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Synergistic Homopolysaccharide:Heteropolysaccharide Interactions-Rheological Investigation and Development of Sustained Release Tablets

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ABSTRACT

Polymers used in combinations, the net effect produced by them is much greater than that given when used alone. Pronounced synergistic interactions have been observed when homopolysaccharide (galactomannan) and heteropolysaccharide, xanthan gum (XG) used together. Polymers from galactomannan category like guar gum (GG) and locust bean gum (LBG) and heteropolysaccharide were evaluated for optimum viscosity synergism. Viscosity studies of aqueous solutions of individual polymers and their combinations were carried out to find out the optimum ratio for synergism. The polymeric synergism and nature was confirmed using modern techniques of analysis like x-ray diffractometry (XRD), Differential scanning calorimetry (DSC) and Fourier Transform Infrared Spectrophotometry (FTIR). Matrix tablets were formulated using Metoprolol tartarte as a model drug and evaluated for erosion and swelling indices to correlate with the *in vitro* dissolution data. The *in vitro* dissolution data of the optimized formulation batches was compared with the matrices formulated using different grades of HPMC. XG:LBG and XG:GG in the ratio of 2:8 and 6:4 shown maximum viscosity synergism. Erosion was found to decrease in the order of LBG>>>>GG>XG>XG>XG:GG>XG:LBG. The highest swelling index, axial and radial, was obtained for the matrices containing combination of XG:LBG and XG:GG. XRD and FTIR spectra did not show any change in polymeric characteristics and chemical interactions respectively. However, the physical origin of synergistic interactions has been confirmed by DSC study. The advantage of using synergistically interacting materials to control drug release is that relatively smaller tablets can be produced that have a more precisely tailored drug delivery profile.

Keywords: Erosion, Galactomannan, Heteropolysaccharide, Homopolysaccharide, Swelling, Viscosity synergy.

INTRODUCTION

The natural materials are readily available, cost-effective, eco-friendly, capable of multitude of chemical modifications, potentially degradable and compatible and thus have been extensively used in the field of drug delivery. Purely some natural gums even at higher concentrations were unable to sustain the drug release for a longer period of time. Therefore, the study of new drug-release-retarding materials is the motive of research even after the advent of synthetic, semi-synthetic and natural polymers.[1,2]

Xanthan gum (XG) is a soluble, anionic-bacterial heteropolysaccharide, while Locust bean gum (LBG) is a neutral plant galactomannan. Both materials have been extensively studied.[3-5] In earlier studies, the performance of XG as a potential excipient for oral controlled release tablet dosage forms was thoroughly evaluated and characterized by *in vitro* tests.[6-12] The extent of synergism, effect of temperature and ionic environment on synergism of XG with LBG in dilute solution were studied.[13-17]

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In solution, one XG molecule associates with a second molecule by hydrogen bonding to produce a helical structure. These XG helices are dispersed through the solution and act to create sufficient inhibition of free movement of water molecules to produce the thickening observed. As there is no interlinking of separate helixes, XG does not produce a true gel on its own and this is a weakness that restricts its value as a controlled release material when used alone.[18] XG superstrands form three dimentional network, interconnected by the galactomannan itself adsorbed or linked onto the surface of these superstrands.[13] The keys that switch the polymer molecules on and off are the London-vander Waals, hydrogen and/or ionic bonds between the two heterodisperse polysaccharides.[1,19] Physical intermolecular interactions occur, either involving cooperative associations of chain segments belonging to different polymers in the formation of mixed junction zones, analogues to the junctions in many single-component gel systems, or via chain-chain association by virtue of opposite charge attractions.[20] The intermolecular binding occurred between XG and galactomannan molecules, and galactomannan forced XG to change from a stiff ordered helix to a more flexible conformation.[15]

