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Studies on Kinetics of Drug Release from Modified Guar Gum Hydrophilic Matrices

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Guar gum, a naturally occurring galactomannan polysaccharide, has very high intrinsic viscosity and can be used as hydrophilic matrix for controlled release tablets. In the present investigation guar gum has been methylated using sodium hydroxide and dimethylsuphate. Guar gum and methylated guar gum have been evaluated as hydrophilic matrices for controlled release tablets. Effect of the composition of matrices and the method of preparation of tablets on the drug release kinetics from the guar gum and methylated guar gum matrices have been studied and compared.

HYDROPHILIC polymer matrices are widely used in the formulation of sustained release dosage forms. Various synthetic polymers like cellulose ethers, polyalkylmethacrylates used for this purpose have been reviewed. It is established that these hydrophilic polymers release freely soluble drug at fairly constant rate[1-3]. Only few investigators mention the possible use of natural gums in the formulations of sustained release preparations[4,5].

Guar gum (GG) is a natural macromolecular galactomannan polysaccharide with high intrinsic viscosity[6]. It can be an interesting polymer for the development of hydrophilic matrix controlled release tablets but for certain limiting factors like poor interaction coefficient and uncontrolled rate of hydration. In this investigation GG has been chemically modified as methylated guar gum (MGG) and used to prepare hydrophilic matrix controlled release tablets, using chlorpheniramine maleate (CPM) as a model drug. The drug release kinetics for GG and MGG matrices and factors affecting it have been evaluated *in vitro* and compared.

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MATERIALS AND METHODS

Materials:

Guar gum (National Chemicals, Bombay, India), Lactose, microcrystalline cellulose, magnesium stearate, talc (Chemicals Supply Corporation, India), Sodium hydroxide A. R. (S.d. Fine Chemicals, Biosar, India). Dimethyl sulphate (SRL, Bombay, India), Methanol A. R. (Qualigens, India), Glacial acetic acid A. R. (Loba-Chemie, India)

Methylation:

40% w/v aqueous solution of sodium hydroxide was prepared and 45 ml of it was transferred to a clean 250 ml round bottom flask. This was maintained at temperature of around 4° (using ice bath) and 10 g of GG was slowly dispersed to it with constant stirring at 600 ± 10 rpm using overhead mechanical stirrer. Stirring was continued to achieve uniform dispersion. After 30 minutes of stirring, dimethylsulphate was added dropwise to GG dispersion in aqueous sodium hydroxide solution under constant stirring. The temperature of the reaction mixture was raised gradually to 70° using heating mantle and the reaction continued for 3 h. After the completion of the reaction

time the mixture was cooled gradually, dispersed in methanol and the excess alkali was neutralized with glacial acetic acid to pH 7. The product was finally washed with 3 successive portions of methanol, filtered and then dried under vacuum of 20 in. of Hg at 40° to a constant weight in a vacuum dryer. 5, 10, 15, 20, 25 and 30 ml of dimethylsulphate was used for methylating GG to different degrees. The MGG products were characterized as under:

KBr pellets of GG/MGGs were made using hydraulic press at a pressure of 100 kg/cm^2 for 30 secs and I. R. spectra was recorded from 400 cm^{-1} to 4000cm^{-1} using IR460 Shimadzu infrared spectrophotometer as shown in Fig. 1. Methoxy content of the MGGs was determined using semi-micro Zeisel method as per USP XXII[7] 1% w/v aqueous solutions of GG/MGGs were made by hydrating 1 g of GG/MGGs in 100 ml purified under continous stirring. Viscosity measurements were made using Brookefield synchrolectric viscometer LVT model spindle no. 2 at the rate of 12 rpm at room temperature. The results are recorded in Table 1.

Tabletting:

The composition of the formulations is shown in Table. 200 mg controlled release matrix tablets were compressed using 8 mm round flat face beveled edged punches with GG/MGGs matrices at same pressure on single stroke compression machine. Tablets were subjected to routine quality tests of tablet parameters and then used for further investigations.

