Research Article

COMPARATIVE EVALUATION STUDY OF MATRIX PROPERTIES OF NATURAL GUMS AND SEMI-SYNTHETIC POLYMER

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ABSTRACT

Purpose: The objective of this study was to compare the granulation and tablet properties of natural gums with the extensively investigated hydrophilic matrices hydroxypropyl methylcellulose as suitable hydrophilic matrix systems. Methods: The granules were prepared by wet granulation method and granulation properties like angle of repose, bulk density, tapped density, Carr's compressibility index, Hausner's ratio and drug content were compared. Various sustained release matrices of prepared granules were prepared using HPMC (F1), Guar gum (F2), Xanthan Gum (F3), Locust bean gum (F4) and chitosan (F5). The matrix tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness and *in vitro* dissolution using USP XXIV dissolution apparatus. Results: All the formulations showed compliance with pharmacopoeial standards. A significant difference in release pattern was observed between the formulation F1, F2, F3, F4 and F5. F1, F3 and F5 release almost ~9% compare to initial burst effect of ~31% for F4 and F2 after 1h of dissolution period. At the end of 8 h of dissolution period it was found that 71.36%, 85.91%, 96.98%, 68.76% and 45.5% of drug release for F2, F4, F5, F3 and F1, respectively. Conclusions: Thus, natural gums show granulation and tablet properties that are similar to those of the extensively investigated hydrophilic matrices, HPMC. This suggests that the natural gums may be an ideal candidate in the formulation of matrix tablets on controlled drug delivery.

KEY WORDS: Guar gum, Locust bean gum, Xanthan gum, Chitosan, HPMC, Flow properties, Matrix tablet

INTRODUCTION

Natural gums and their derivatives are used widely in pharmaceutical dosage forms as biodegradable polymeric materials to deliver bioactive agents have been hampered by the synthetic materials. These natural polysaccharides do hold advantages over the synthetic polymers, generally because they are nontoxic, less expensive, and freely available. Natural gums can also be modified to have tailor-made materials for drug delivery systems and thus can compete with the synthetic biodegradable excipients available in the market. Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Guar gum is a nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, family Leguminosae. It consists of linear chains of (1?4)-â -D-mannopyranosyl units with á-D-galactopyranosyl units attached by (1?6) linkages. In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant [1-3]. A few reports appear on the use of guar gum, as a hydrophilic matrix, for designing oral controlled release dosage forms [4-6]. Xanthan gum (XG) is another natural hydrophilic, biosynthetic, edible gum and an extracellular polysaccharide produced by the bacterium Xanthomonas campestris. XG consists of glucose, mannose, and glucuronic acid and is recently being use in thickening, suspending, and emulsifying water-based systems [7]. It appears to be gaining appreciation for the fabrication of matrices with uniform drug release characteristics [8-11]. LBG is another plant seed galactomannan, composed of a 1-4-linked â-*D*-mannan backbone with 1-6-linked á-*D*galactose side groups [12]. The physico-chemical properties of galactomannan are strongly influenced by the

galactose content [13] and the distribution of the galactose units along the main chain [14]. LBG is also used to treat elevated plasma cholesterol levels in healthy subjects [15]. Chitosan, a deacetylated derivative of chitin, is another natural polysaccharide found abundantly in marine crustaceans, insects and fungi. Properties such as biodegradability, non-toxicity, good biocompatibility, especially mucoadhesive property and swelling behavior make it suitable for use in biomedical and pharmaceutical formulations [16-18]. In recent years, chitosan has been proposed as a useful excipient for obtaining a sustained release of water soluble drugs and for enhancing the bioavailability of poor water soluble compounds. Therefore, chitosan may be suitable for preparing a controlled release formulation. Comparatively, Hydroxypropylmethylcellulose (HPMC), semi synthetic non ionic cellulose ether, is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems [19]. Numerous studies have been reported in literature investigating the HPMC matrices to control the release of a variety of drugs from matrices [20-24].