The advantage of using synergistically interacting materials to control drug release is that smaller tablets can be produced

that have a more precisely tailored delivery profile using a conveniently flexible system that does not require specialist manufacturing hardware or demand that processes or materials be changed to accommodate different product developments. In the present study, Metoprolol tartrate (MT), very water soluble drug was used as a model drug. Half-life of MT is 3 to 4 h, hence can also be considered as a suitable candidate for the sustained release dosage form formulations. The polymeric interactions between hydrophilic polymers, XG and GG or LBG were envisaged to evaluate and investigate the optimum combination for synergism using viscometry and analytical techniques like Differential scanning calorimetry (DSC), X-ray diffractometry (XRD) and Fourier Transform Infrared Spectrophotometry (FT-IR). The study compares swelling and erosion behavior of polymers and combinations. The sustained release tablets were formulated using optimum combinations of synergistically interacting polymers and compared with the various grades of extensively used sustained release polymeric material, Hydroxypropyl metyl cellulose (HPMC).

MATERIALS AND METHODS

Metoprolol tartrate was obtained as gift sample from Novartis India Limited. Xanthan gum, Locust bean gum and Guar gum as gift samples from TIC Gums, USA. Hydroy propyl methyl cellulose (HPMC K4M, K15M and K100M) were generously gifted by Colorcon Asia Pvt. Ltd., Goa. Microcrystalline cellulose (Avicel PH 101) was sourced from Signet Chemical Corporation, Mumbai. Dibasic calcium phosphate, talc and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. All other chemicals and reagents were of analytical grade and were used as received.

Viscosity studies of XG, GG, LBG and their combinations:

The ratio of combinations of XG with GG and LBG for development of matrix tablets was based on synergistically enhanced gel properties by viscosity measurement of 1 %w/v polymer solution. The combination of aqueous gum dispersions containing gums individual as well as in combinations were prepared and hydrated for 24 h. Polymeric solutions were evaluated for viscosity using Brookfield viscometer at 100 rpm (RVT, Brookfield Engineering, Labco Inc., Masschuetts) and the ratio of combination of gums which shown the maximum viscosity as compared to other combination dispersions was chosen as optimum combinations of polymers for synergism and were used for development of tablets.

Preparation of matrix tablets:

Different tablet formulations were prepared by wet granulation technique [21] (Formulations X1–X3, G1–G4, L1–L5, XG1–XG3, XL1-XL3 and K1-K9 as depicted in Table 1 and Table 2). All the powders were passed through ASTM (American Society for Testing and Materials) 80 mesh sieve. Required quantities of MT and polymer were mixed thoroughly. Microcrystalline cellulose (MCC) and Dibasic calcium phosphate (DCP) blended with above mixture. The blend was granulated, using distilled water as a granulating fluid. After enough cohesiveness was obtained, the mass was sieved through 30 mesh. The granules were dried at 50° C for 4 h and thereafter kept in desiccator for 12h at room temperature. The granules were lubricated with magnesium stearate (1 %w/w) and talc (1 %w/w), and compressed on pilot press tablet compression machine (Chamunda Pharma Machinery Pvt. Ltd.), equipped with beveled flat-faced punches of 8 mm diameter at a tablet weight of 300 ± 5mg. MCC and DCP in the ratio of 1:1 were used as filler in the formulations to compress the tablets with desired parameters.

Evaluation of physical properties of granules:

Properties of granules have pronounced effect on the physical properties of compressed tablets, leading to affect the drug release from the tablets. Thus, prior to compression, lubricated granules were characterized for their characteristic parameters.[22, 23] Angle of repose, bulk and tapped densities, % compressibility and Hausner ratio were determined. The drug content in granules was determined by extracting an accurately weighed amount of powdered granules (300 mg) with water. The solution was filtered through 1µm finer porosity filter and absorbance was measured at 274 nm wavelength using UV spectrophotometer (Shimadzu 1700 (E) 23, Japan). Results are depicted in Table 3.

Table 2: Composition of matrix tablets of Metoprolol tartrate (50 mg) containing HPMC (%w/w).

