Chapter 8

SUMMARY AND CONCLUSIONS

8.1 INTRODUCTION

Recent years have witnessed a greater focus on the development of sustained/controlled release drug delivery systems. See-saw fluctuations of drug concentrations are observed in systemic circulation and tissue compartments on administration of drugs in conventional dosage forms. Drug concentrations can be maintained within a narrow therapeutic range by the use of controlled release drug delivery systems, which also minimize the incidence and severity of adverse side effects. In developing sustained or controlled release oral delivery systems, formulation scientists face difficulties of restraining and localising the system at targetted areas of the gastro-intestinal tract (GIT). Hydrophilic polymers have been widely used nowadays in the development of oral controlled release delivery systems, which include the cellulose ethers, acrylates and also the natural gums.

Gums are naturally occurring polysaccharides and have found widespread applications because of many advantageous properties they impart to their solutions/dispersions. These properties are mainly manifestations of gums' molecular shape and chemical structure, as interactions take place between the solvent and dissolved or suspended material. Guar gum (GG), a galactomannan polysaccharide gum, is obtained from the endosperm of seeds of a legume, *Cyamopsis tetragonolobus,* structurally comprising of a straight chain of d-mannose with pendant d-galactose side chain on almost every other mannose unit. GG has a molecular weight of the order of 2,20,000. It is a colorless or pale yellowish white colored powder. It hydrates in either cold or hot water to give high viscosity solutions. GG has various pharmaceutical applications which include its use as a suspending agent, thickening agent and disintegrating agent. Cold water swellability, nontoxicity, indigenous availability and

low cost make GG an interesting natural polymer for use in the development of hydrophilic matrices for controlled release drug delivery.

Despite the advantages, there are certain limitations in the use of GG such as non-uniform rate of hydration, microbial contamination, loss of viscosity on storage and inconsistent quality and reproducibility. In the present investigation, GG was procured, characterised and modified to overcome its limitations and also to improve its interaction coefficient. For the present studies, it was assumed that modification of physico-chemical nature of the low priced naturally occurring polysaccharide gum, GG, may introduce the desired qualities in it and thus help to overcome the associated problems in its use as hydrophilic matrix for controlled release tablets. Water soluble drugs, such as chlorpheniramine maleate, diltiazem hydrochloride, and phenylpropanolamine hydrochloride, which are known to pose greater challenge to a formulation scientist for producing cost effective and rational controlled release dosage forms, were selected as model drugs.

8.2 ANALYTICAL METHODS

An extremely important micromeritic parameter, powder density, defined as the ratio of mass to volume, was determined for the products. This included determination of bulk density and tapped density of GG and modified GGs.

Viscosity of the polymer is related to its molecular weight by Mark-Houwink equation. Viscosity of 1% w/v aqueous solutions of GG and modified GGs was determined using spindle no.2 of Brookefield synchro-lectric viscometer LVT model at 12 rpm at room temperature (33°C ± 2°C) .

GG and modified GGs were also characterised by I.R. spectroscopy. I.R. spectra were recorded on IR460 Shimadzu Spectrophotometer between

400cm^{-1} and 4000cm^{-1} to identify any changes in the functional groups of the molecule.

Differential Scanning Calorimetry(DSC), a technique to measure the uptake of heat by a compound, provides a record of temperature at which phase changes. These temperatures are useful for characterising substances. DSC thermograms of GG and modified GGs were recorded on DSC20 Mettler Differential Scanning Calorimeter.

Hydrolysed GGs (HGGs) were also characterised by the degree of hydrolysis measured in terms of sugars liberated on hydrolysis. Estimation of sugars was done by using phenol-sulphuric acid method. Standard galactose solutions were treated with phenol solution and concentrated sulphuric acid for color development, and the absorbance of developed color solutions was measured at 490nm using HitachiU-2000 Uv-Visible spectrophotometer. The linearity of curve in the range of 40 mcg/ml to 140 mcg/ml was proved by regression analysis.

A quantitative methoxy determination was carried out for methylated GGs (MGGs) by hydrolysing the derivative with hydroiodic acid. The resulting methyliodides distilled in stream of nitrogen and trapped in bromine were titrated against sodium thiosulphate to calculate the methoxy content (1ml 0.1M sodium thiosulphate ≡ 0.0005172g of methoxy).

Consumption of alkali by free carboxy groups of oxidised GGs (OGGs) was determined, to estimate its carboxy content. OGGs were dispersed in 0.01M sodium hydroxide solution containing sodium chloride and it was allowed to stand for 18h. The excess alkali was titrated against 0.02N hydrochloric acid, using bromocresol purple as an indicator. The carboxy content values

were reported in milliequivalents of sodium hydroxide consumed per gram of OGGs.

Calibration curves of chlorpheniramine maleate (CPM), diltiazem hydrochloride (DIL) and phenylpropanolamine hydrochloride (PPA) were prepared by direct UV-spectroscopy and used for estimation of these drugs in the dosage forms and the dissolution medium. Standard solutions of the drugs were prepared in water, 0.1N hydrochloric acid and phosphate buffers of pH5.4, 6.8 and 7.4. The absorbance maxima was determined in each case by scanning standard solutions of concentration 10mcg/ml for CPM and DIL and 200mcg/ml for PPA. Absorbance of the standard solutions was measured at the absorbance maxima and plotted graphically to get calibration curves. Regressional analysis of the data proved the linearity of the plots in the concentration range used. Interference of excipients in the concentration range used was also checked.

A high performance liquid chromatographic method was used for determination of PPA in urine without prior derivatisation as reported by R.Dowse et al. High performance liquid chromatograph, Waters 501, equipped with C18 column and 254 nm detector, was employed for the estimation. Calibration curve of peak area against the concentration of solution was plotted and its linearity proved by regressional analysis in the concentration range of 20 - 200 mcg/ml.

8.3 MODIFICATION AND CHARACTERISATION OF GG

GG was chemically modified by partial acid hydrolysis, methylation, oxidation, and carboxymethylation to overcome its limitations.

Hydrolysis was performed using a mixture of dilute hydrochloric acid with a polar organic solvent, methanol, in 1:1 ratio. The presence of polar O-

containing organic solvent like methanol provides resistance to hydrolysis. It also prevents complete hydration of gum, resulting in controlled hydrolysis of GG. The degree of hydrolysis was varied using hydrochloric acid of strengths 0.1N, 0.2N, 0.3N and 0.5N and allowing the reaction to continue for 1 to 5 hours. Product was recovered by drying under vacuum (15 inches Hg at 40°C). The presence of organic solvent, which prevents complete hydration of gum, also results in faster drying and easier recovery of HGGs. HGGs were characterised with respect to their bulk and tapped densities, viscosities and the degree of hydrolysis in terms of amount of reducing sugars liberated on hydrolysis. No significant change in the bulk and tapped densities was observed with change in degree of hydrolysis. Viscosity values reduced with increased degree of hydrolysis (8266.65 ± 15.28 cps of GG to 1448.91 ± 11.12 cps of HG52). The amount of sugars liberated on hydrolysis, was used as a measure to degree of hydrolysis, which was found to increase (33.75 ± 1.71 mg/10g of GG to 856.90 ± 5.79 mg/10g of HG52) with increased strength of acid and duration of hydrolysis.

GG was methylated using dimethylsulphate as the methylating agent in the presence of strong alkali, 40% w/v aqueous solution of sodium hydroxide, which serves to promote ionization of pertinent hydroxyl function. GG has high intrinsic viscosity, so hydration leads to gelling of the reaction mixture. Gelling of the reaction mixture was prevented by using low temperature (4°C ± 0.5°C) and high pH which suppresses hydration of GG. A polar organic solvent, methanol was added to the reactants to prevent hydration of gum when the temperature of reaction was raised, after addition of dimethylsulphate. This also allows the reaction to proceed at favorable kinetic rates, by preventing the solvation of hydroxyl groups. The degree of substitution of the methylated gum was altered by changing the amount of dimethylsulphate. MGGs were characterised by

the I.R. spectroscopy, methoxy content, viscosity determination and differential scanning calorimetry. I.R. spectra of MGGs confirmed the presence of methoxy group (peaks at 1080 - 100 cm^{-1}). Methoxy content values were determined using semi-micro Zeisel method, which increased with increase in the amount of methylating agent, dimethylsulphate, used for methylation (MG1 - 2.20% ± 0.05 to MG6 - 4.04% ± 0.02). Viscosity values were determined using Brookefield viscometer. A sharp decline in viscosity of MGGs was observed with increased degree of methylation (8266.65 ± 15.28 cps of GG to 327 ± 14 cps of MG6) which reflects some chain cleavage of GG polysaccharide on methylation. Hence, methylation of GG was done at relatively mild conditions and in presence of organic solvent.