Powder flow is a key requirement for pharmaceutical manufacturing process. Tablets are often manufactured on a rotary multi-station tablet press by filling the tablet die with powders or granules based on volume. Thus, the flow of powder from the hopper into the dies often determines weight, hardness, and content uniformity of tablets. In case of capsules manufacturing, similar volume filling of powders or granules is widely used. Understanding of powder flow is also crucial during mixing, packaging, and transportation. And thus, it becomes essential to measure the flow properties of these materials prior to tabletting or capsule filling. There are various methods available to measure the powder flow. The compendial methods include measurement of angle of repose [25], bulk density, tapped density [26], Carr's compressibility index [27], or Hausner's ratio [28].

For instance, powder flow measurement by angle of repose and avalanching has limitations for very cohesive powder which doesn't flow through the funnel and vibrating the funnel introduces inherent variability in measurement technique. These methods suffer from various limitations including reproducibility, performance conditions, and predictability. So far no single test has been accepted as a standard for measurement of powder flow.

Thus, the objective of this study was to compare the granulation and tablet properties of natural gums with the extensively investigated hydrophilic matrices (hydroxypropyl methylcellulose, HPMC) as suitable hydrophilic matrix systems.

MATERIALS

Theophylline: Lifeline Industries Limited, Mumbai
Guar gum: Dabur Research Foundation, New Delhi, India
Xanthan gum: Lucid colloids, Mumbai
Locust bean gum: Lucid colloids, Mumbai
Chitosan: Central Fisheries Technology, Cochi
HPMC (K15): Loba Chemie Pvt. Ltd., Mumbai
Others: S.D. Fine-chem Ltd. Mumbai

PREPARATION OF SUSTAINED RELEASE MATRIX TABLET

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in Table 1. Theophylline and polymer were mixed in a polybag, and the mixture was passed through 60 mesh sieve. Granulation was done using a solution of PVP K90 in sufficient isopropyl alcohol by using Micro crystalline cellulose as diluent. The wet mass was passed through mesh No 8. The wet granules were air dried for ~2 hours. The granules were then sized by mesh No. 16 and mixed with magnesium stearate and talc. Tablets were compressed at 500 mg weight on a 10-station mini rotary tableting machine (General Machinery Co, Mumbai, India) with 12-mm punches. Five different formulas, having different polymers viz. guar gum, xanthan gum, chitosan, locust bean gum and HPMC K15, were developed to evaluate the drug release and to study the effect of different polymer on drug release.

CHARACTERIZATION OF GRANULES

The characteristic parameters of the granules were evaluated. The angle of repose and flow rate were determined by the funnel method.

Angle of Repose

Flow properties of the prepared granules were evaluated by determining the angle of repose and compressibility index. Static angle of repose ($?^0$) was measured according to the fixed funnel and freestanding cone method of Banker and Anderson. The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a stainless steel funnel and the size of the orifice was 10 mm and the height from the beginning of funnel to end of orifice was 111 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured. The angle of repose (?) was calculated as follows:

$$\text{è} = \tan\text{-}1(h/r)$$

Results were only considered valid when a symmetrical cone of powder was formed.

Bulk and Tap Density

Bulk and tap density were determined in triplicate in a weighed 250-mL cylinder using a volumeter (Erweka GmbH, Heusenstamm, Germany).

A quantity of 100 g of the powder was gently filled into the cylinder. Bulk volume was read and bulk density calculated. Following that procedure, the cylinder was tapped at least 2500 times up to a constant volume. Tap volume was read and tap density calculated. Mean and standard deviations were determined.

Compressibility Index (CI) and Hausner's Ratio (HR)

Carr's index was calculated using the equation

$$\frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

and

$$\frac{\text{tapped density}}{\text{bulk density}}$$

is the Hausner ratio.

Drug Content of granules

An accurately weighed amount of powdered theophylline granules (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (Nunc, New Delhi, India). The absorbance was measured at 272 nm using a diode array UV-visible spectrophotometer (Hewlett-Packard, Agilent Technologies, New Delhi, India) after suitable dilution.

EVALUATION OF PHYSICAL PROPERTIES OF MATRIX TABLETS [29-31]:

All prepared matrix tablets were evaluated for uniformity of weight and drug content, as per I.P. method.