Formulation	K1	K2	K3	K4	K5	K6	K7	K8	K9
K4M	20	30	40	–	–	–	–	–	–
K15M	–	–	–	20	30	40	–	–	–
K100M	–	–	–	–	–	–	20	30	40

Table 1: Composition of matrix tablets of Metoprolol tartrate (50 mg) containing natural polymers (%w/w).

Formulation	X1	X2	X3	G1	G2	G3	G4	L1	L2	L3	L4	L5	XG1	XG2	XG3	XL1	XL2	XL3
XG	20	30	40	–	–	–	–	–	–	–	–	–	12	18	24	4	6	8
GG	–	–	–	20	30	40	50	–	–	–	–	–	8	12	16	–	–	–
LBG	–	–	–	–	–	–	–	20	30	40	50	60	–	–	–	16	24	32

Table 3: Characterization of granules and matrix tablets of MT. All values indicate mean ± SD (n=3)							
Parameters	**X2**	**G3**	**XG2**	**XL2**	**K3**	**K5**	**K8**
Granules							
Angle of repose (°)	25 ± 1.2	28 ± 0.9	26 ± 1.1 2	4 ± 0.8	22 ± 2.1	25 ± 1.6	24 ± 1.8
Bulk density (g/cm^3)	0.54	0.36	0.36	0.42	0.51	0.54	0.50
Tapped density (g/cm^3)	0.63	0.42	0.40	0.49	0.58	0.61	0.56
Compressibility index	13.4	14.6	10.6	14.0	12.07	11.48	10.71
Moisture content (%)	2.0 ± 0.3	2.3 ± 0.2	2.1 ± 0.5	2.2 ± 0.3	2.1 ± 0.5	2.4 ± 0.3	2.2 ± 0.4
Total drug content (%)	98.2±2.5	98.8±3.3	99.7±3.2	100.1±3.0	100± 2.3	99.1±2.7	98.9±3.4
Tablets							
Weight variation (%)	± 2.6	± 3.7	± 1.3	± 2.4	± 2.7	± 2.8	± 3.0
Thickness (mm)	4.785 ± 0.05	5.240 ± 0.09	4.793 ± 0.07	4.855 ± 0.04	4.037 ± 0.05	3.990 ± 0.05	4.003 ± 0.03
Hardness (Kg/cm^2)	3 – 4	3 – 4	3 – 4	3 – 4	3 – 4	3 – 4	3 – 4
Friability (%)	0.59	0.84	0.76	0.63	0.38	0.41	0.35
Content uniformity (%)	97.9±2.1	98.6±4.0	100.3±3.5	99.1 ± 3.9	100.5±2.2	98.7±3.8	100.7±2.9

Table 4: Correlation coefficient (R^2) and n values of optimized formulation batches							
Formulation	**Correlation coefficient (R^2) values**					**n values**	**k values**
	Zero order	**First order**	**Matrix**	**Peppas**	**Hixson-Crowell model**		
X2	0.8608	0.9770	0.9973	0.9940	0.9750	0.5110	28.0536
G3	0.8643	0.9770	0.9976	0.9938	0.9814	0.5184	26.9467
XG2	0.8935	0.9919	0.9988	0.9983	0.9926	0.5500	26.9467
XL2	0.8754	0.9943	0.9987	0.9966	0.9839	0.5323	27.1316
K3	0.9549	0.9527	0.9879	0.9965	0.9844	0.5975	23.5822
K5	0.9408	0.9574	0.9921	0.9970	0.9851	0.5940	24.3119
K8	0.9566	0.9633	0.9878	0.9977	0.9894	0.6200	22.8767

Characterization of matrix tablets:

The properties of the compressed matrix tablet, such as hardness, friability, weight variation, and content uniformity were determined using reported procedure.[24] Briefly, hardness was determined by using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. To determine content uniformity, twenty tablets from each formulation were powdered and quantity of powder equivalent to 50 mg of metoprolol tartrate was added to 100 ml distilled water, stirred and filtered through 0.45µ membrane filter. The filtrate was suitably diluted with distilled water and analyzed spectrophotometrically at 274 nm.