Small amounts of periodate preferentially oxidise the galactose moiety leaving the mannose backbone intact, and reduced galactose-mannose ratio in the GG molecule show better interaction properties . Taking these facts into consideration, GG was oxidised using aqueous solution of sodium metaperiodate in presence of water miscible organic solvent, acetone. The strength of sodium metaperiodate solution used was varied to change the degree of oxidation. The aqueous solution causes hydration of gum which makes both the recovery of the product and control over the degree of oxidation, difficult. The reaction was, therefore, carried out in a solvent mixture of water and acetone. The products were easily recovered by filtration and the costly precipitation method for recovery of gum product was eliminated. OGGs were characterised by the bulk density, tapped density and carboxy content. No significant change was observed in the bulk and tapped densities. Carboxy content values increased (OGG1 - 60.53 ± 1.65 meq/g to OGG5 - 112.80 ± 1.85 meq/g) with increased amount of periodate used for oxidation.

Sodium carboxymethylguar(NaCMG) was synthesized using 75% w/v aqueous solution of monochloroacetic acid solution after dispersing GG in 40%w/v aqueous solution of sodium hydroxide. The reaction was carried out in a hydroalcoholic medium to control the reaction rate by restricting the hydration of GG. To alter the degree of carboxymethyl substitute in GG, the reaction was carried out with increased amount of monochloroacetic acid solution. Synthesized NaCMGs were subjected to viscosity determination, differential scanning calorimetry. The fall in viscosity may be attributed to the hydrolysis of GG in alkaline medium alongwith formation of sodium salts. Shift in endothermic peak in thermograms confirmed the formation of new compound after the reaction. The reaction conditions were altered and optimised with objective to control the viscosity of NaCMG, so as to use the polymer in aqueous dispersion as a film former. Optimised conditions were (a) 20 ml of 75% w/v aqueous solution of monochloroacetic acid, (b) 6h duration of reaction and (c) 3h duration of exposure of GG to alkali before addition of the derivatizing solution, the solution of monochloroacetic acid .

8.4 MODIFIED GGs AS HYDROPHILIC MATRICES FOR CONTROLLED RELEASE

Controlled release matrix tablets were prepared using GG and the modified GG products (HGGs, MGGs, OGGs, NaCMGs). Preliminary screening of these tablet preparations was done by measuring the gel strength of the matrix tablets after hydration for 8 hours as described by van Aerde *et al.* When tablets come in contact with water, water enters into the pores of the tablet and hydrates the gum. On hydration, the polymeric chains of the gum undergo transition from glassy state to dynamic rubbery state which is manifested in the formation of a gel. The strength of this gel layer was measured for preliminary screening of the matrix preparations. It was observed that matrix tablets with OGGs and NaCMGs either disintegrate within 2 hours or form soft mass. Partial acid hydrolysis and methylation of

GG to very low degrees give products that have sufficient gel strength required for matrix formation. Thus, the modified GG products can be arranged in the following order of gel strength :

OGGs < NaCMGs < MGGs < HGGs

Hence, only HGG and MGG matrix controlled release tablets were subjected to further investigations.

The water penetration and subsequent swelling characteristics of these products were studied by hydrating the tablets with purified water and recording the changes in the surface area of the tablets with respect to time. A comparison of swelling characteristics of GG , HGGs, MGGs and a commercially available hydrogel, hydroxypropyl methylcellulose K4M (HPMC) was made. In initial half an hour and one hour of exposure to water, GG tablets were found to be covered with non-cohesive loose spongy mass on their surface. On the other hand, the surface of HPMC matrix tablets were seen to gel immediately on exposure to water. This behavior of GG may be attributed to its poor rate of hydration. HGG and MGG matrices show similar gelling characteristics as those of HPMC matrix tablets. HGG and MGG matrices exhibiting similar swelling behavior as of HPMC were subjected to *in vitro* dissolution studies and *in vivo* evaluation.

GG, HGGs, MGGs and HPMC were used in the concentrations of 40 % w/w of matrices. The data of mean cumulative percent drug release as a function of time show that GG matrix tablets released 37.06% (±2.13) of drug in initial half an hour and 48.32% (±2.93) in one hour. In case of HPMC matrix tablets, a release of 29.3% (± 0.99) in first half an hour and 40.58% (± 0.07) in one hour was observed, which is significantly lower as compared to GG matrix tablets. The reason for the burst effect in case of GG matrix tablets may be due to the erosion of matrix surface because of poor

rate of hydration. The presence of water in the pores of tablet not only hydrates the gum but also dissolves the drug *in situ*, which gets released from the matrix by diffusion. The gel layer once formed acts as a barrier to water penetration into the tablet matrix. The rate of drug release decreases with time. Results also reveal that the decrease in the rate of drug release with time is more in case of GG compared to HPMC. This may be attributed to the formation of a thick and dense gel layer on the surface of GG matrix tablets due to its high intrinsic viscosity compared to HPMC.

The drug release profiles from HGG matrices reveal a significant reduction (10 - 15 %) in the amount of drug released in first half an hour and one hour compared to GG. It was observed that the hydrolysis of GG to a controlled degree gives HGG with improved interaction coefficient and satisfactory gel strength for matrix formation. The process parameters for hydrolysis of GG were altered and optimised to obtain HGG of desired qualities.

Use of MGGs (methylation of GG to low degree) reduced the burst effect which was observed in case of GG matrices. Methylation of GG with dimethylsulphate in presence of strong alkali involves the liability of GG, whereby the chain length of the molecule gets reduced. Methylation, when carried out under controlled and mild conditions, like low temperature and addition of a polar organic solvent, results in MGG with faster rate of hydration and good gel forming abilities.

The effect of composition of matrix, method of preparation of matrix tablets and pH of dissolution media, on the drug release was studied. The composition of matrix was altered using different proportions of water-soluble and water-insoluble diluents. It was observed that the use of water soluble diluents caused faster gelling of the tablet surface compared to the

water-insoluble diluent and hence reduced the burst effect to a greater extent. Dissolution studies of matrix tablets prepared by wet granulation technique show that a lower amount of drug is released in first half an hour and one hour compared to tablets prepared by direct compression. Results also revealed that there was an increase in burst effect at low pH(1.2), whereas there was no significant change in release profile at pH 5.4, 6.8 and 7.4.

The promising HGG (HG23) and MGG (MG3) products were subjected to comparative *in vivo* evaluations using phenylpropanolamine hydrochloride as a model drug. Phenylpropanolamine hydrochloride is excreted unchanged in urine and it can be easily estimated by high performance liquid chromatography in urine samples. These formulations were evaluated *in vivo* using 12 male healthy human volunteers. The volunteers were divided into 4 groups, each group containing 3 volunteers. Each group was subjected to all the 4 types of formulations. A tablet containing 75 mg of phenylpropanolamine hydrochloride was administered to each volunteer with 200 ml of water following overnight fast. Urine samples were collected at definite time intervals and the volume was measured. Representative samples were retained and refrigerated till analysed. One week wash out period was allowed after each study and the study was conducted by complete cross over design. Samples were analysed by HPLC. *In vivo* urinary excretion data confirmed the dissolution profiles of the drug.