Thickness

The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX- 100, Arvada, Colorado), and the test was performed according to the official method.

Drug Content

Five tablets were weighed individually, and the drug was extracted in water. The drug content was determined as described above.

Dissolution studies

Determination of theophylline release from different formulated tablets was performed using USP XXIV dissolution apparatus 2 (Tab-Machines, Mumbai, India) at 50 rpm. Dissolution was tested either in 900 ml simulated gastric fluid (without pepsin) at pH 1.2 for the first 2 hour followed by dissolution in simulated intestinal fluid (without enzymes) at pH 7.5 for the remained six hours at 37 ± 0.5 °C. Drug release was monitored at 272 nm as a function of time using a diode array UV-visible spectrophotometer (Hewlett-Packard, Agilent Technologies, New Delhi, India).

RESULTS AND DISCUSSION

The prepared granules of the floating layer were characterized with respect to the angle of repose, flow rate, bulk density, tap density and Carr's index (Table 2).

No important differences of apparent density were observed among the granules with lower bulk density and higher tapped density were found for all granules which favours packing behaviour, resulting in good mass and content uniformity of dosage forms formulated from such granules.

The prepared granules of the floating layer were characterized with respect to the angle of repose, flow rate, bulk density, tap density and Carr's index (Table 2). Preliminary results showed that dried granules of particle size range 500-800 ìm were suitable to produce granules with acceptable physical characteristics.

Angle of repose

The angle of repose, a traditional characterization method

for pharmaceutical powder flow, is also used in geology to characterize solids. There is a correlation between the flow rates and angles of repose: the better the flow rates, the smaller the angles of repose. It is well known that angle of repose decreases with an increase of powder flowability, and so it was used as an index of the powder flowability. The height of the granules forming the cone, h and the radius, r of the base were measured. The angle of repose (è) was calculated from Equation. Flowability is indicated based on the angle of repose. A value of <30° indicates 'excellent' flow whereas >56° indicates 'very poor' flow. The intermediate scale indicates 'good' (è between 31–35°), 'fair' (? between 36–40°), 'passable which may hang up' (è between 41–45°), and 'poor which must be agitated or vibrated' (? between 46–55°). Based on this, the flow was rated as 'poor, must agitate or vibrate' for F1, F2 and F3 whereas F4 an F5 were rated as 'very poor flow'.

Carr's Index

Bulk and tap density can provide information on the flowability of the powders, and hence while using both these values, the Carr Index was calculated. The lower the Carr Index is, the better the flowability of the powder. The CI value demonstrated that granules with lower CI, relates to better powder bed stability and flow properties of the granules [32].

Lower CI or lower Hausner ratios of a material indicate better flow properties than higher ones. A Carr's CI of <10 or HR of <1.11 is considered 'excellent' flow where as CI>38 or HR>1.60 is considered 'very very poor' flow. There are intermediate scales for CI between 11–15 or HR between 1.12–1.18 is considered 'good' flow, CI between 16–20 or HR between 1.19–1.25 is considered 'fair' flow, CI between 21–25 or HR between 1.26–1.34 is considered passable flow, CI between 26–31 or HR between 1.35–1.45 is considered 'poor' flow, and CI between 32–37 or HR between 1.46–1.59 is considered 'very poor' flow. If powders are readily compressed by tapping, their flow energy requirement increases. Based on the results obtained, flow of F1 was rated as 'fair', that of F2 and F3 were rated as 'very poor', and F4 and F5 were considered to be 'very very poor' in terms of its flow based on CI and HR values. This discrepancy might be due to very qualitative nature of the scale of measurements and ratings for flow properties based on these compendial methods.

Physical evaluation of matrix tablets

The general appearance of tablet, its visual identity and overall "elegance" is essential for consumer acceptance, for control of lot to lot uniformity, and for monitoring trouble-free manufacturing. The control of the physical appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odour, taste, surface texture, physical flaws and consistency, and unique identification markings (Figure 1).

The weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Table 2). Thus, all the physical properties of these tablets were satisfactory as specified in the Indian Pharmacopoeia [33].

