Xanthan and locust bean gum (from *Ceratonia siliqua*) matrix tablets for oral controlled delivery of propranolol hydrochloride

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Abstract

Purpose: To develop a controlled delivery system for propranolol hydrochloride (PPHCL) using the synergistic activity of locust bean gum (LBG) and xanthan gum (X). **Methods:** Granules of PPHCL were prepared by using different drug: gum ratios of X, LBG alone and a mixture of XLBG (X and LBG in 1: 1 ratios). To increase the flowability and compressibility of the granules, and to prevent its adhesion to the punch and die, magnesium stearate (Mg. st) and talc were added to the granules in a 1: 2 ratio before punching. The tablets were analysed to determine their hardness, friability, and composition% and an *in vitro* release study was carried out. **Results:** The release of PPHCL from a gelatinous swollen mass controls the diffusion of drug molecules through the polymeric material into aqueous medium. The XLBG matrices exhibited precise controlled release than the X and LBG matrices because of burst effect and fast release in case of X and LBG alone respectively and there was no chemical interaction between drug and polymers in the XLBG formulation as confirmed by FTIR studies. The first-pass effect of PPHCL can be avoided by using this formulation. **Conclusion:** The XLBG matrices offer more precise results than X and LBG matrices due to the effect of a synergistic interaction between the two biopolymers and the lower average size allowing uniform tablet hydration in dissolution media.

Keywords: Locust bean gum; Xanthan gum; Propranolol hydrochloride; Controlled release

1. Introduction

The use of biopolymeric matrix devices to control the release of a variety of therapeutic agents has become important in the development of modified release dosage forms [1-4].

X is a soluble, anionic-bacterial heteropolysaccharide, while LBG is a neutral plant galactomannan. Both materials have been extensively studied [5, 6] under a variety of conditions and they have been found to be sensitive to pH and ionic strength. The synergistic gelation of X and LBG has also been reported to fall dramatically below pH 5, although it is independent of pH over the range of 5–10 [6].

Xanthan is a commercial hydrophilic polymer, secreted from *Xanthomonas campestris* [7]. In earlier studies, the performance of X as a potential excipient for oral controlled release tablet dosage forms was thoroughly evaluated and characterized by *in vitro* tests [3, 4, 8-10]. It was found that Fickian diffusion was dominant during the first half of the dissolution period of diclofenac sodium mini-matrices with X of different ratios, while erosion predominated during the second, encouraging zero-order release.

LBG is a plant seed galactomannan, composed of a 1-4-linked β-*D*-mannan backbone with 1-6-linked α-*D*-galactose side groups [11]. The physico-chemical properties of galactomannan are strongly influenced by the galactose content [12] and the distribution of the galactose units along the main chain [13]. Longer galactose side chains produce a stronger synergistic interaction with other polymers [12] and greater functionality [13]. LBG is also used to treat elevated plasma cholesterol levels in healthy subjects [14].

Propranolol, a nonselective beta adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. It is highly lipophilic and is almost completely

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absorbed after oral administration. However, its bioavailability is very limited (30%) due to the hepatic first-pass effect. Its elimination half-life is also relatively short (about 2–6 h) [15, 16]. Therefore, it was chosen as a model drug for the preparation of an oral controlled delivery system.

Drug release from hydrophilic matrices is known to be a complex interaction involving swelling, diffusion and erosion mechanisms [17-20]. This work was an attempt to determine the relative contribution of the different drug release mechanisms exhibited by propranolol hydrochloride matrix tablets produced with commercial xanthan and the highly hydrophilic LBG from the seeds of *Ceratonia siliqua*. Different concentrations of gums, alone (X or LBG) and in a physical mixture (XLBG) of X and LBG in the ratio of 1: 1, were tested to evaluate their performance as release-controlling agents. Previous work has demonstrated that naturally occurring X has useful hydrogel properties for producing a constant *in vitro* drug release [8, 9].