8.5 MODIFIED GG AS TABLET DISINTEGRANT

Tablet disintegration is a necessary first step to achieve rapid bioavailability of the active ingredients. Many compounds have been proposed as tablet disintegrants that act through different mechanisms. GG has been used as a tablet disintegrant because of its cold water swellability. But its role as a

disintegrant is limited because of formation of cohesive gel on hydration. Oxidation of GG by sodium metaperiodate results in product which is hydrophilic and water-insoluble. The rate and amount of water uptake, which control the penetration of liquid into the tablet matrix causing tablet disintegration by swelling, were evaluated and compared. The amount of water uptake by GG (0.51 ± 0.02 ml/g) is significantly increased on oxidation (OGG2 - 2.60 ± 0.23 ml/g). The gelling tendency of GG decreases significantly and so water uptake by capillary action is increased significantly. The amount of water uptake increases with increase in degree of oxidation upto a limit (carboxy content - 71.38 ± 1.54 meq/g) and then decreases. The rate of swelling also follows pattern similar to that for amount of water uptake. OGGs with excellent swelling ability and water uptake capacity were found to be good tablet disintegrants. It was also observed that though the degree of oxidation of GG does not change rate of water uptake, it affects the degree of swelling and hence the rate of disintegration. OGG2 was found to be the best of the prepared OGGs as tablet disintegrant. The performance of OGG2 was compared with disintegrants commonly used like crosslinked polyvinylpyrrolidone, crosslinked sodiumcarboxy methyl cellulose, sodium starch glycollate, starch, and microcrystalline cellulose. The tablets with OGG2 as disintegrant show the least DT compared to the tablets with other disintegrants except those with PVP-CL. The examination of the physical parameters show that the density of PVP-CL (0.35) is very less compared to that of OGG2 (0.71), which means that for the same amount of the material the number of particles of PVP-CL will be very high. This leads to better distribution of PVP-CL particles in the tablet matrix and provides a continuous network which can convey water from one grain to other and so on thus reducing DT. Further studies of OGG2 as disintegrant, for the effect of tablet parameters like composition of tablets, compressional forces and pH of disintegrating fluid, revealed no significant effect of these parameters on the disintegration properties of OGG2.

8.6 MODIFIED GG AS A FILM FORMER

Tablet coating is one of the oldest arts employed by pharmaceutical industry. Film coating involves the deposition of a thin, but uniform, membrane of pharmaceutically acceptable resin onto the surface of the substrate. The main prerequisite for the film former is its ability to form a coherent film on the surface of the substrate under the prevailing conditions. Film coatings of HPMC have become popular since they give a superior appearance, act as protective coatings for fragile tablets and can mask the color and unpleasant taste. Modified GGs were evaluated as film formers by casting film in petri plates. It was observed that NaCMGs formed films of excellent qualities in regards to clarity and tensile strength. Further investigations with respect to glass transition temperature and a suitable plasticizer were made by differential thermal analysis. The type and concentrations of plasticizers - propylene glycol (PG), polyethylene glycol 400 (PEG) , and glycerin (GLY), were altered for optimisation of film composition. The films were evaluated for water vapour transmission rate and breaking strength. It was observed that the low viscosity NaCMG with 30% of PEG was a good film former. The results show a significant increase in the breaking strength of NaCMG films when used in combination of 30%PEG (2.88 kg cm^{-4} of NaCMG alone to 6.06 kg cm^{-4} of NaCMG with 30% PEG) Dummy tablets were successfully coated using aqueous solutions of NaCMG with requisite excipients and compared with that coated with HPMC 15cps. The results suggested that NaCMG can be a very useful alternative to HPMC 15 cps for aqueous based film coating of tablets.

8.7 CONCLUSIONS

GG was chemically modified by hydrolysis, methylation, oxidation and carboxymethylation. These chemically modified GG products were

characterised and evaluated for their possible applications in tablet dosage form. The results of this investigation reveal following conclusions:

- Partial hydrolysis of GG and desired degree of methylation of GG enhance rate of hydration of GG and thereby cause rapid onset of cohesive obstructive gel layer around the matrix tablets. Hence HGGs and MGGs were studied as matrix former for controlled release tablets and compared with HPMC matrix tablets using water soluble drugs such as chlorpheniramine maleate, diltiazem hydrochloride, phenylpropanolamine hydrochloride. Both HGG and MGG were found to be very effective in prolonging release of soluble drugs. The release of drug was mainly via diffusion and release profile was close to zero order. Drug release from these matrices was slightly faster in acidic media, due to more rapid initial surface erosion. After hydration of the gum, drug release was essentially pH independent. Composition, compressional force and method of preparation of matrix were also found to slightly influence the release profile of drug. Hence HGG and MGG may be used as alternatives to HPMC and other commercially available hydrogel in designing sustained release solid dosage forms.
- Oxidation of GG was found to impart water-insolubility and increase in rate and amount of water uptake by capillary action as required for an ideal disintegrant. On using OGGs as disintegrants and comparing with commercially available disintegrants such as starch, sodium starch glycollate, crosslinked sodium carboxymethylcellulose and crosslinked polyvinyl pyrrolidone, OGGs were found to be excellent disintegrants.
- Carboxymethylation of GG was found to possess good film forming abilities and hence was evaluated for aqueous based film coating of the tablets. NaCMG was found to be efficient film former and suitable for coating of tablets in aqueous dispersions.

Summing up, it may be safely concluded that chemically modified GG may be used as hydrophilic matrix former, disintegrant and film former in the coatings of tablet. It can be very cost effective and indigenously available substitute for many currently imported expensive excipients used in development of tablet dosage forms. However, the role of these modified GG products can only be settled after toxicological evaluations and pilot plant studies of manufacturing these products for commercial use.

MODIFIED GUAR GUM AS HYDROPHILIC MATRIX FOR CONTROLLED RELEASE TABLETS

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ABSTRACT

Guar gum (GG) a galactomannan polysacchande, has a very high intrinsic viscosity but poor interaction coefficient. Hence an attempt was made to improve its interaction coefficient by controlled hydrolysis using hydrochloric acid (HCl) Hydrolysed GG products (HGGs) were characterised and used as hydrophilic matrix for controlled release tablets containing phenylpropanolamine hydrochlonde (PPA) as a model drug Preliminary screening was done by measuring the gel strength of hydrated matrix tablets The swelling characteristics and dissolution profile from GG\HGG matrices were studied and compared with that from hydroxypropyl methyl cellulose K4M (HPMC) The results suggest controlled hydrolysis produces GG with improved interaction coefficient and dissolution profile. Finally GG/HGG/HPMC matrix tablets were evaluated for *in vivo* performance using male healthy human volunteers Amount of urinary excretion of drug at various sampling time were found to be comparable in case of HGG\HPMC matrix tablets.

Key Words : Guar gum, Hydrolysis, Swelling characteristics, Dissolution profile.

INTRODUCTION

GG[1] is an interesting polymer for preparation of hydrophilic matrix tablets because of its high water swellability, non toxicity and low cost. Inspite of the wide pharmaceutical application of GG, uncontrolled rate of hydration, fall in viscosity on storage and microbial contamination, limit its use. The present investigation was undertaken to suitably modify GG and evaluate modified GGs for its use in development of controlled release tablets using PPA as a model drug The prepared products will be compared with the products made with GG and HPMC as hydrophilic matrices

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EXPERIMENTAL PROCEDURES

Materials

Guar gum (National Chemicals, Bombay, India) Hydroxypropylmethylcellulose K4M (Colorcon, USA) lactose, microcrystallinecellulose, magnesium sterate and talc (Chemicals Supply Corporation, India) phenylpropanolamine hydrochloride (Alembic Chemicals, Baroda, India) methyl alcohol A.R. (Qualigens, India) liquefied phenol (Shreyas Research Laboratories, Bombay, India) dilute ammonia solution I.P. (S.D. fine chem. pvt. ltd. Boisar, India) sulphuric acid I P. (Sara fine chemicals, Baroda, India).