Dissolution Studies:

Dissolution studies were performed using USP XII[8] dissolution apparatus with basket assembly at 100 ± 5 rpm. 900 ml of purified water maintained at 37° ± 0.5° was used as dissolution medium. 5 ml samples were withdrawn at specific time points and were replaced with equal volumes of fresh dissolution medium. Samples were filtered and absorbance was measured at 261 nm on Carl-Zeiss-Jena VSU2-P UV-Vis spectrophotometer. The data of mean cumulative per cent drug release and time (h) are recorded in Table 2.

DATA ANALYSIS

Mean cumulative per cent drug release alongwith its standard error value calculated at each sampling time point from the dissolution data of 6 samples of each of the 3 batches evaluated on 3 consecutive days (no. of samples = 54). The dissolution data were fitted to the following exponential release model equation[9] to study the release kinetics of the drug from the matrix tablets:

$$Mt/Moo = k \times t^n$$

Where Mt/Moo = the fractional drug released into the dissolution medium, k = a constant which incorporates the properties of macromolecular polymeric matrix and the drug, n = diffusional exponent which characterizes the drug transport kinetics. The values of n, k, and squared coefficient of correlation (R^2) were calculated and are recorded in Table 2.

All the data were compared using ANOVA technique. The values at $p < 0.05$ (95% confidence) were considered statistically significant.

RESULTS AND DISCUSSION

Methylation of GG:

GG was methylated with dimethylsulphate and sodium hydroxide as reported by Rafique[10] after suitable modifications. GG has very high intrinsic viscosity so on hydration gelling of the reaction mixture occurs. The gelling of the reaction mixture was prevented by using low temperature (4±0.5°) and the high pH which depresses the hydration of GG. I. R. spectra of MGGs show a peak at 1080- 1100 cm^{-1} suggesting the presence of methoxy group. GG, a natural macromolecular polysaccharide consists of straight chain of d-mannose units as backbone with pendant d-galactose groups. Small quantities of dimethylsulphate may be preferentially methylating the galactose moieties (methoxy content 3.05 ± 0.02 upto MG3) and further increase in dimethylsulphate may be causing cleavage of d-mannose chain

Table 1: Methylation and Characterisation of GG and Composition of Formulations.

Sr. No.	Prod.	Form. No.	Amount of DMS (ml)	% Methoxy. content (±S.E.)	Viscosity (cps) (±S.E.) (cps)	quantity (mg/tab)						
						CPM	Prod.	Lact	MCC	PVP	Mag.St.	Talc
1.	GG	F#1	-	-	8025.00±24.21	8.0	80.0	98.0	-	10.0	2.0	2.0
2.	MG1	F#2	5.0	2.20±0.05	6078.01±42.71	8.0	80.0	98.0	-	10.0	2.0	2.0
3.	MG2	F#3	10.0	2.69±0.05	2541.24±45.67	8.0	80.0	98.0	-	10.0	2.0	2.0
4.	MG3	F#4	15.0	3.05±0.02	2436.44±20.27	8.0	80.0	98.0	-	10.0	2.0	2.0
5.	MG4	F#5	20.0	3.29±0.07	916.94±16.43	8.0	80.0	98.0	-	10.0	2.0	2.0
6.	MG5	F#6	25.0	3.60±0.02	419.17±07.71	8.0	80.0	98.0	-	10.0	2.0	2.0
7.	MG6	F#7	30.0	4.04±0.02	327.48±14.28	8.0	80.0	98.0	-	10.0	2.0	2.0
8.	GG	F#8	-	-	8025.00±24.21	8.0	80.0	49.0	49.0	10.0	2.0	2.0
9.	GG	F#9	-	-	8025.00±24.21	8.0	80.0	-	98.0	10.0	2.0	2.0
10.	MG3	F#10	15.0	3.05±0.02	2436.44±20.27	8.0	80.0	49.0	49.0	10.0	2.0	2.0
11.	MG3	F#11	15.0	3.05±0.02	2436.44±20.27	8.0	80.0	-	98.0	10.0	2.0	2.0
12.	GG	F#12	-	-	8025.00±24.21	8.0	80.0	98.0	-	10.0*	2.0	2.0
13.	MG3	F#13	15.03	0.05±0.02	2436.44±20.27	8.0	80.0	98.0	-	10.0*	2.0	2.0

* used as 20 % w/v solution in methanol.

alongwith methylation of mannose moeities (methoxy content 3.29 ± 0.07 of MG4 and beyond). The problems involved in methylation of natural products include the liability of the compounds to the methylating conditions and some chain cleavage may take place causing reduction in molecular weight. Reduction in molecular size of GG increases with increase in degree of substitution as expressed in terms of viscosities of MGGs[11]. This fall in viscosities of MGGs was found to be gradual till preferential methylation of galactose moieties occurred and then sharp fall in viscosities was noticed as methylation progressed.