2. Materials and methods

2.1. Materials

PPHCL was a gift from Ipca Laboratories Ltd., Mumbai, LBG was purchased from Sigma Aldrich, Germany, and X was obtained from Ranbaxy, New Delhi. dicalcium cium phosphate (DCP), polyvinylpyrolidinek-30 (PVPK-30), alcohol, talc and Mg. st were of analytical reagent grade and used without further purification.

2.2. Preparation of matrix tablets

Matrices were prepared by the wet granulation method using PVPK-30 as the binding agent, alcohol as the wetting agent and DCP as the diluent. Granules were prepared, and talc and Mg. st were used as a lubricant in a ratio of 2: 1. Then 400 ± 5 mg of the prepared granules was compressed using a manesty (Cadmach, India) single punch tablet machine, with 9.5 mm flat beveled edge punches producing matrix tablets 4.8 mm in height with a mean crushing strength of 5.8 kg/cm^2 (Pfizer, Mumbai). Under the same conditions all the formulations of PPHCL tablets containing X, LBG and XLBG (X: LBG ratio was 1: 1) were prepared and the formulation details are shown in Table 1.

2.3. Analysis of tablets

The hardness and friability of the tablets were measured in a Hardness Tester (Pfizer, Mumbai) and friabilator (Electrolab, Mumbai), respectively. The uniformity of drug content of all batches (10 units tablets) was analysed in a spectrophotometer (model UVPC 1601, Shimadzu, Japan), in a 1 cm quartz cell, at 290 nm.

2.4. Water uptake and erosion determination

Measurement of hydration and erosion rates of XLBG3 were carried out, after the immersion of the tablets in the test medium [21], to correlate the observed drug release phenomena with the rates of polymer hydration. Weighed tablets were placed in the baskets of the dissolution apparatus rotating at 50 r/min, with the dissolution medium of phosphate buffer pH 7.2 at 37 ± 0.5˚C. After 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h, each dissolution basket containing the sample was withdrawn, blotted to remove excess water and weighed on an analytical balance (Shinko Sansui, Japan). The wet samples (basket + sample) were then dried in an oven at 110–120˚C for 24 h, allowed to cool in a desicator and finally weighed until constant weight was achieved (final dry weight). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The increase in weight due to absorbed liquid (Q) was estimated at each time point from the following equation 1:

$$Q = \frac{W_w - W_f}{W_f} \times 100 \qquad (1)$$

where W_w is the mass of the hydrated sample before drying and W_f the final weight of the same dried and partially eroded sample. The percentage erosion (E) was estimated from the following equation 2:

$$E = \frac{W_i - W_f}{W_f} \times 100 \qquad (2)$$

where W_i is the initial dry sample weight.

Table 1
Composition (mg per tablet) and analysis of PPHCL (80 mg) tablets (400 mg).

Formulation (drug: gum)	Xanthan (mg)	LBG (mg)	DCP (mg)	PVPK-30 (mg)	Talc (mg)	Mg. st (mg)	Hardness (mean ± SD, kg/cm²)	Friability (%)	Assay% (mean ± SD)
X1 (1: 1)	80	—	216	15	6	3	5.9 ± 0.95	0.3	97 ± 0.83
X2 (1: 1.5)	120	—	176	15	6	3	5.6 ± 0.63	0.2	96 ± 0.75
X3 (1: 2)	160	—	136	15	6	3	5.4 ± 0.51	0.2	95 ± 0.71
X4 (1: 2.5)	200	—	96	15	6	3	5.5 ± 0.45	0.1	97 ± 0.35
LBG1 (1: 1)	—	80	216	15	6	3	4.9 ± 0.92	Capping	96 ± 0.86
LBG2 (1: 1.5)	—	120	176	15	6	3	4.6 ± 0.56	Capping	98 ± 0.56
LBG3 (1: 2)	—	160	136	15	6	3	6.1 ± 0.51	0.4	98 ± 0.38
LBG4 (1: 2.5)	r	200	96	15	6	3	5.5 ± 0.34	0.3	97 ± 0.58
XLBG1 (1: 1)	40	40	216	15	6	3	5.7 ± 0.34	0.2	96 ± 0.95
XLBG2 (1: 1.5)	60	60	176	15	6	3	5.9 ± 0.41	0.1	98 ± 0.71
XLBG3 (1: 2)	80	80	136	15	6	3	5.6 ± 0.34	0.1	99 ± 0.78
XLBG4 (1: 2.5)	100	100	96	15	6	3	5.8 ± 0.45	0.2	99 ± 0.69