Hydrolysis and Characterisation of GG

20 gm of GG was dispersed in 50 ml HCl : Methanol (1:1) mixture in beaker by stirring at a

Table I : Hydrolysis and characterisation of guar gum

Sr. No.	Product	Normality of HCl (N)	Duration of Hydration (H)	Amount of Red. Sug. mg/10g (S.E.)	Viscosity (cps) (S.E.)
1.	G G			33 75 (1 71)	8266 65 (15 23)
2.	H11	0 10	1 00	261.00 (3.56)	6230.50 (14 48)
3.	H1,2	0.10	2 00	400.45 (3.83)	6093 00 (14.94)
4.	H1,3	0 10	3 00	420.65 (7.08)	5585.90 (12.27)
5.	H1,4	0 10	4 00	490.80 (4.20)	5383 00 (12 83)
6	H1,5	0 10	5 00	510 45 (6 25)	523(50 (12 99)
7	H2,1	0 20	1 00	423 55 (5 07)	5746 36 (14 77)
8	H2,2	0 20	2 00	429.45 (4 34)	5536 77 (12 28)
9.	H2,3	0 20	3 00	534.95 (4.85)	4908 01 (14.96)
10	H2,4	0 20	4 00	559.50 (5.68)	4646 03 (15.72)
11	H2,5	0 20	5 00	633.60 (3.84)	4305 45 (12.28)
12	H3,1	0.30	1.00	579.14 (5.77)	3305.45 (10.34)
13	H3,2	0.30	2 00	662.60 (5.23)	2881 82 (9.73)
14.	H5,1	0.50	1 00	697.35 (5.23)	2122.06 (10.71)
15.	H5,2	0 50	2 00	856 90 (5.79)	1448.91 (11 22)

rate of 200 ± 10 rpm using overhead mechanical stirrer (Remi. India). Stirring was continued for a period varying from 1 to 5 hours at room temperature (33 ± 2°C). The reaction was terminated by raising the pH of the mixture to 7 0 with dilute ammonia solution The product was dried under vacuum at 40°C to a constant weight. Hydrolysis was done using dilute HCl of strengths 0.1N, 0.2N, 0.3N and 0.5N to vary the degree of hydrolysis.

Estimation of Sugars was done using the phenol - sulphuric acid method of Dubois, M et al[2]. Viscosity

Table II : Swelling behaviour of GG/HPMC/HGGs Tablet formulations

Sr. No.	Prod. (Formul)	Surface area (Sq.cm) x 3.14 after Hydration for time (Hrs) (S.E.)						Gel Strength ml (S.E.)
		0.0	0.5	1.0	2.0	4.0	24.0	
1	GG(F#1)	20 26 (0 06)	68 50 (2 87)	88 15 (2 87)	107 50 (2.58)	117 50 (91 19)	122 20 (2 78)	31.73 (0 76)
2	HPMC(F#2)	20.23 (0 23)	56 41 (0 55)	56 65 (0.88)	65 89 (1 02)	78.90 (1.07)	89 93 (1 89)	19 23 (0 77)
3	H1,3(F#5)	20 18 (0 10)	65 92 (0.49)	78 10 (1 23)	102 48 (1 09)	120.00 (1 33)	131 30 (1 69)	27 40 (0.57)
4	H1,4(F#6)	19 98 (0.09)	64.89 (0 55)	77 00 (0 92)	99 60 (0 9[illegible]	116.85 (1 54)	131.30 (2 10)	22 30 (0 68)
5.	H1,5(F#7)	20.43 (0.78)	65.42 (0.67)	82 80 (1 64)	102.48 (2 67)	[illegible]17 80 (2 44)	[illegible]33.62 (3 37)	18 55 (0 79)
6	H2,1(F#8)	19 45 (0 10)	65 52 (0.43)	77 0 (0 78)	102 48 (0 99)	117.80 (1 47)	131 42 (1 78)	27 77 (0 89)
7	H2,2(F#9)	20.18 (0 23)	64 48 (0 67)	77 00 (0 99)	100 43 (1 04)	117.50 (2 08)	133 62 (1 99)	25 65 (0 88)
8	H2,3(F#10)	20 62 (0 06)	63 24 (0 45)	74 12 (0 74)	93.60 (0 99)	112 24 (1 77)	[illegible]29 00 (1.78)	21 05 (0 56)
9.	H2,4(F#11)	19 96 (0.33)	63 86 (0 34)	77 39 (0.86)	97.16 (1.16)	117 80 (1.39)	129 28 (2.54)	12.45 (0.093)

of 1% w/v aqueous solution of GG and HGGs was measured using spindle no. 2 of Brookefield Viscometer LVT model at 12 rpm (Brookefield engineering equipments, Stoughton, Massuchetts, U.S A.). The results are recorded in the Table 1.

Tabletting

Tablets were prepared by direct compression on single stroke compression machine (Cadmach machinenes, Ahmedabad) using 8 mm round flat face die punch set. 200mg tablets were compressed as per the following composition :

Ingredients	Quantity/tablet(mg)
Phenylpropanolamine Hydrochloride	75.00
Hydrogel (GG/HPMC/HGGs*)	70.00
Lactose	51.00
Magnesium Sterate	2.00
Talc	2.00

* HGGs used in the formulations are shown in Table 2

Swelling characteristics and Gel Strength

To evaluate the water penetration and subsequent swelling characteristics, tablets were exposed to purified water and the evolution of tablet surface area was determined by recording the change in the radius and thickness. Tablets subjected to dissolution studies were removed at the sampling time points and dried completely to a moisture content value of below 1% w/w and the weight of the dried tablets was noted, to study the erosion of the tablet surface. The gel strength of hydrated matrix tablets

Table III
Comparative dissolution profile of tablet formulations and drug release kinetics

	Cumulative percent drug release (S.E.) in time (Hrs.)								Kinetic Parameter	
Formulat	0.0	0 5	1.0	2.0	3 0	4.0	5 0	6.0	'n'	'k'
F#1	0.00	41.06 (2 24)	51 34 (1 65)	65.29 (1.59)	80 56 (0.98)	85 91 (0.91)	88 41 (0.99)	90.92 (0.68)	0.1841	0.7606
F#2	0.00	29 31 (0 99)	40.58 (0 07)	51.25 (0 17)	62 99 (0.53)	72.85 (0.60)	82.70 (0 42)	94.36 (0.76)	0.1298	0.7532
F#5	0.00	29.29 (1 06)	44.51 (0 63)	60 28 (1.47)	77.74 (0.65)	84 13 (0.38)	89.58 (0 69)	93.63 (0 42)	0.1306	0.7725
F#6	0.00	29 93 (0 54)	43 43 (0 97)	58.90 (1.41)	79 00 (0 85)	85 41 (0.40)	90 23 (0.49)	93 20 (0.27)	0.1304	0.7728
F#7	0.00	30 26 (0 66)	45 21 (1 01)	64.88 (1.26)	79 04 (0 97)	85 42 (0.68)	90 58 (0.67)	94.64 (0.67)	0.1403	0 7744
F#8	0 00	27 34 (1 75)	42 80 (1.29)	59 91 (1.38)	73 13 (1 16)	77 74 (0 61)	84 13 (0 40)	92 91 (0 42)	0.1256	0.7657
F#9	0.00	26 76 (0 69)	40 46 (0 51)	58 04 (0 44)	69 70 (0 95)	81 37 (0 98)	88 06 (0 69)	94 32 (0 64)	0.1145	0.7703
F#10	0 00	25 65 (0 25)	39.81 (0 96)	53.73 (0 54)	65 55 (0 34)	75:68 (0.34)	83 72 (0 47)	90.31 (0.26)	0.1140	0.7599
F#11	0 00	29 78 (0 81)	44 62 (0.42)	59 78 (0.94)	72 13 (0 93)	84.68 (0 55)	90 22 (0 28)	95.48 (0.13)	0.1316	0 7711

was determined using method reported by P. van Aerde[3]. A breaker was balanced on one plate of two armed balance, at the underside of which a cone shaped pin was fixed (Fig. 1). Water was continously added to the beaker because of which the pin exerted an increasing force on the tablet The gel strength was defined as total amount of water(ml) necessary to perforate the tablet and was determined after complete hydration of matrix (8 hrs) Results are recorded in Table 2

Dissolution Studies

Dissolution studies were performed using USP XXII[4] apparatus (basket assembly) (Veego apparatus, India) at 100 rpm 900 ml of purified water maintained at 37 ± 0.5°C was used as dissolution medium. 5 ml samples were withdrawn at regular intervals, and replaced with fresh dissolution media. Samples were filtered and assayed spectrophotometrically at 257 nm on Carl Zeiss Jena VSU2-P spectrophotometer All dissolution studies were carried out in triplicate for three different batches of each formu-

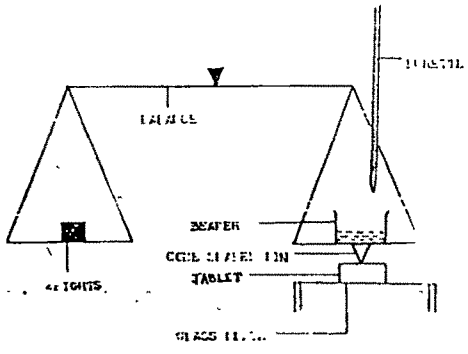

Fig. 1: Gel strength measurement apparatus

lation made on three consecutive days The average of these values alongwith the standard error and recorded in the Table 3.