Generally, all the prepared theohpylline tablet batches showed good appearance and were non-disintegrating. The diameter of tablets was chosen to be 12 mm in order to minimize differences in surface area. The tablets of different formulations were subjected to various evaluation tests, such as weight variation, friability, hardness, and content uniformity according to procedure specified in Indian Pharmacopoeia. The weight variation and friability was less than 6% and 1.0%, respectively. Good uniformity in drug content was found among different batches of the tablets, and the drug content was more than 95% (Table 2).

Dissolution study

Figure 2 shows the effect of various polymers on theophylline anhydrous matrix tablet. A significant difference in release pattern was observed between the formulation F1, F2, F3, F4 and F5. F1, F3 and F5 release almost ~9% compare to initial burst effect of ~31% for F4 and F2 after 1h of dissolution period. The burst phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core [34]. At the end of 8 h of dissolution period it was found that 71.36%, 85.91%, 96.98%, 68.76% and 45.5% of drug release for F2, F4, F5, F3 and F1, respectively. This varied kind of release pattern may attribute to the difference in the properties of the polymers especially the viscosity and hydration properties. Drug release was generally linear for most of the formulations, especially F4 matrices. Such linear release from hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer.

LBG is a nonionic polysaccharide and the hydration process is independent of pH but will degrade at pH extremes at higher temperatures. Locust bean gum is

less soluble and lower viscosity than guar gum as it has fewer galactose branch points makes release faster. Guar gum hydrates fairly rapidly in cold water to give highly viscous pseudoplastic solutions of generally greater low-shear viscosity when compared with other hydrocolloids and much greater than that of LBG gives some what slower release than LBG. During the test, all the formulations swelled and the outer layer of most of the tablets appeared to be hydrated after being placed in dissolution medium, with a progressive increase in the size of this hydrated layer, especially evident for matrices containing xanthan (F3), followed by a gradual loss of integrity, resulting from the hydrodynamic stress induced by the dissolution apparatus. Thereafter, it remained more or less unchanged until the final stages of the dissolution test, when the inner dry core became wet. Xanthan gum is mainly considered to be non-gelling and used for the control of viscosity due to the tenuous associations endowing it with weak-gel shear-thinning properties. It hydrates rapidly in cold water without lumping to give a reliable viscosity. Its most important property being its very high low-shear viscosity coupled with its strongly shear-thinning character. The relatively low viscosity at high shear means that it is easy to mix, pour and swallow but its high viscosity at low shear gives good suspension and coating properties and