In X1–X4, LBG1–LBG4, and XLBG1–XLBG4. 1, 2, 3 and 4 are the ratios of 1: 1, 1: 1.5, 1: 2 and 1: 2.5 drug: gum concentration in the tablets, respectively.

2.5. In vitro analysis

The dissolution test was carried out using apparatus 1 USP (Model No. TDT-08L, Electrolab, Mumbai) at 100 r/min. In order to reproduce the digestive physiological phases, 900 ml samples of dissolution medium at different pH values were used at 37 ± 0.5˚C. The dissolution medium with a pH of 1.2 was changed to 7.2 after 2 h and used for up to 24 h. At suitable intervals, samples were withdrawn, filtered, diluted when necessary with suitable buffer and analyzed spectrophotometrically (model UVPC 1601, Shimadzu, Japan) at 290 nm. The mean cumulative percentage of drug was calculated and plotted against time. During the drug release studies, all the formulations were check at intervals for their physical integrity.

2.6. Drug release kinetics

The Korsmeyer and Peppas equation was used to analyze the data obtained from the *in vitro* release studies to evaluate the kinetic models and release mechanism of PPHCL from the matrices. The software PCP Disso V2.08 was used.

The Korsmeyer and Peppas equation [22] is: $M_t/M_\infty = k\,t^n$. Where M_t/M_∞ is the fraction of drug released at time t, k is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is an exponent used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $0.45 < n < 0.89$ for anomalous behaviour or non-Fickian transport, $n = 0.89$ for Case II transport, and $n > 0.89$ for Super Case II transport [23]. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion [18].

3. Results and discussion

3.1. Analysis of PPHCL matrices

Tablets with a weight of 400 mg, a diameter of 9.5 mm and a height of 4.8 mm were obtained and subjected to quality control tests such as hardness, friability and drug

content (Table 1). The contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the 10 units tested was within the range of 97.1%–100.5% and the relative standard deviations were less than 2.0%, indicating uniform mixing of gums, DCP and drug. The mean values for hardness were over 5.8 kg/cm^2 and all formulations exhibited a friability of less than 0.5% during the friability determination.

3.2. In vitro drug release

The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the periphery towards the centre, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium. The hydrated gel layer thickness determines the diffusional path length of the drug.

The *in vitro* drug release profiles of PPHCL from tablets containing X, LBG and XLBG in different gum proportions are shown in Fig. 1. After 2 h, the initial pH 1.2 was changed to 7.2 and dissolution was continued up to 24 h. It was found that as the amount of gum in the matrix increased, there was a greater degree of gum hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway and drug release rate.

Drug release was generally linear for most of the formulations, especially XLBG 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. 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, 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.

The profiles of the formulation of X, LBG, XLBG, and the erosion and drug release at different drug: gum ratios of 1: 1, 1: 1.5, 1: 2 and 1: 2.5 are shown in Fig. 1. In each case of X there was an initial burst of X erosion from the matrices during the acidic pH phase and thereafter, the erosion of X slowed considerably. It follows, therefore, that the hydrated X network maintains its tight integrity with drug release by erosion and dissolution of the drug accounting for most of the weight loss during the remainder of the experimental period. Furthermore, there is a greater burst of X erosion in the formulation containing the lower proportion of X, 1: 1 and 1: 1.5, then the 1: 2 and 1: 2.5 drug: gum ratios. LBG tablets formulations showed a higher tendency to lose their integrity than X and XLBG. The swelling process of LBG tablets was not uniform and the zones of high LBG concentration appeared more swollen. In the case of LBG matrix, a rapid erosion of the hydrated layer was observed, releasing most of the drug content after 4 h. This is because LBG does not exhibit a controlled release effect but has a synergistic action with the X to produce a controlled release effect.