In vivo Evaluations

In vivo evaluations were performed taking six male healthy human volunteers weighing between 55 - 70 kgs. The volunteers were divided in three groups containing two volunteers each. The volunteers of each group received one matrix (GG(F#1)/HPMC(F#2)/HGG(F#10) tablet each containing 75 mg of PPA, with 200ml water following overnight fast. Urine samples were collected at 0, 1, 2, 4, 6, 8, 12, 20, 24 hours and representative samples were frozen until analysis. One week of wash out period was allowed after each study till each volunteer received all three types of tablets. Samples were extracted and analysed by HPLC (Waters 501) as reported by R. Dowse et al[5]

DATA ANALYSIS

The surface area (S.A) of the tablets was calculated using following equation

$$A = 2 \pi r h,$$

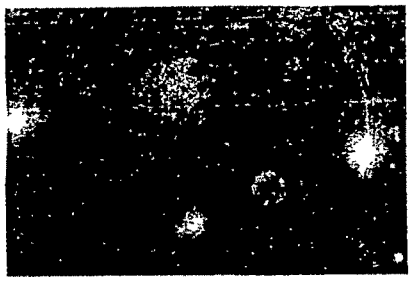

Fig. 2: Comparative Evaluation of Swelling Characteristics GG (F#1)/ HPMC (F#2)

where A is surface area of the tablet; r is the radius of the tablet; h is the thickness of tablets. Mean value of six tablets of each batch was taken and 3 similar batches were evaluated on three different days for determination of rate of increase of S.A , reduction in weight of dried tablets after dissolution and gel strength determination.

Similarly *in vitro* dissolution studies were carried out on 6 tablets and three similar batches were evaluated on three different days. Mean (n=18) cumulative per cent drug release alongwith standard error values are recorded in Table 3.

In vivo evaluations were performed on six volunteers divided in three groups containing two volunteers each. Each group was subjected to all the three types of formulations. Each sample was taken in duplicate for analysis and mean (n=12) cumulative amount of unchanged drug excreted in urine was determined and is shown in Fig. 1.

All comparisons of data were done by ANOVA

RESULTS AND DISCUSSIONS

GG has a very high intrinsic viscosity but very poor interaction coefficient[6]. Hence an attempt was made to improve its interaction coefficient by con-

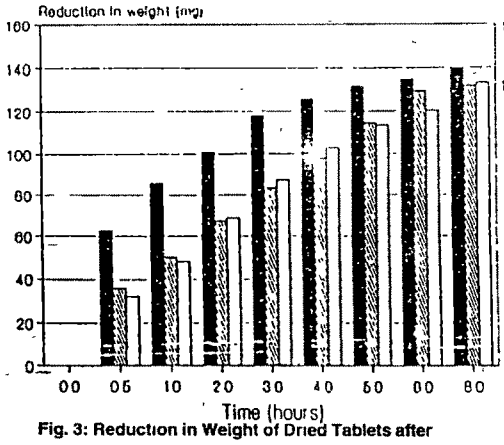

Fig. 3: Reduction in Weight of Dried Tablets after dissolution for time (F#1, F#2, F#10)

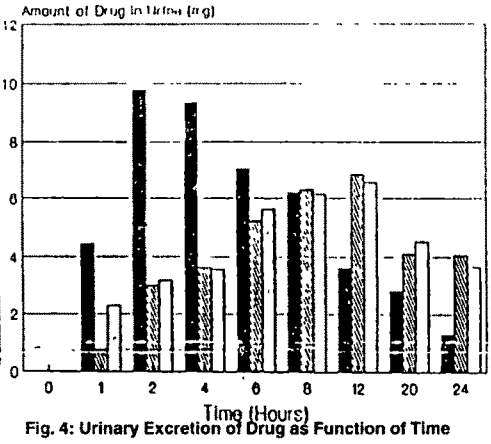

Fig. 4: Urinary Excretion of Drug as Function of Time from GG (F#1)/HPMC (F#2)/HGG (F#10)

trolled hydrolysis Initial attempts made to hydrolyse GG with weak organic acids viz acetic acid, salicylic acid and benzoic acid and mineral acid, HCl failed to give desired results and to control the rate of hydrolysis. The hydrolysis of GG was then carried out using mixture of HCl and a polar O-containing organic solvent, MeOH, not only controlled the hydrolysis, by preventing the hydration of the gum, but also helped in faster recovery of the hydrolysed gum from the reaction mixture Results of viscosity and reducing sugars (Table 1) confirm the change in the degree of hydrolysis with change in the reaction conditions.

The preliminary screening of the tablet formulations was done by measuing the gel strength of the tablets[3] hydrated for 8 hours (Table 1). The formulations with HGGs of higher degrees of hydrolysis (F#13 to F#18) show low gel strength and fail to retain the dimensions after 8 hours hydration, hence were withdrawn from further investigations Reduction in the intrinsic viscosity, due to reduced chain length on hydrolysis may be the reason for lower gel strength of these matrix tablets.

Results of evolution of surface area on hydration, as a function of time (Table 2) show that in case of GG tablets (F#1) the major change in surface area due to swelling is noticed in first hours (0.5 h - 3.425 times; 1h - 4.408 times). GG tablets are seen to be covered with half gelled non-cohesive mass. The formation of strong and cohesive gel, a prerequisite for retarding drug release from gel matrix, develops slowly over a period of time. In contrast to GG tablets, HPMC tablets (F#2) gel on surface instantaneously on exposure to purified water (Fig. 2) Increase in surface area after 1 hour of exposure to water was observed to be only 2.8 times. When water comes into contact with tablet matrix, it enters into the pores of the tablet and hydrates the gum. On hydration the polymer chain of the gum undergo transition from glassy to dynamic rubbery state, which is manifested in the formation of gel. The slower rate of hydration of GG due to its poor rate of interaction coefficient delays the complete gel layer formation as compared to HPMC. Weight of the dried tablet matrix after dissolution of tablet determined at each sampling time point show a sharp decline in the weight of GG matrix tablets in the initial one hour,

which confirms the erosion of GG matrix surface (Fig 3).

HGG tablet formulations F#5 to F#12 show significant change in their swelling characteristics in the first hour of hydration in purified water compared to GG. Results of the weight of the dried tablets determined at fixed time intervals reveal that the reduction in the weight of the tablets of F#10 (H2,3) on dissolution determined as a function of time is similar to that of HPMC matrix tablets (F#2). A comparison of the reduction in the weight of tablets of GG(F#1), HPMC(F#2) and HGG(F#10) is shown in Fig. 3.

The data of mean cumulative percent drug release as a function of time, recorded in Table 3, show that GG tablets release 41.06% (±2.24) of drug in the first half hour and 51.34% (±1.65) in one hour. In case of HPMC tablets (F#2) there is a release of 29.31% (±0.99) in the first half hour and 40.58% (±0.07) in one hour, which is significantly lower as compared to GG tablets (F#1). The reason for this large amount of release may be the erosion of matrix surface as explained in terms of reduction of weight after dissolution for fixed durations and swelling characteristics. The presence of water in the pores of the tablet not only hydrates the gum but also dissolves the drug *in situ*, which gets released from the matrix The gel layer once formed acts as a barrier to water penetration into the tablet matrix and also diffusion of drug from the matrix. The rate of drug release decreases with time. Results also reveal that the decrease in rate of drug release with time is more in case of GG compared to HPMC This may be attributed to formation of a thick and dense gel layer on the surface of GG matrix tablet due to its high intrinsic viscosity compared to HPMC.