Figure 1 Physical Appearance of the Tablet

Figure 2 Drug release study

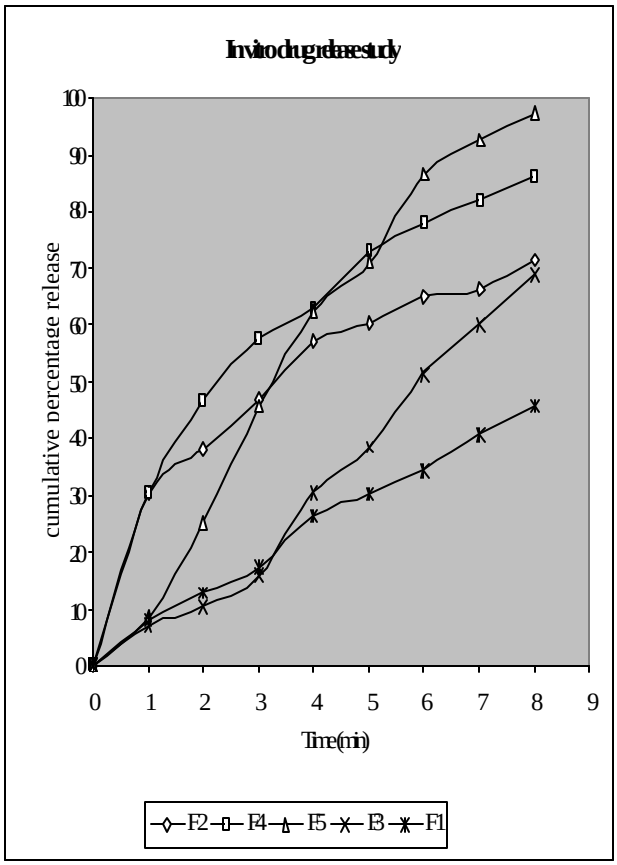

Table 1 Formulation of 500 mg matrix tablet of theophylline

Name of the component	Quantity per tablet (mg)				
	F1	F2	F3	F4	F5
Drug	150	150	150	150	150
HPMC K15	150	—	—	—	—
GG	—	150	—	—	—
XG	—	—	150	—	—
LBG	—	—	—	150	—
Chitosan	—	—	—	—	150
IPA	qs	qs	qs	qs	qs
PVP K 30	60	60	60	60	60
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5
MCC	qs to 500	qs to 500	qs to 500	qs to 500	qs to 500

Note:

qs: quantity sufficient, HPMC K15: Hydroxypropyl methyl cellulose of K15 viscosity grade, PVP K 30: Polyvinyl pyrrolidone of K 30 viscosity grade, GG: Guar gum, XG: Xanthan gum, LBG: Locust bean gum, IPA: Iso propyl alcohol, MCC: Microcrystalline cellulose.

Table 2 Properties of granulation

Code	Angle of repose (?^{0})	Bulk density (g/mL)	Tapped density (g/mL)	CI (%)	HR	Drug content (%)
F1	51.78 ± 4.7	0.280 ± 0.11	0.345 ± 0.13	18.84 ± 3.2	1.23	98.34
F2	47.70 ± 0.8	0.234 ± 0.11	0.371 ± 0.11	36.92 ± 0.6	1.61	99.34
F3	48.61 ± 4.7	0.355 ± 0.12	0.541 ± 0.12	34.38 ± 0.6	1.52	99.15
F4	63.40 ± 3.2	0.266 ± 0.12	0.533 ± 0.14	50.09 ±0.4	2.00	97.56
F5	56.74 ± 0.4	0.264 ± 0.12	0.542 ± 0.13	51.29 ± 0.4	2.05	97.75

*All values are expressed as mean ± SE, n = 5., CI- compressibility index, HR- Housner's ratio

Table 3 Physical properties of matrix tablets of theophylline

Code	Tablet wt (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
F1	500 ± 5.23	12.075 ± 0.04	3.0 ± 0.12	4.50 ± 4.67	0.84	109.78
F2	500 ± 5.43	12.075 ± 0.03	3.0 ± 0.15	4.00 ± 4.98	0.98	109.71
F3	500 ± 5.16	12.075 ± 0.04	3.0 ± 0.14	4.50 ± 5.46	0.86	109.45
F4	500 ± 5.49	12.075 ± 0.03	3.0 ± 0.12	4.00 ± 5.23	0.97	109.64
F5	500 ± 5.32	12.075 ± 0.03	3.0 ± 0.13	4.25 ± 5.16	0.93	108.98

lends stability to colloidal suspensions may responsible for slower release profile. Chitosan owe their solubility in water-based solvents to their charged groups, because except for these groups, the polymer backbones are quite hydrophobic [35-40]. At pH 1.2, free amino groups of chitosan were protonated, resulting in the electronic repulsions and solvation of ionic groups thus contributing to the maximum swelling. At acidic pH, chitosan molecules are ionized to a substantial extent and may form polyelectrolyte complex resulting in retarded drug release. The sustained release from HPMC matrices may attributed to the Higher viscosity of HPMC might have formed a more viscous gel like network around the delivery device which results drug release to be slowed down due to increased thickness.

CONCLUSION

The flow properties and tablet properties of natural gums were compared with the extensively investigated hydrophilic matrices, HPMC. The determination of granule flow gives information the cohesivity and caking tendency of granules which affects the tablet properties. The natural gums show granulation and tablet properties that are similar to those of the extensively investigated hydrophilic matrices, HPMC. Natural

gums were also found to control the release of theophylline from a matrix system as that of HPMC especially the formulation containing XG and GG. This study suggests that natural gums may be an ideal candidate in the formulation of matrix tablets on controlled drug delivery.

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