For all the formulations, the polymer concentrations higher than 1: 1, *i.e.* 1: 1.5, 1: 2 and 1: 2.5 drug: gum ratios exhibited a marked sustained release effect. In order to evaluate the role of XLBG mixture, the drug release of PPHCL tablets with X or LBG alone, with the same concentration of polysaccharide, was investigated and the results are shown in Fig. 1.

The drug release was slower from the matrices with XLBG compared with X and LBG matrices with the same total polymer concentration. The release of X and XLBG was similar but in the case of X, the release of PPHCL at low concentrations of X a starting burst effect of release was seen at acidic pH. In the case of XLBG this type of burst effect was not seen at acidic pH values. The XLBG formulations exhibited a well controlled effect by the use of the synergistic interaction between two biopolymers to produce a strong and elastic gel around the core of the matrices in the presence of a ternary component by controlling the drug release from the matrices containing the XLBG formulation.

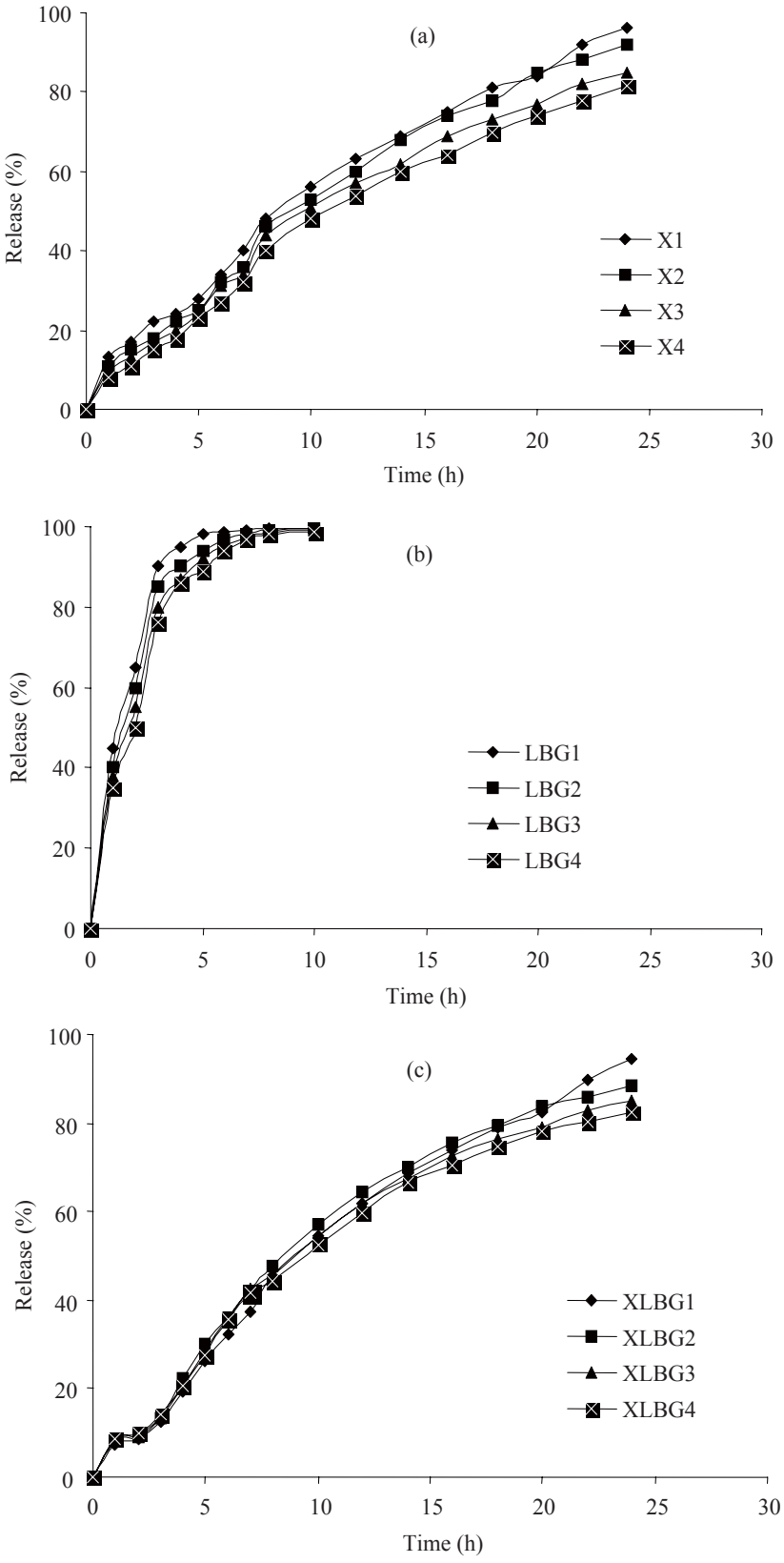

Fig. 1. *In vitro* release profile of PPHCL from tablets with drug: gum, ratio of 1: 1, 1: 1.5, 1: 2 and 1: 2.5. (a) X; (b) LBG; (c) Mixture of X and LBG. In X1–X4, LBG1– LBG4, and XLBG1–LBG4. 1, 2, 3 and 4 are the ratios of 1: 1, 1: 1.5, 1: 2 and 1: 2.5 drug: gum concentration in the tablets.

3.3. Water uptake and erosion studies

The swelling behaviour and erosion were investigated with the XLBG formulation with a drug: gum ratio of 1:2, which resulted in a better dissolution profile. The results of the swelling and erosion tests are shown in Fig. 2. The swelling behaviour indicates the rate at which this formulation absorbs water from dissolution media and swells. The change in weight is characteristic of the water uptake and swelling which started immediately and continued for 8 h (Fig. 2a). This matrix exhibited a high degree of swelling. Visual observation showed that the matrices appeared swollen almost from the beginning, and a viscous gel mass was created when they came into contact with the liquid. The matrix erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. The weight loss of the tablets was steady up to 8 h (Fig. 2b) and was about 70%. A similar observation has been reported with xanthan matrices containing Diclofenac sodium obtained by wet granulation [24].

3.4. Determination of the release kinetics

To evaluate the drug release kinetics, formulations showing a significant slow release were chosen. In