HGG tablet formulations show a reduction of 10 - 15% in drug released in first half hour and one hour compared to GG. In fact F#10 (HGG) shows a similar profile as that of F#2 (HPMC). The decrease in the rate of drug release with time is less compared to GG because of lower gel strength but is more compared to HPMC

On comparison of cumulative percent drug release data, within the same batch and among the three batches, it was observed that GG tablet formulations show a significant variation in release characteristics of drug while HPMC tablets and HGG show non-significant difference in cumulative percent drug release at each sampling point.

Drug release kinetics were studied by fitting the dissolution data to the following exponential release equation.

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

where Mt/Moe is the fractional drug release into the dissolution medium, k is a constant which incorporates the properties of macromolecular polymeric matrix and the drug, n is the diffusional exponent which characterizes the drug transport kinetics[7]. The values of n and k (Table 3) indicate that the drug release from the matrix follows non-Fickian type anomalous drug diffusion mechanism. The values of n of F#2 (0.7532) and F#10 (0.7599) show a significant similarity in the drug release profiles.

Data of GG(F#1)/HPMC(F#2)/HGG(F#10) matrix tablets subjected to in vivo evaluation (Fig 1) indicate significant differences in the drug release profiles. The amount of drug excreted from GG matrix is much higher in initial hours compared to HPMC. Amount of drug excreted from HGG/HPMC matrix tablets were found to be without any significant differences at each sampling point. This behaviour of the drug release from GG\HPMC\HGG matrices is in accordance with the results of *in vitro* dissolution within the limits of error

GG seems to be an interesting indigenous macromolecular hydrogel and may find its use in

development of matrix controlled release tablets dosage forms We may conclude that the controlled hydrolysis of GG by an appropriate method does improve its interaction coefficient Suitable modification in matrix composition may enable to achieve a zero order release kinetics.

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The ether extracts were collected and dried over anh. sodium sulfate, evaporated to dryness with a nitrogen stream and after dissolving each sample in 1000 µl of methanol 20 µl of this solution were injected into the column. Analysis was performed in duplicate and the mean result were taken. The correlation coefficient was found to be 0.9907; regression equation: $y = 0.007855\ x + 0.00333$.

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Modified guar gum as a tablet disintegrant

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The use of guar gum as disintegrant in tablets is limited inspite of its high swelling characteristics due to its slow rate of swelling in aqueous medium, which is the principal mechanism of disintegration. Hence, an attempt was made to chemically modify guar gum (GG) by periodate oxidation to improve its utility as disintegrant. The degree of oxidation was altered and the reaction parameters optimized. Oxidised guar gum products (OGGs) so obtained were evaluated for the chemical and physical properties. Finally GG/OGGs were evaluated as tablet disintegrants and compared with other disintegrants. The results suggest that the OGGs can be suitable or even better alternatives compared to the most popular disintegrants used in tablet formulations.

Modifizierter Guar-Gummi als Tablettensprengmittel

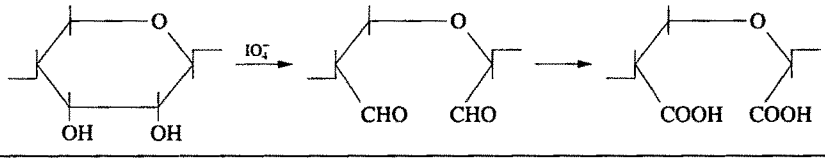
Der Einsatz von Guar-Gummi (GG) als Tablettensprengmittel wird – bei ausgeprägten Quellungseigenschaften – durch eine geringe Quellungsgeschwindigkeit eingeschränkt. Um die Eigenschaften als Sprengmittel zu verbessern, wurde GG durch Periodat-Oxidation modifiziert. Die so erhaltenen oxidierten Guar-Gummi-Produkte wurden mit anderen Sprengmitteln verglichen. Sie erwiesen sich als gleichwertig oder besser als die üblichen in der Tablettenherstellung eingesetzten Produkte.

1. Introduction

Tablet disintegration is a necessary first step to achieve rapid bioavailability of the active ingredients. Many compounds that act through different mechanisms have been proposed as tablet disintegrants [1–3]. Guar gum (GG), a naturally occurring macromolecular galactomannan polysaccharide, has also been used as a tablet disintegrant [4] because of its cold water swellability. But its role as a disintegrant is limited because of the formation of cohesive gel on hydration.

In the present investigation, an attempt has been made to chemically modify GG, by periodate oxidation, to different degrees to suit the requirements of an ideal disintegrant. Oxidised guar gum products (OGGs) have been compared, for various physicochemical properties with GG. The important factors that influence tablet disintegration like rate and amount of water uptake, have been evaluated and compared. Disintegration time (D.T.) of tablets made using GG, OGGs and disintegrants available in the market have been determined and compared. The effect of tablet parameters such as composition, compressional

Scheme



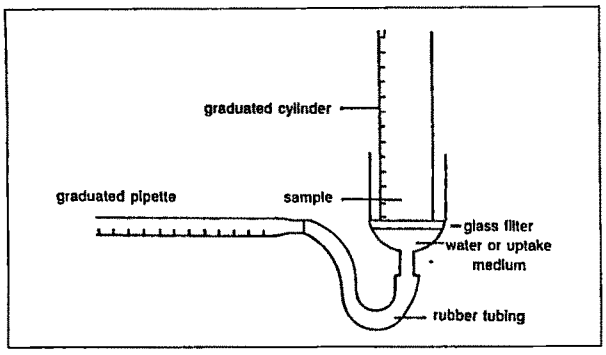


Fig. 1: Water uptake measurement apparatus

force and the pH of disintegration media on D.T. of tablets prepared with OGG as disintegrant have also been studied.

2. Investigations, results and discussion

2.1. Oxidation of GG

GG, a natural macromolecular polysaccharide, consists of D-mannose units with pendant D-galactose groups. Small quantities of periodate preferentially oxidise the galactose moiety [9, 10] as shown in the Scheme.

The reaction was carried out in a solvent mixture of water [5] and an unreactive water-miscible solvent such as acetone, which prevents complete hydration of GG and thereby restricts the rate of oxidation. Thus the addition of an organic solvents helps to control the degree of oxidation and also allows easy separation of oxidised products. A yield of 98.16% (±1.08) was obtained by this method. The amount of periodate for oxidation was altered to get products of different degrees of oxidation.

2.2. Characterisation of OGGs

Bulk and tapped densities were determined before and after oxidation and no significant change was observed. The results of carboxyl content of GG/OGGs (Table 1) indicate an increase in carboxyl content with an increase in the amount of periodate used for oxidation of 10 g of GG.

The amount of water uptake in 2 h by 1 g of GG/OGGs was determined using the apparatus shown in Fig. 1 and the results are recorded in Table 1. GG shows poor amount of water uptake (0.51 ± 0.02 ml/g) due to its gelling at the interface and formation of an obstructive cohesive gel layer which prevents penetration of water inside the GG bed. Oxidation of GG reduces the gelling tendency of the gum and thereby helps in water uptake by capillary action which is also due to unchanged hydrophilicity (and reduced water gelling). The degree of oxidation also influences the amount of water uptake by

Tabelle 1: Oxidation and characterisation of GG

Prods	0.1 M NaIO4 (ml)	Bulk density (g/ml)	Tappet density (g/ml)	Carboxy content (meq/g)	Water uptake (ml/g)
GG	0.0	0.40	0.65	6.28 ± 0.29	0.51 ± 0.02
OGG1	5.0	0.43	0.71	60.53 ± 1.65	1.61 ± 0.12
OGG2	10.0	0.39	0.71	71.38 ± 1.58	2.60 ± 0.23
OGG3	15.0	0.40	0.67	79.34 ± 0.94	2.35 ± 0.07
OGG4	20.0	0.38	0.64	94.90 ± 1.36	2.21 ± 0.13
OGG5	25.0	0.41	0.66	112.80 ± 1.85	2.00 ± 0.04

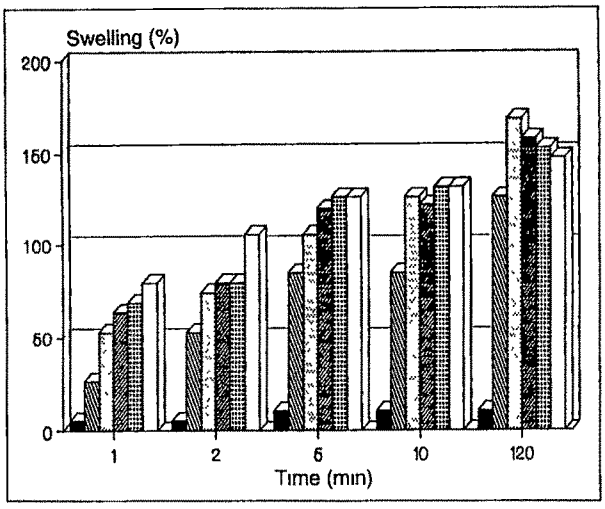


Fig. 2: Swelling characteristics of GG/OGGs

OGGs. The amount of water uptake increases with an increase in the degree of oxidation up to a carboxyl content of 71.38 ± 1.54 meq/g (2.60 ± 0.23 ml/g) and then decreases. Increasing the degree of oxidation further, leads to oxidation of the mannose backbone thereby reducing the chain-length as well as the molecular size and weight of the polymer and hence decreasing water uptake.