***In vitro* drug release studies:**

The *in vitro* dissolution studies were carried out using USP XXIV, type I dissolution test apparatus (Veego Scientifics, Mumbai) at 50 rpm. The dissolution medium consisted of pH 1.2 buffer for the first 2 h and phosphate buffer pH 6.8 from 3 to 10 h (900 ml), maintained at 37 ± 0.5 C. An aliquot (10 ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer (Shimadzu 1700 (E) 23, Japan) at 274 nm. The release studies were conducted in triplicate. The dissolution profiles of the matrix tablets were compared.

Matrix tablets erosion studies:[9]

The method used was similar to the method of determining *in vitro* dissolution profile as described above. However, single matrices were placed in thoroughly clean wire mesh baskets and then weighed accurately. During the dissolution process at 60 min time intervals a basket containing the remnants of matrix was removed and dried at 60 ºC for 24 h. After cooling in a desiccator to room temperature these were weighed accurately and the percentage weight loss (% erosion) calculated.

$$\text{Erosion}(\%) = \frac{\text{Initial weight of tablet} - \text{final weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

Swelling studies:[9,21]

Measurement of axial swelling:

A single tablet was placed on a glass slide in a petri dish (60 mm in diameter) containing 30 ml of 1.2 pH buffer for 2 h. The medium was replaced with equal volume of pH 6.8 phosphate buffer for 4 h. The change in thickness of tablet was measured at every 60 min time intervals with the help of magnifying lens and axial swelling indices were calculated.

$$\text{Axial swelling index (\%)} = S - \frac{1}{a} \times 100$$

Where,

s = Original thickness of tablet

a = Thickness of swollen tablet

Measurement of radial swelling:

A single tablet was placed in identical conditions as described for axial swelling determination, but on the surface of glass slide concentric circles were drawn at the distance of 0.5 mm apart. Visual measurements of the diameter were taken at every 60 min time intervals for 6 h and radial swelling indices were calculated.

$$\text{Radial swelling index (\%)} = S - \frac{1}{a} \times 100$$

Where,

s = Original diameter of tablet

a = Diameter of swollen tablet

Interaction studies:

Synergistic hydrophilic polymeric interaction studies were carried out by x-ray diffraction spectroscopy (XRD), Fourier Transform Infrared Spectroscopy (FT-IR) and Differential scanning calorimetry (DSC).

XRD:

The X-ray powder diffraction patterns were obtained by using Philips PW 1700 with Cu K (= 1.54056A°) radiation and a crystal monochromator, voltage: 45 mv and current: 20 amp. The diffraction patterns were run at 2^0/min in terms of 2 angle.

FT-IR spectroscopy:

Small amount of finely ground sample was mixed with potassium bromide. Samples were prepared by KBr press pellet technique at 25000 psi/g pressure and IR spectra of sample was obtained with FT-IR spectrophotometer (FTIR-8001, Shimadzu, Japan) operated with omnic software.

DSC:

Glass transitition temperature was assessed by differential scanning calorimetry (DSC) using Perkin Elmer. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min., over a temperature range of 30-250°C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min.

Drug release kinetic model:

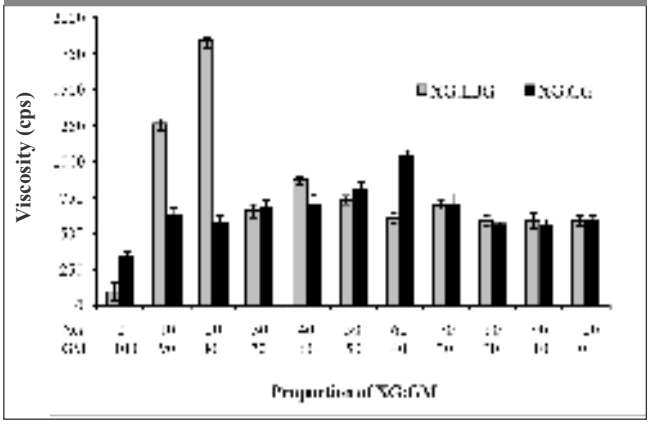
To describe the kinetics of drug release from the tablets batches, mathematical models zero-order, first order, Higuchi, Hixon-crowell, Korsmeyer-Peppas were used. The criterion for selecting the best fit model was chosen on the basis of the goodness fit test. Equations previously stated were used to determine the best fit model for release kinetics.[25]