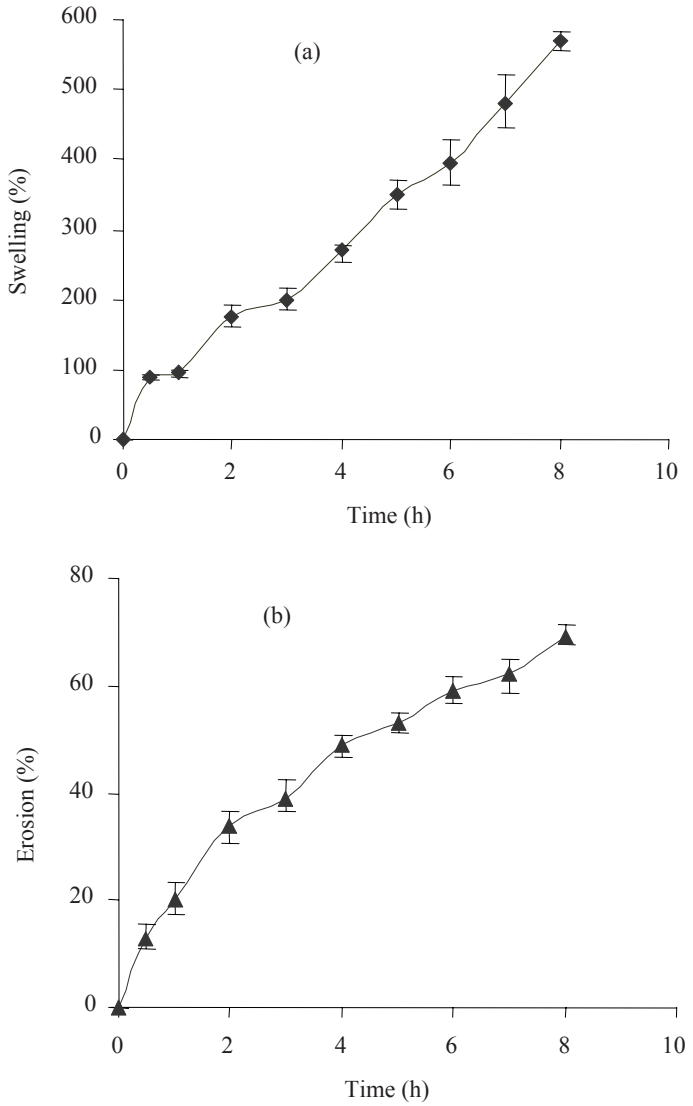

Fig. 2. Analysis of XLBG at a drug: gum ratio of 1: 2 at pH 7.2: (a) Swelling behaviour; (b) Erosion behaviour. Each point represents the mean value of three samples.

general, the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front" defined at an exact speed; simultaneously, the thickness of the area increases with time in the opposite direction. The mechanism of drug release can be described by a second phenomenon that involves the disentanglement and erosion of the polymer [25, 26] and for guar-galactomannan tablets, the release process involves the penetration of water into the dry matrix, followed by hydration and swelling of the polymer, and diffusion of the drug dissolved in the matrix.

By using the Korsmeyer and Peppas model [22] Equation, the *n* values were obtained between 0.49 and 1.18 (Table 2) for all formulations. These values are characteristic of anomalous kinetics (non Fickian) and super case–II transport, suggesting that more than one mechanism may be involved in the release kinetics. The release pattern of PPHCL from different formulation was obtained by plotting log M_t/M_∞ versus log time as shown in Fig. 3. In the case of X and XLBG all formulations show super case II transport kinetics but in the case of LBG both the anomalous (LBG1, LBG2 and LBG3) and super case II (LBG4) transport was found.

For all the PPHCL matrix formulations, the contribution of polymer relaxation occurs throughout the entire dissolution period. This was also apparent from the *n* values obtained (Table 2), which approach anomalous and super case–II transport. In general, the relaxational contribution was higher for the formulations with higher *n* values (Table 2). The XLBG formulation showed the highest contribution of polymer relaxation, and swelling/erosion (Fig. 3). The formulations of X and LBG, showed the lowest *n* values, with XLBG making a smaller relaxational contribution. In the XLBG formulations, the ratio of 1:2 reflects controlled delivery of PPHCL.

3.5. FTIR studies

The FTIR spectra of pure drug and formulations containing XLBG are shown in Fig. 4. From this it is clear that the characteristic peaks at 3282(O-H stretching), 1450(C-H bending), 1240(O-H bending), 1100(C-C and C-O stretching), 800(C-H rocking, C-C stretching and C-H bending) cm^{-1} are present in both the pure PPHCL drug and its formulation containing XLBG3 matrices, without any change in their positions, indicating no chemical interaction between PPHCL and XLBG3, as confirmed by the FTIR studies.

Table 2
Values of *n* (exponent for release kinetics).

Formulation	*n* values	R^2	Transport mechanism
X1 (1: 1)	0.97	0.977	Super case II
X2 (1: 1.5)	1.00	0.989	Super case II
X3 (1: 2)	1.03	0.994	Super case II
X4 (1: 2.5)	1.03	0.998	Super case II
LBG1 (1: 1)	0.49	0.980	Anomalous
LBG2 (1: 1.5)	0.72	0.998	Anomalous
LBG3 (1: 2)	0.87	0.999	Anomalous
LBG4 (1: 2.5)	0.99	0.993	Super case II
XLBG1 (1: 1)	1.12	0.999	Super case II
XLBG2 (1: 1.5)	1.17	0.999	Super case II
XLBG3 (1: 2)	1.18	0.998	Super case II
XLBG4 (1: 2.5)	1.16	0.998	Super case II

In X1–X4, LBG1–LBG4, and XLBG1–XLBG4. 1, 2, 3 and 4 are the ratios of 1:1, 1:1.5, 1:2 and 1:2.5 drug: gum concentration in the tablets, respectively.