In the same apparatus (Fig. 1) the swelling characteristics of the products were studied. The data of rate and degree of swelling of GG/OGGs (Fig. 2) suggest that swelling behaviour follows a similar pattern as that found in the amount of water uptake. The rate of swelling increased with an increase in the degree of oxidation but the degree of swelling reduced beyond OGG2. This phenomenon may be explained by a reduction in molecular size/weight which increases hydrophilicity but reduces water swellability.

2.3. Comparison of GG and OGGs disintegrants

All the formulations were subjected to a disintegration test using U.S.P. XXII disintegration test apparatus. The tablets made with 5% GG (F#2) shows reduction in disintegration time (D.T.) from >30 min to 13.0 ± 1.5 min compared to tablets made without a disintegrant (F#1). Similarly, tablets containing 5% of OGGs (F#3 to F#7) show a noticeable reduction in D.T. (7.43 ± 1.75 times to 3.25 ± 0.51 times) compared to the tablets containing 5% GG (F#2) as disintegrant. The reason for this noticeable reduction in D.T. of tablets containing OGGs compared to GG as disintegrant may be the increased rate and amount of water uptake and degree of swelling which are the major parameters playing a role in the disintegration of these tablets.

Among OGG containing tablets (F#3 to F#7) D.T. increases with an increase in the degree of oxidation up to a carboxyl content of 71.38 ± 1.54 meq/g (OGG2) Along with a further increase in the degree of oxidation, i.e. carboxyl content 79.39 ± 0.94 meq/g and beyond (OGG3, OGG4 and OGG5), D.T. decreases. Oxidation of GG beyond a point (carboxyl content 79.39 ± 0.94 meq/g and beyond) may involve oxidation of the mannose backbone reducing the chain-length as well as molecular weight and size of the polymer leading to a reduction in rate and amount of water uptake and increased solubility of the polymer in water.

Table 2: Composition of tablets and their evaluation

Formulation	Ingredients (% w/w)						
	Lact.	DCP	MCC	Starch	Disintegrants[a]	D.T.[b] (min)	Time[c] reduction
F#1	68.0	25.0	–	–	–	>30	–
F#2	63.0	25.0	–	–	GG	13.0 ± 1.50	1.0 ± 0.00
F#3	63.0	25.0	–	–	OGG1	3.50 ± 0.50	3.71 ± 0.44
F#4	63.0	25.0	–	–	OGG2	1.75 ± 0.50	7.43 ± 1.75
F#5	63.0	25.0	–	–	OGG3	2.50 ± 0.50	5.20 ± 0.90
F#6	63.0	25.0	–	–	OGG4	3.50 ± 0.50	3.71 ± 0.44
F#7	63.0	25.0	–	–	OGG5	4.00 ± 0.70	3.25 ± 0.51
F#8	63.0	25.0	–	–	PVP-CL	1.25 ± 0.20	10.40 ± 1.78
F#9	63.0	25.0	–	–	NaCMC-CL	3.00 ± 0.50	4.33 ± 0.61
F#10	63.0	25.0	–	–	SSG	5.50 ± 0.50	2.36 ± 0.17
F#11	63.0	25.0	–	–	MCC	9.00 ± 1.00	1.44 ± 0.13
F#12	63.0	25.0	–	–	Starch	8.00 ± 1.00	1.63 ± 0.13
F#13	–	68.0	–	25.0	–	1.25 ± 0.20	10.40 ± 1.78
F#14	–	63.0	–	25.0	OGG2	0.80 ± 0.10	16.25 ± 2.59
F#15	–	68.0	25.0	–	–	1.50 ± 0.20	8.67 ± 1.22
F#16	–	63.0	25.0	–	OGG2	0.25 ± 0.00	52.0 ± 10.49
F#17	25.0	68.0	–	–	–	>30	–
F#18	25.0	63.0	–	–	OGG2	4.00 ± 0.50	3.25 ± 0.33
F#19	–	25.0	68.0	–	–	2.50 ± 0.50	5.20 ± 0.89
F#20	–	25.0	63.0	–	OGG2	0.25 ± 0.00	52.0 ± 8.92
F#21	–	–	68.0	25.0	–	0.15 ± 0.00	86.67 ± 15.80
F#22	–	–	63.0	25.0	OGG2	0.15 ± 0.00	86.67 ± 15.80
F#23	25.0	–	68.0	–	–	22.00 ± 2.00	0.59 ± 0.04
F#24	25.0	–	63.0	–	OGG2	6.00 ± 1.00	2.17 ± 0.30
F#25	68.0	–	25.0	–	–	>30	–
F#26	63.0	–	25.0	–	OGG2	2.00 ± 0.50	6.50 ± 1.43
F#27	68.0	–	–	25.0	–	>30	–
F#28	63.0	–	–	25.0	OGG2	2.50 ± 0.50	5.20 ± 0.90

[a] 5% w/w of the disintegrants have been used in all cases
[b] Measured at constant hardness (4.5 ± 0.05 kg/cm²) and pH of the dismtegration media (6.8)
[c] 13.0 ± 1.5/D.T. (min) of respective formulation

Table 3: Effect of compression forces on D.T. of tablets at constant pH

Formulation	D.T. (min) at hardness (kg/cm²)				
	3.5 ± 0.5	4.5 ± 0.5	5.5 ± 0.5	6.5 ± 0.5	8.0 ± 0.5
F#4	1.25 ± 0.1	1.75 ± 0.5	2.25 ± 0.2	2.75 ± 0.3	3.50 ± 0.2
F#8	1.00 ± 0.0	1.25 ± 0.2	1.50 ± 0.2	1.50 ± 0.2	1.75 ± 0.5
F#9	2.00 ± 0.2	3.00 ± 0.5	3.50 ± 0.3	4.50 ± 0.1	6.00 ± 0.7
F#10	5.25 ± 0.2	5.50 ± 0.5	6.00 ± 0.5	6.50 ± 0.3	7.25 ± 0.2
F#11	8.00 ± 0.8	9.00 ± 1.0	10.00 ± 1.0	12.00 ± 0.7	13.00 ± 0.5
F»12	7.00 ± 1.5	8.00 ± 1.0	8.00 ± 0.5	8.25 ± 0.5	8.50 ± 1.0

Table 4: Effect of pH of disintegration medium on D.T. of tablets at constant hardness (4.5 ± 0.5 kg/cm²)

Formulation	D.T. (min) of formulations at pH				
	1.2	5.8	6.8	7.4	9.0
F#4	1.50 ± 0.2	1.75 ± 0.2	1.75 ± 0.2	1.75 ± 0.3	1.75 ± 0.2
F#8	1.00 ± 0.1	1.25 ± 0.2	1.25 ± 0.5	1.25 ± 0.5	1.50 ± 0.1
F#9	3.00 ± 0.5	3.00 ± 0.5	3.25 ± 0.5	3.50 ± 0.2	3.50 ± 0.1
F#10	5.25 ± 0.5	5.50 ± 0.5	5.50 ± 0.7	6.00 ± 0.5	6.00 ± 0.5
F#11	8.50 ± 0.5	8.50 ± 0.7	8.75 ± 0.7	9.00 ± 0.2	9.00 ± 0.2
F#12	8.00 ± 1.0	8.00 ± 0.5	8.00 ± 0.5	8.00 ± 0.2	8.25 ± 0.2

The performance of OGG2 was compared with disintegrants commonly available in the market. The tablets with OGG2 as disintegrant show faster disintegration compared to the tablets with other disintegrants except those with PVP-CL. Examination of the physical parameters show that the bulk density of PVP-CL is very small (0.35) compared to that of OGG2 (0.71), which means that for the same amount of material the number of particles of PVP-CL will be very high. This leads to better distribution in the tablet matrix and provides a continuous network which can convey water from one grain to the next and thereby reduce D.T.