RESULTS AND DISCUSSION

The rheological studies carried out for the individual polymers as well as their combinations in aqueous solutions revealed that polymers in the ratio of 2:8 for XG:LBG and 6:4 for XG:GG showed maximum synergism (Fig. 1). The viscosity of the formed gel was relatively high in case of combination of LBG with XG as compared to that of GG with XG and given stiff gel.

The granules of different formulations prepared were evaluated with respect to angle of repose, bulk density, tapped

Fig. 1: Viscosity studies (1 %w/w aqueous solutions) of XG, GG, LBG and their combinations using Brookfield viscometer (mean values ± SD; n=3).

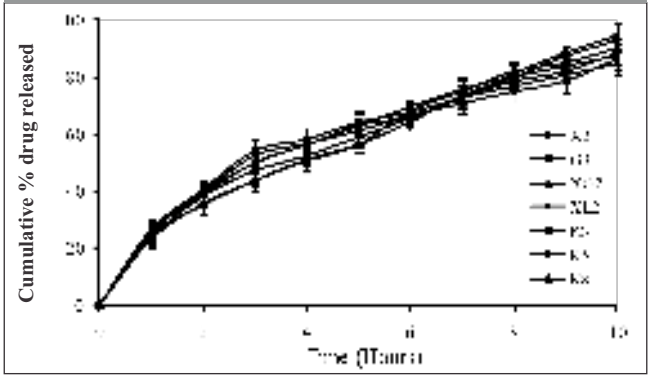


density, compressibility index, moisture content and drug content (Table 3). The values of angle of repose indicated satisfactory flow behavior. Moisture content of less than 2.5% indicates optimum drying of granules. Moisture content below 2% and above 2.8% in the granules had shown capping and sticking problems during compression run. Other parameters for granules were found to be in acceptable range.

All the physical parameters of the tablets were well within the range. Drug content was found to be uniform among different batches of the tablets and was more than 95% (Table 3).

The matrix tablets containing natural polymers in the concentration below 20 %w/w of the total tablet weight were unable to sustain the drug release for 10 h. As the concentrations of the gums were increased to 30 %w/w, the matrices released the drug for more than 10 h except for the formulation containing GG. The formulations with 30 %w/w of XG (X2), XG:GG (XG2), XG:LBG (XL2) and 40 %w/w of GG (G3) released 86.55, 87.46, 84.82 and 88.57% of drug after 10 h (Fig. 2). When polymer concentration was increased from 30 to 40 %w/w for XG (X3), XG:GG (XG3), XG:LBG (XL3) and from 40 to 50 %w/w for GG (G4), the increase in drug release was observed due to increased hydrophilicity of the matrices. The medium penetrated the matrices at a faster rate as compared with that containing relatively low proportion of the gums. The formulations batches X2, G3, XG2 and XL2 were found to be comparable for the drug release and hence, considered as optimized formulation batches and compared with formulation batches containing HPMC.

Fig. 2: Cumulative percentage of MT released versus time (h) in 0.1N HCl for 2 h and pH 6.8 phosphate buffer, 900 ml at 50 rpm using USP type I dissolution test apparatus (mean ± SD, n = 3).