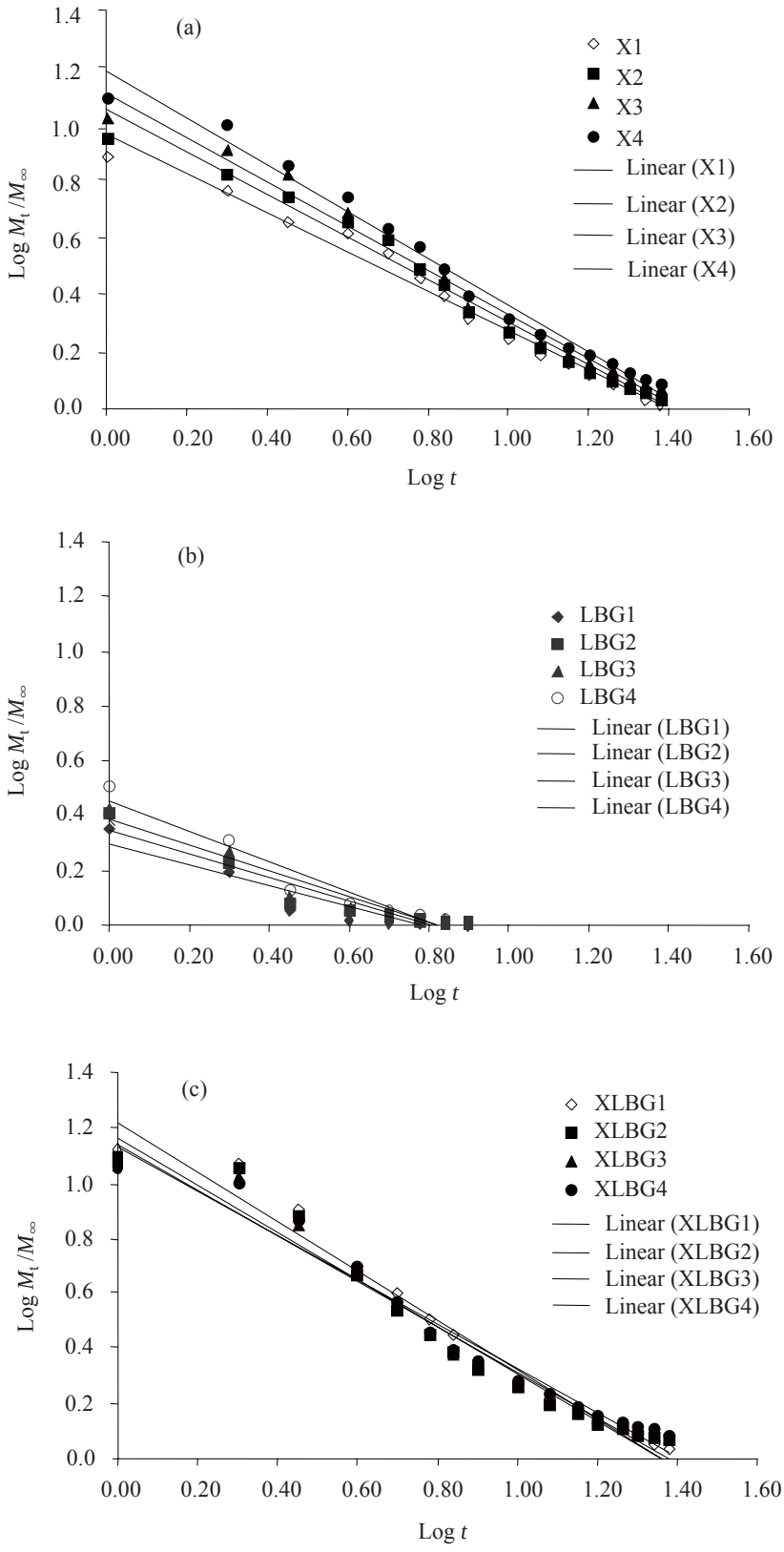

Fig. 3. Release kinetics of PPHCL from (a) X, (b) LBG and (c) Mixture of X and LBG. In X1–X4, LBG1–LBG4, and XLBG1–XLBG4. 1, 2, 3 and 4 are the ratios of 1: 1, 1: 1.5, 1: 2 and 1: 2.5 drug: gum concentration in the tablets.