2.4. *Influence of diluents*

The composition of water soluble/insoluble excipients was varied and the D.T. of tablets with and without OGG2 as disintegrant (F#13 to F#28) was determined. The results (Table 2) of these variations reveal that the composition of the tablet matrix has a significant effect on D.T. of the tablets and OGG2 is effective as a disintegrant in all cases.

2.5. *Influence of compression forces*

Tablets containing GG, OGG2 and other disintegrants were prepared at varying compression forces and subjected to hardness and D.T. tests (Tables 3, 4). An increase in D.T. was observed with an increase in hardness of the tablets and the disintegrants can be ranked, with respect to the effect of hardness as

PVP-CL < Starch < SSG < OGG2 < NaCMC-CL < MCC

The rate of penetration of fluids into a tablet is proportional to the mean pore diameter or porosity, change in degree of deformation of disintegrant under pressure, when other factors are constant, which decrease with increase in compressional forces.

2.6. *Influence of pH*

D.T. of tablets with OGG2 as disintegrant (F#4, F#8 to F#12), determined at the physiological pH range (Table 3) suggest no significant variation in D.T. with change in pH of the disintegration media.

3. Experimental

3.1. *Materials*

Guar gum I P (National Chemicals, Bombay, India), sodium metaperiodate A.R., sodium hydroxide A R , sodium chloride A.R. (S D. Fine Chem Pvt Ltd., Boisar, India), dibasic calcium phosphate I P (DCP), microcrystalline cellulose (MCC), starch (Modern Chemical Corporation, Bombay, India), magnesium stearate I P., purified talc I.P (Comet chemicals, Bombay, India), sodium starch glycollate (SSG) (D P chemicals, Solapur, India), bromocresol purple (B D H Laboratory Chemicals division, Poole, England), crosslinked polyvinyl pyrrolidone (PVP-CL), crosslinked sodium carboxymethylcellulose (NaCMC-CL) (courtesy M J Institute of Research, Baroda, India), acetone A.R., hydrochloric acid A R (Merck (India) Limited, Bombay, India).

3.2. *Equipment*

Single stroke compression machine (Cadmach Machinery, Ahmedabad, India) Tablet friability tester, hardness tester (Magumps Instruments, Bombay, India), tablet disintegration test apparatus (Veego Scientific Instruments, Bombay, India)

3.3. *Methods*

3.3.1 *Oxidation of GG*

GG (10 g) was oxidised to different degrees using variable quantities of 0.1 M sodium metaperiodate (Table 1) for a fixed duration of 2 h [5] The product was filtered and dried under vacuum of 20 inches at 40 °C to a constant weight

3.3.2 *Characterisation of OGGs*

Bulk density and tapped density: Five g of powder was transferred to a measuring cylinder to determine the volume Bulk density was calculated as the ratio of the sample weight to sample volume A measuring cylinder was dropped from a height of a half inch at the rate of 20 times/min and tapped density was determined (Table 1).

Carboxyl content: 40 ml of 0.01 M sodium hydroxide solution containing 25 g/l sodium chloride was transferred to a 250 ml conical flask and 1 g of sample (GG/OGG) was added to the flask [6]. The reaction was carried out at room temperature for 18 h and excess alkali was back titrated with 0.02 N HCl using bromocresol purple as indicator A blank titration was also carried out in parallel Each titration was done in triplicate and the mean values of carboxyl content in meq/g were calculated The values are recorded in Table 1

Water uptake: The water uptake capacity of GG/OGGs was determined using the apparatus shown in Fig. 1 [7] and calculated as

$$U = W_{t_\infty}/W_{t_0} \quad 1/p \qquad (1)$$

where U is water uptake of powder bed (ml/g), W_{t_∞} is final weight of the powder bed (g), W_{t_0} is the initial weight of the powder bed (g), and p is the specific gravity of water (g/ml)

The results of average water uptake from six samples of each product along with the standard error values are shown in Table 1

Rate of swelling: In the same apparatus (Fig. 1) the swelling of the powder bed with respect to time (n = 6) was calculated using eq. 2.

$$S = (h_t - h_0)/h_0 \quad 100 \qquad (2)$$

where S is the degree of swelling (%), h_t is the height of powder bed at time t, h_0 is the height of powder bed at time t = 0

3.3.3 *Tabletting*

Tablets of average weight 250 mg were compressed by wet granulation technique on a single stroke compression machine using an 8 mm die punch set The composition of the formulations is shown in Table 2 Disintegrants in the concentration 5% w/w of tablets were used in all cases

OGG formulations showing promising results were taken for further investigation of the effect of composition of formulation, compression force and pH of the disintegration media on D T. of tablets

3.3.4. *Disintegration test*

One tablet was placed in each of the six tubes of the basket of the U S P XXII [8] disintegration test apparatus and the apparatus was operated using water maintained at 37 ± 2 °C as the disintegration medium The time required for the tablets to disintegrate was noted and recorded in Tables 2, 3 and 4.

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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 dimethylsulphate. 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.

Key Words : **Guar gum , Methylated guar gum , Hydrophilic matrix , Drug release.**

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 formulation 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 from GG and MGG matrices and factor affecting it has been evaluated *in vitro* and compared.

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, Boisar, 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 45ml of it was transferred to a clean 250 ml round bottom flask . This was maintained at temperature of around 4° using ice bath and 10g 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 hours 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 inches at 40 ° to a constant weight in a vaccum 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 100kg/cm^2 for 30 sec and I R spectra was recorded from 400cm^{-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 1g of GG/MGGs in 100ml purified water 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 values are recorded in Table 1.

Tabletting :

The composition of the formulations is shown in Table 1. 200mg controlled release matrix tablets were compressed using 8 mm round flat face beveled edged punches with GG/MGGs matrices at same ressure 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 XXII[8] dissolution apparatus with basket assembly at 100 ± 5 rpm. 900 ml of purified water maintained at 37° ± 0.5 °C was used as dissolution medium. 5ml 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-visible spectrophotometer. The data of mean cumulative per cent drug release and time (hours) are recorded in Table 2 and a comparision of dissolution profiles of different formulations for 2 hours are shown graphically in Fig 2.

DATA ANALYSIS

Mean cumulative per cent drug release alongwith its standard error value were 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 C M Rafique[10] after suitable modifications GG has very high intrinsic viscosity so on hydration leads to gelling of the reaction mixture. 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 (Fig 1). The results (Table 1) reveal an increase in the degree of substitution with increase in the amount of dimethylsulphate used for methylating GG. However with increase in methoxy content viscosity of MGGs declines sharply (from 8000 ± 24 of GG to 327±14 cps of MG6), hence controlled methylation was done to produce desired characteristics in naturally occurring GG polymer Reduction in viscosity may be due to chain cleavage of the guar galactomannan polyasaccharide

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 shown in Fig 2. Drug release profile from GG matrix tablets show high per cent 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 factor 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 & 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[11] 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 the 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. This effect was observed to increase with increase in the degree of methylation upto MG3 and then decreased. The results also show that the rate of drug release increased with increase in degree of methylation (MG1 - 15.24 ± 2.95 % / hour to MG6 - 23.83 ± 2.05 % / hour) . This signifies a reduction in gel strength of the MGG matrix tablets, 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) does change 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#13) 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 a 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.

CONCLUSIONS

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 & method of preparation of MGG matrix tablets as compared to GG matrix tablets.

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