Influence of methylation of GG on the drug release:

Data of mean cumulative per cent CPM release as a function of time have been determined and the results are recorded in Table 2. Drug release profile from GG matrix tablets show high percent drug release (31.06 % ± 2.56) in the first half an hour and then the rate of drug release decreases with time. The release rate of drug from hydrophilic gum matrices is a complex mechanism. One of the major influencing factors is the rate of erosion of the gel layer of the wetted matrix tablets. Two properties dominate the erosion of gel layer : gel strength of the swelling gel and the cohesiveness. The dissolution data reveals that formation of obstructive barrier layer is a slow process for GG matrices due to its poor interaction coefficient[6]. The slow rate of hydration leads to the delayed transition of polymer chain of GG from glassy to a dynamic rubbery state and is manifested in the burst effect in first half hour of dissolution studies. Decrease in drug release rate after an hour is because of formation of strong cohesive gel layer around the tablet due to branched structure[12] and a very high intrinsic viscosity of GG. The value of n (0.7653±0.0597) shows that release of drug from GG matrix follows the non-Fickian diffusion mechanism.

Methylation of GG leads to a significant reduction in molecular size, as expressed in terms of viscosities, with change in methoxy content (Table 1). These changes in GG cause significant reduction in the

Table 2. Data of mean Cumulative percent drug release as a function of time

Sr. No.	Formul. No.	Percent Drug Release (S.E.) at time (H) 0.0	0.50	1.0	2.0	3.0	4.0	6.0	K	n(S.E.)	R^2
1.	F#1	0.00	31.06 (1.41)	41.34 (0.66)	55.29 (1.62)	70.56 (1.31)	80.91 (1.73)	88.41 (0.84)	1.35	0.7653 (0.0597)	0.9647
2.	F#2	0.00	30.55 (1.60)	45.65 (0.71)	62.05 (0.51)	79.44 (1.17)	93.72 (0.61)	96.80 (0.84)	1.10	0.7585 (0.0071)	0.9959
3.	F#3	0.00	30.11 (1.05)	42.76 (1.39)	60.28 (0.96)	71.48 (0.65)	84.85 (0.38)	95.05 (1.22)	1.12	0.7296 (0.0082)	0.9945
4.	F#4	0.00	18.77 (0.66)	30.34 (0.51)	45.69 (0.43)	61.48 (0.74)	78.28 (1.02)	92.48 (0.34)	1.10	0.7805 (0.0099)	0.9958
5.	F#5	0.00	27.09 (0.50)	39.50 (0.39)	55.69 (0.66)	64.52 (0.66)	77.11 (1.34)	96.00 (0.43)	1.06	0.7690 (0.0053)	0.9983
6.	F#6	0.00	27.37 (2.20)	38.27 (1.05)	54.37 (0.53)	74.98 (1.58)	94.23 (2.26)	98.90 (0.13)	1.22	0.8213 (0.0163)	0.9848
7.	F#7	0.00	32.67 (0.77)	45.56 (0.53)	65.61 (1.65)	96.07 (0.78)	98.63 (0.41)	99.79 (0.46)	1.39	0.8381 (0.0216)	0.9741
8.	F#8	0.00	34.43 (2.07)	44.63 (1.23)	58.08 (1.43)	70.86 (0.57)	79.03 (0.83)	85.57 (2.30)	1.42	0.7570 (0.0700)	0.9512
9.	F#9	0.00	41.23 (2.68)	51.34 (2.73)	64.71 (1.98)	79.91 (1.71)	85.71 (0.66)	88.44 (0.74)	1.52	0.7611 (0.0832)	0.9330
10.	F#10	0.00	25.46 (0.51)	35.28 (1.11)	54.35 (1.47)	67.13 (1.33)	79.08 (0.59)	85.46 (0.57)	1.27	0.7648 (0.4700)	0.9778
11.	F#11	0.00	29.14 (1.71)	47.17 (1.02)	66.78 (2.12)	74.58 (2.14)	80.63 (0.99)	87.16 (0.72)	1.38	0.7677 (0.0652)	0.9585
12.	F#12	0.00	22.23 (1.41)	32.41 (0.77)	45.35 (1.23)	56.90 (0.67)	65.82 (0.79)	73.89 (0.43)	3.92	0.5128 (0.0054)	0.9993
13.	F#13	0.00	10.22 (0.69)	17.29 (0.72)	28.12 (1.01)	41.75 (0.79)	55.41 (1.23)	68.74 (1.45)	0.93	0.7261 (0.0616)	0.9938