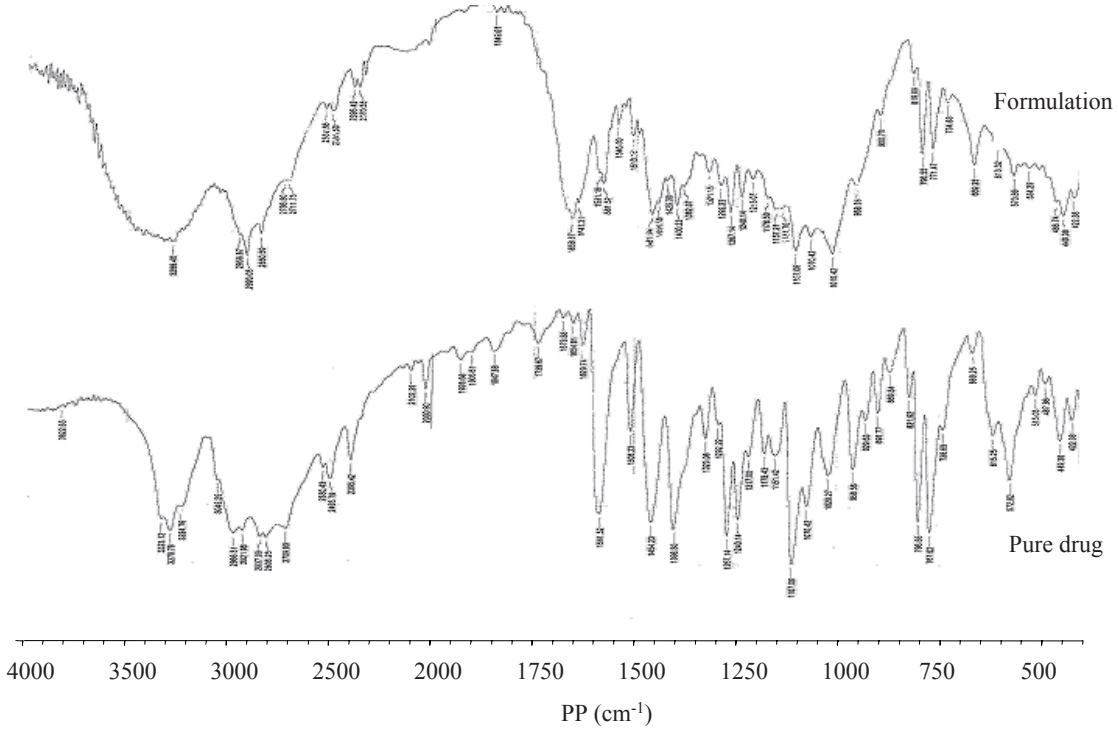

Fig. 4. FITR spectral obtained for pure drug and formulation containing XLBG3.

4. Conclusion

The tablets with XLBG resulted in more uniform drug release matrices than X and LBG, due to the synergistic interaction of the two biopolymers to produce a strong and elastic gel in the presence of a ternary component to control the drug release process, and the smallest average particle size. X produced had a more marked sustained effect on the release of PPHCL than LBG (*Ceratonia siliqua*) matrices alone. The XLBG formulation was found to provide the required release rate, with zero-order release kinetics and there was no chemical interaction between drug and polymer as confirmed by FTIR studies. At the same total concentration, LBG alone did not exhibit controlled release because LBG has a synergistic action with xanthan while LBG alone has no controlled release effect. The predominant release mechanism varied with matrix composition and drug release was controlled by both diffusion and relaxation, with predominance of the latter mechanism mainly in XLBG tablets.

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