The dissolution profiles were found to be consistent with the swelling and erosion studies, which showed that GG matrices has shown relatively lower swelling and higher erosion rate as compared with XG and its combination with GG and LBG compensates to some extent for the gradual increase in release rate due to the decreasing diffusional path length. LBG displayed highest erosion rate, a low swelling index and consequently the faster release rate. XG (X2), XG:GG (XG2) and XG:LBG (XL2) with its slow erosion rate and moderate swellability provided the slower rate of drug release. Erosion increases the drug dissolution rate thus compensating to some extent for the high swelling index and the consequent slowing of drug diffusion by the increasing diffusional path length. With LBG, on the other hand, the high erosion rate consequently coupled with shorter diffusional path length and lowest solution viscosity, account for the high drug release rate. Matrix integrity was destroyed due to increase in porosity as a result of drug release and possibly to a decrease in bonding between expanding polymer chains at a low polymer proportion explained the loss of matrix strength and increased drug release rate.[9]

In case of HPMC matrices, formulation batches with 20 %w/w of K4M (K1), K15M (K4) and 30 %w/w K4M (K2) sustained the drug release for 9 h. The tablet formulation with 40 %w/w HPMC K4M (K3) and 30 %w/w of K15M (K5) and K100M (K8) has shown nearly similar release profiles of 93.28, 94.72 and 90.48% at the end of 10 h which was comparable to that of the formulation batches containing natural polymers (Fig.2). The formulation batches with 20 %w/w of K100M (K7) also sustained the drug release for more than 10 h but the release after 1 h in 1.2 pH buffer was found to be high as compared to that of the optimized formulation batches containing natural gums. The reason for this higher drug release may be the higher cross-linking of the polymer due to which the penetration of the dissolution media was rapid initially. However, as the proportion of polymer (HPMC K15M, K100M) was increased from 30 to 40 %w/w, the drug release was further sustained.

Formulation batches XG2 and XL2 retarded the drug release for more than 10 h which is due to formation of firm stiff gel layer surrounding the tablet surface. The viscosity synergy helped in the reduction in the total proportion of GG and LBG of total polymer content. Hence formulations can be suitably modified so as to reduce the total weight of tablets using minimum amount of synergistically interacting polymers. Also LBG has been used successfully in the formulation of matrices for sustained drug delivery in combination with XG (2 parts of total polymer content).

The matrix tablet formulations containing LBG (formulation batches L1-L5) showed the maximum erosion. The matrix erosion was pronounced within first h of erosion study. Formulation batches containing XG:LBG has shown minimum erosion and LBG containing matrices shown maximum rate of erosion. However, erosion was found to increase in the order of XG:GG < XG < GG (Fig. 3). As the proportion of polymer was increased, the erosion was found to decrease due to the formation of stable matrix. Solubility of the drug candidate has shown marked effect on erosion. Since drug candidate used is water soluble, during penetration of the dissolution media, it solublized and formed pores in the matrix through which, further drug release was observed.[25] Matrix integrity was reduced due to increase in porosity as a

result of drug release and possibly due to a decrease in bonding between expanding polymer chains. It was responsible for increased rate of erosion in the formulation batches containing low proportion of polymer (X1, XG1, XL1 and G1).

The matrix containing the combination of XG:LBG and XG:GG has shown the greatest swelling index in both axial and radial dimensions after 6 h (Fig. 4 and 5). The XG displayed intermediate swelling index, while the lowest swelling index was observed for GG. In contrast, the matrix tablets containing LBG was unable to withstand the matrix strength due to low swelling index and shown erosion within 15 min. The matrices with a low polymer proportion have shown a disintegration of matrix structure due to sudden increase in the axial and radial swelling index.[25]

The x-ray diffractogram (Fig. 6) of XG, GG and LBG and interacted samples of XG with GG and LBG have shown diffused pattern indicating that the polymorphic characteristic of XG, GG, LBG and their interacted sample was not changed. The interacted samples showed amorphous nature which is similar to the individual polymer structure.