amount of drug released in the first half an hour (from 31.06 % ± 2.56 of GG to 18.77 % ± 0.68 of MG3). The rate of hydration increases and hence onset of obstructive gel layer formation is faster as compared to GG. The results also show that the rate of drug release increased in degree of methylation (MG1- 15.24±2.95 % / h to MG6- 23.83±2.05 % / h), which can also be explained in terms of reduced viscosity of the MGGs. The drug release in all cases follows non-Fickian diffusion mechanism (Table 2).

Influence of composition of formulation on drug release from GG and MGG matrices:

The effect of addition of water soluble diluent, lactose, and water insoluble diluent, MCC, to GG or MGG matrix tablets of CPM was studied. The tablets (F#1, F#4, and F#8 to F#11) were subjected to dissolution test. Increasing the amount of lactose from 0 % (about 50 % MCC) through 25 % (25 % MCC) to 50 % w/w (0 % MCC) changes the release profile

significantly in case of both GG and MGG matrix tablets. Drug release from GG and MGG matrices during first half an hour decreases significantly (GG-41.23±2.68 to 31.02 % ± 2.56 and MGG-29.14 % ± 1.71 to 18.77 % ± 0.66) with increase in amount of water soluble diluent lactose. The difference in the drug release rate diminishes with time in both the cases. GG and MGG matrices containing about 50 % MCC do not form a cohesive obstructive layer around the tablet due to slower liquid penetration but swell progressively with the formation of a porous spongy layer. This layer erodes quickly resulting in a fast drug release initially. On the contrary, increasing lactose concentration in matrices results into faster installation of an integral gel layer and there is reduction in the drug release in initial half an hour in both GG and MGG matrices. The values of n (Table 2) show that the drug release from these formulations follow non-Fickian diffusion mechanism.

Influence of method of preparation of GG & MGG matrix tablets on drug release:

The dissolution data from GG (F#1; F#12) MGG (F#4; F#3) matrix show a significant reduction in drug release in first half an hour by changing from direct compression to wet granulation method of preparation of matrix tablets. Faster erosion of obstructive gel layer in direct compression compared to wet granulation may be explained on the basis of the porosity of the matrices and lack of cohesiveness and gel strength. In case of MGG matrix tablets also there is significant reduction in the rate of drug release from the tablet matrix. However compared to MGG matrix tablets, GG matrix tablets still show substantial burst effect in initial half an hour and the difference in drug release from GG and MGG matrices reduces significantly. There is change in drug release kinetics from GG matrix tablets as is seen from the values of n(F#1 - 0.7653±0.0597; F#12 - 0.5128±0.0054) but MGG matrix tablets do not show any significant change in drug release kinetics (n value of F#4 - 0.7805 ± 0.0206 ; F#13 - 0.7261 ± 0.0256) on changing the method of preparation of tablets from direct compression to wet granulation.

In conclusion, from the data it may be concluded that in MGG matrix tablets interaction coefficient and subsequent installation of a cohesive gel around the tablet improves significantly compared to GG matrix tablets. Degree of methylation, composition of matrix and method of preparation of matrix tablets are important parameters that influence the formation of obstructive barrier layer around the tablet and subsequent erosion of gel matrix. The desired drug release rate can be obtained without any burst effect by controlling the degree of methylation, changing the composition and method of preparation of MGG matrix tablets as compared to GG matrix tablets.

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