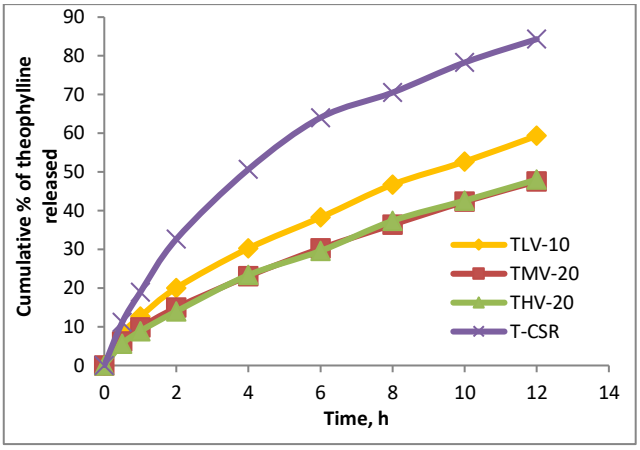

Figure 1: Comparative % drug release profiles of theophylline matrix tablets containing 10% low-viscosity (TLV-10), 20% medium-viscosity (TMV-20), 20% high-viscosity (THV-20) guar gum and commercial SR tablets (T-CSR)

To confirm the exact mechanism of drug release from the formulations TLV-10, TMV-20, THV-20 and T-CSR, the data were fitted to Korsmeyer-peppas equation. The diffusional exponent values (n) obtained for formulations TLV-10, TMV-20, THV-20 and T-CSR were 0.62, 0.64, 0.68 and 0.64 respectively indicating that theophylline release from these formulations followed non-fickian diffusion. The results of the present study indicated that the release of theophylline from guar gum matrix tablets and commercial SR tablets followed first order kinetics via non-fickian diffusion mechanism.

Table 4: Dissolution kinetics of theophylline matrix tablets containing 10% low-viscosity (TLV-10), 20% medium-viscosity (TMV-20), 20% high-viscosity *Guar gum* (THV-20) and commercial theophylline SR tablets (T-CSR)

Formulation	Zero order	First order	Korsmeyer-peppas		Higuchi
	R^2	R^2	R^2	n	R^2
TLV-10	0.9668	0.9942	0.9997	0.62	0.9929
TMV-20	0.9748	0.9935	0.9998	0.64	0.9892
THV-20	0.9782	0.9952	0.9996	0.68	0.9851
T-CSR	0.9259	0.9960	0.9884	0.64	0.9917

The performance of a sustained release dosage form, especially a hydrophilic matrix tablet, depends on its biodegradability in GI tract. The present study involves the preparation of matrix tablets containing various proportions of guar gum, a naturally occurring polysaccharide. Earlier reports indicated the susceptibility of guar gum to the action of colonic bacterial enzyme[14]. In this context, it is essential to study the influence of colonic bacterial enzymes on theophylline release characteristics from the guar gum matrix tablets. This is assessed by conducting in vitro drug release studies in rat caecal content medium[15].

In the presence of rat caecal contents, the matrix tablets containing 10% of low-viscosity guar gum (TLV-10) were found intact up to 8 hours and disintegrated into four pieces at 12 hours, releasing about 87% (Table 5) of the drug. All the three tablets were found disintegrated within 24 hours of testing and released almost the entire quantity of theophylline in the rat caecal content medium (simulated colonic conditions). Based on the drug release studies in the rat caecal contents, the formulation TLV-10 may provide a controlled delivery of theophylline all along the GI tract.

Table 5: Mean Cumulative percent of theophylline released from matrix tablets containing different viscosity grades of guar gum with or without rat caecal contents

Time (h)	Mean (± S.D.) cumulative percent of theophylline released from matrix tablets					
	TLV-10		TMV-20		THV-20	
	Without rat caecal contents	With rat caecal contents	Without rat caecal contents	With rat caecal contents	Without rat caecal contents	With rat caecal contents
0	0	0	0	0	0	0
1	12.61±0.45	11.95±0.20	9.79±0.33	9.76±0.32	8.87±0.75	9.00±0.25
5	34.54±1.32	32.63±0.56	26.56±0.48	27.67±0.41	26.69±0.36	26.75±0.81
8	46.74±1.51	45.53±0.74	36.38±0.63	78.46±0.27	37.37±0.91	90.50±0.93
12	59.34±1.27	87.13±0.91	47.56±1.51	91.90±0.92	48.03±1.23	94.59±1.05
24	---	99.70±1.14	---	93.74±0.27	---	94.93±0.83