Fig. 3: Erosion (%) against time (h) from matrices containing mixtures of various hydrophillic gums in 0.1N HCl for 2 h and phosphate buffer pH 6.8 (mean values ±SD, n =3)

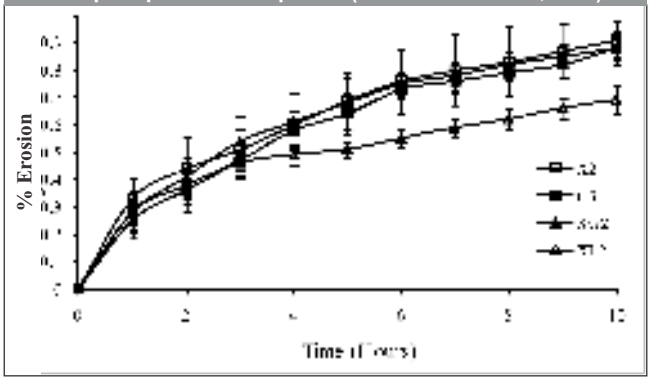
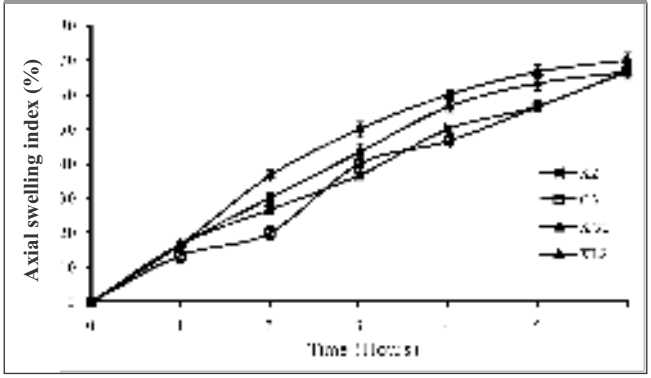


Fig. 4: Axial swelling indices (%) against time (h) of matrices containing various mixtures of hydrophilic gums in 0.1N HCl for 2 h and phosphate buffer pH 6.8 (mean values ±SD, n=3).



The polymeric interaction did not change the polymeric nature of the polymer samples.

From the DSC thermograms (Fig. 7), it was observed that the peak of XG at 370.77 °C was disappeared in its interacted sample. Also, the enthalpy value of XG, -297.10 J/g, was reduced to -222.40 and -139.64 J/g indicating a less disorderly structure due to interaction of XG with GG and LBG respectively as homopolymer and heteropolymer interaction.

The FT-IR spectra (Fig. 8) showed no additional peak in the interacted sample as compared to their individual IR spectrum. This indicates that there is no chemical interaction but interaction may be of physical in nature, confirmed by DSC studies.

The formulation batches containing natural polymers have shown matrix as a drug release kinetic model while Peppas model was observed as best fit model of drug release for formulation batches containing HPMC. The release exponent values (n) ranged from 0.51 - 0.62. For all the optimized

Fig. 5: Radial swelling indices (%) against time (h) of matrices containing various mixtures of hydrophilic gums in 0.1N HCl for 2 hand phosphate buffer pH 6.8 (mean values ±SD, n=3).

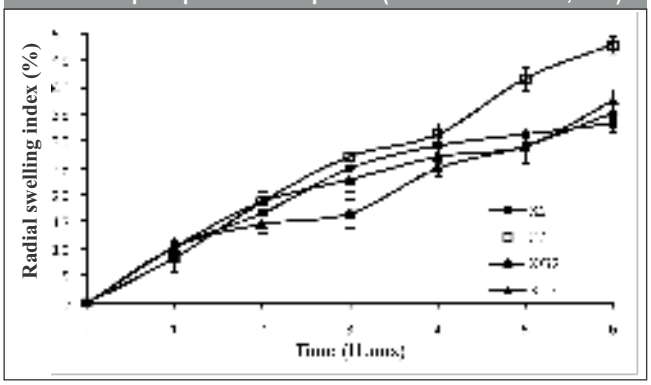


Fig. 6: X-ray diffractogram of XG, GG, LBG and their interacted sample. A, XG; B, GG; C, LBG; D, XG:GG, E, XG:LBG.

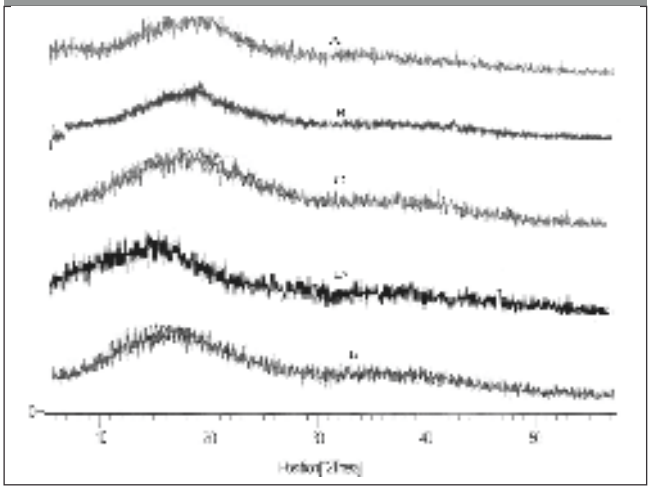


Fig. 7: DSC thermogram of XG, GG, LBG and their interacted sample. A, XG; B, GG; C, LBG; D, XG:GG, E, XG:LBG.

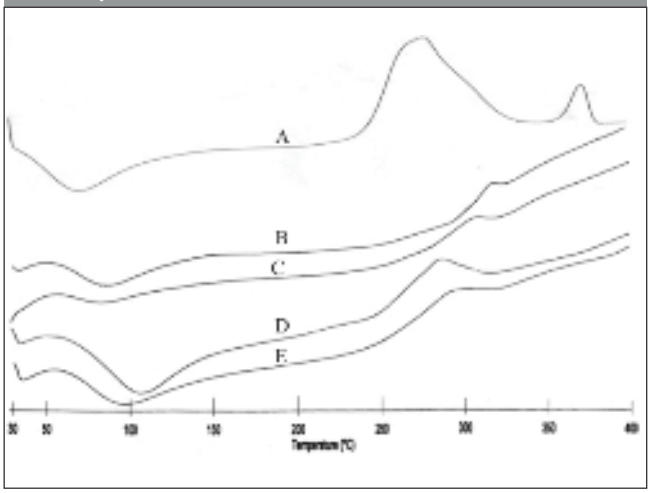
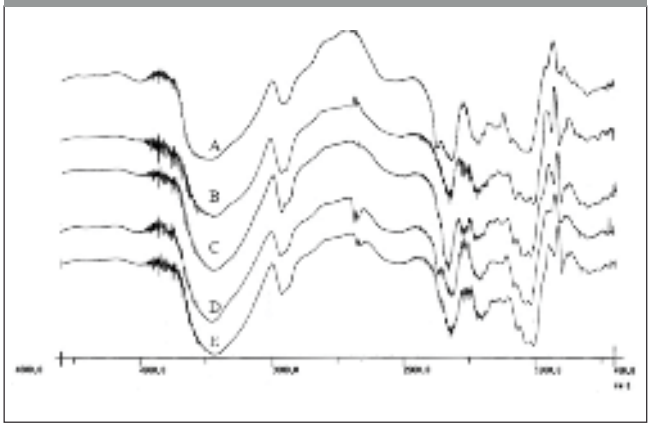


Fig. 8: FT-IR-spectra of XG, GG, LBG and their interacted sample. A, XG; B, GG; C, LBG; D, XG:GG, E, XG:LBG.



formulation batches containing natural gums or HPMC the dominant mechanism for drug release through matrix systems was found to be anomalous transport.

CONCLUSION

LBG interacted with XG to greater extent when compared with GG. Polymeric synergism reduced the total quantities of galactomannan used in the tablets. Formulations with synergistically interacting natural polymers sustained the drug release for 10 h and showed comparable release profiles to that of extensively used polymers HPMC. Combination of XG with GG has shown minimum rate of erosion. Also highest swelling indices were obtained for combinations of synergistically interacting polymers when compared with individual polymers. Thus, synergistically interacting polymers can be used to reduce the total polymer contents in formulations which alternately can be used for the development of relatively smaller dosage forms.

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