The matrix formulations containing 20% of medium (TMV-20) and high-viscosity guar gum (THV-20) started disintegrating after 7 hours and released 80% and 90% of theophylline respectively at the end of 8 hours. Unlike the formulation TLV-10, both TMV-20 and THV-20 formulations disintegrated almost completely releasing the entire quantity of the drug between 8 and 9 hours (Table 5). In dissolution studies with rat caecal contents, it was observed that drug release was relatively more rapid in TMV-20 and THV-20 compared to TLV-10 (Fig. 2). The possibility of higher number of voids in TMV-20 and THV-20 might be responsible for the observed phenomenon. Thus, the formulations TMV-20 and THV-20 may be inferior to TLV-10 in providing controlled delivery of theophylline.

The present study clearly showed that the matrix formulations of theophylline prepared with different viscosity grades of guar gum (TLV-10, TMV-20 and THV-20) were able to control the drug delivery on par with commercial SR tablets (T-CSR). Hence, stability studies were conducted on theophylline matrix tablets containing various viscosity grades of guar gum (TLV-10, TMV-20 and THV-20) as per ICH guidelines i.e., at 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH for 6 months to assess their stability with respect to their physical appearance, drug content and drug release characteristics. From the results it was found that there was no significant difference in the various physico-chemical parameters indicating that theophylline matrix formulations were stable after the storage period.

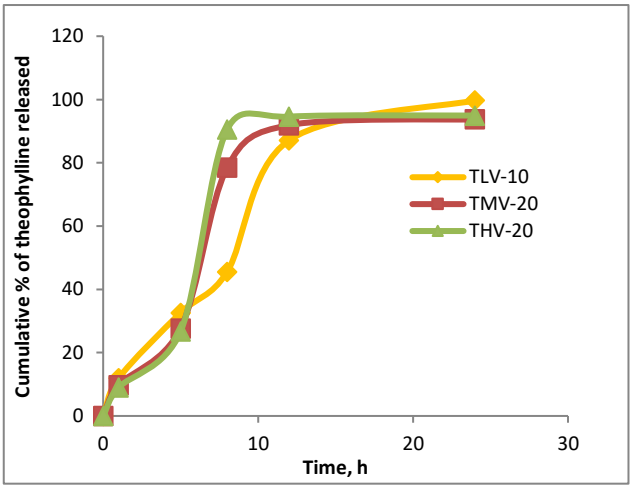

Figure 2: Comparative % drug release profiles of theophylline matrix tablets containing 10% low-viscosity (TLV-10), 20% medium-viscosity (TMV-20), 20% high-viscosity (THV-20) guar gum with rat caecal contents

Differential Scanning Calorimetry (DSC) was used to examine the possible interaction of guar gum with theophylline taking low-viscosity guar gum as a representative gum sample. A sharp endothermic peak corresponding to the melting point of pure drug (theophylline) was found at 276.3°C. The endothermic peak corresponding to theophylline in the thermogram of the formulation granules was found at 268.4°C. The minor peak variation of about 8°C in the endothermic peak of theophylline in the granules might be due to differences in the moisture contents of the samples as reported by Biliaderis[17]. The results of the DSC studies indicate no possibility of interaction of guar gum with theophylline when incorporated as a hydrophilic polymer.

CONCLUSION

Theophylline matrix tablets containing either 10% low-viscosity guar gum, 20% medium-viscosity guar gum or 20% high-viscosity guar gum were found to provide controlled drug delivery. Since guar gum was reported to be a colon-specific drug carrier, the formulations were also subjected to in vitro drug release studies in rat caecal contents (simulated colonic conditions). Based on the in vitro drug release studies, the low-viscosity guar gum appears to be superior to medium and high-viscosity grades of guar gum in providing controlled delivery of theophylline along the GI tract. However, studies on the in vivo performance either in a suitable animal model or in human volunteers need to be carried out to assess the utility of guar gum as a carrier for controlled drug delivery.

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