Use of Hydrophilic Natural Gums in Formulation of Sustained-release Matrix Tablets of Tramadol Hydrochloride

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Jaleh Varshosaz,[1] Naser Tavakoli,[1] and Fatemeh Kheirolahi[1]

[1]Department of Pharmaceutics, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

The objective of this work was to develop matrix sustained-release tablets of highly water-soluble tramadol HCl using natural gums (xanthan [X gum] and guar [G gum]) as cost-effective, nontoxic, easily available, and suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (ie, hydroxypropyl methylcellulose [HPMC]/carboxymethyl cellulose [CMC] with respect to in vitro drug release rate) and hydration rate of the polymers. Matrix tablets of tramadol (dose 100 mg) were produced by direct compression method. Different ratios of 100:0, 80:20, 60:40, 20:80, 0:100 of G gum (or X):HPMC, X gum:G gum, and triple mixture of these polymers (G gum, X gum, HPMC) were applied. After evaluation of physical characteristics of tablets, the dissolution test was performed in the phosphate buffer media (pH 7.4) up to 8 hours. Tablets with only X had the highest mean dissolution time (MDT), the least dissolution efficiency (DE_8%), and released the drug following a zero-order model via swelling, diffusion, and erosion mechanisms. Guar gum alone could not efficiently control the drug release, while X and all combinations of natural gums with HPMC could retard tramadol HCl release. However, according to the similarity factor (f_2), pure HPMC and H_8G_2 were the most similar formulations to Topalgic-LP as the reference standard.

KEYWORDS: natural gums, xanthan, guar gum, tramadol, sustained-release.

INTRODUCTION

Tramadol is used in the treatment of osteoarthritis when nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief.[1] After oral administration, tramadol is rapidly and almost completely absorbed. Sustained-release tablets reach to peak concentrations after 4.9 hours and have a bioavailability of 87% to 95% compared with capsules. The mean elimination half-life is ~6 hours[2] and requires dosing every 6 hours in order to maintain optimal relief of chronic pain.[3,4] Consequently, once-daily extended-release tablets have been formulated (tramadol ER). Long-term treatment with sustained-release tramadol once daily is generally safe in patients with osteoarthritis or refractory low back pain[5] and is well tolerated.[6] It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance.[7]

Hydrophobic matrix tablets were produced to sustain formulations of tramadol using hydrogenated castor oil[8] and glyceryl behenate.[9] Various monoolein-water systems were also formulated.[10] Tramadol has also been complexed with a sulfonic acid cation-exchange resin in a microencapsulation process by the spray-drying method.[11] Hydrophilic polymers are becoming very popular in formulating oral controlled-release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology. Developing oral controlled-release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentrations when administered orally.[12] Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Guar gum is a natural nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae). In pharmaceuticals, G gum is used in solid dosage forms as a binder and disintegrant.[13] X gum is another natural, biosynthetic, edible gum and an extracellular polysaccharide produced by the bacterium *Xanthomonas campestris*. Zanthan gum consists of glucose, mannose, and glucuronic acid[14] and is used in different foods as thickener and stabilizer.[15] The objective of this study was to develop matrix sustained-release tablets of tramadol using natural gums (xanthan and guar gum) as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (ie, hydroxypropyl methylcellulose [HPMC]/carboxymethyl cellulose [CMC] with respect to in vitro drug release rate) and hydration rate of the polymers.

Corresponding Author: Jaleh Varshosaz, Department of Pharmaceutics, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel: 0098 311 7922579; Fax: 0098 311 6680011;
E-mail: varshosaz@pharm.mui.ac.ir

The probable synergistic effect of triple mixture of natural gums and HPMC on retarding the drug release was also studied.

Materials and Methods

Tramadol HCl was a gift from Chimidaruo Co (Tehran, Iran). Guar gum was obtained from Hercules (East Syracuse, NY); xanthan gum was obtained from Farabi Co (Isfahan, Iran); HPMC K4M was obtained from Sigma-Aldrich Co (Fluka, Switzerland); carboxymethyl cellulose, magnesium stearate, hydrochloric acid, sodium hydroxide, and potassium phosphate monobasic were all obtained from Merck (Darmstadt, Germany); Avicel PH 101 was obtained from FMC Corp (Philadelphia, PA); and Topalgic-LP 100 mg was obtained from Aventis (Lyon, France). All chemicals were pure and from analytical grade.

Preparation of Tramadol HCl Matrix Tablets

Matrix tablets of tramadol HCl (dose 100 mg) were prepared by direct compression method. Magnesium stearate was used as lubricant; Avicel PH 101, as filler-binder for increasing the compressibility and flow of the ingredients; and HPMC, as diluent. The total weight was set at ~400 mg. Table 1 shows the different studied formulations. Before use all ingredients were sieved through a 90-µm sieve, weighed, and mixed during 10 minutes in a mixer (WAB turbula, T2C, Basel, Switzerland). Finally the magnesium stearate was added and mixed for an additional 2 minutes. Tablets were compressed on a single punch tableting machine (type K5, Kilian GmbH, Füllinsdorf, Germany) fitted for of 0.37 mm height and 1.27 mm in diameter.

Table 1. Composition of 100 mg Tramadol HCl Matrices (according to mg)*

Formulation	HPMC	Guar Gum	Xanthan Gum
$G_6X_2H_2$	52	52	156
H	260	-	-
G	-	260	-
X	-	-	260
H_8G_2	208	52	-
H_6G_4	156	104	-
H_2G_8	52	208	-
X_8H_2	52	-	208
X_6H_4	104	-	156
X_2H_8	208	-	52
X_8G_2	-	52	208
X_6G_4	-	104	156
X_2G_8	-	208	52
$H_6X_2G_2$	156	52	52
$X_6G_2H_2$	52	156	52

*The matrices contain 40 mg Avicel and 4 mg magnesium stearate.

The tablets were compressed in order to obtain a 40 to 50 N hardness (tablet hardness tester type TB 42 Erweka, Frankfurt, Germany).

Determination of Drug Content

The tramadol HCl matrix tablets were tested for their drug content. Twenty tablets were finely powdered; 400 mg of the powder was accurately weighed and transferred to a 50-mL volumetric flask. Then the volume was made up with 0.1N HCl and shaken for 10 minutes to ensure complete solubility of drug. The mixture was centrifuged (type: 2000, Clements, Rydalmere, Australia) and 10 mL of the supernatant liquid was diluted 20 times with 0.1N HCl, and after centrifugation the absorbance was determined spectrophotometrically (UV-visible 1240 CE, Shimadzu Corp, Kyoto, Japan) at 272.8 nm.

In Vitro Drug Release Studies

The matrix tablets were subjected to the paddle dissolution method using 900 mL of phosphate buffer solution pH 7.4 ± 0.2 as the dissolution medium. The dissolution test was performed at 100 rpm and the temperature was set at 37°C ± 1°C. At predetermined time intervals over an 8-hour period, 4 mL samples were withdrawn, centrifuged, and assayed spectrophotometrically at 272.5 nm.[11] After each sampling, equal volume (4 mL) of fresh buffer solution with the same temperature was replaced. All experiments were run 3 times, and the calibration curve specifications were $y = 0.006X \pm 0.005$ ($r^2 = 0.9998$, n = 9).

Mass Loss and Water Uptake Studies

Erosion and water uptake of the tableted formulations was determined under conditions identical to those described above for dissolution testing. Water uptake and mass loss were determined gravimetrically according to the following equations:

$$Water\ Uptake\ (\%) = \frac{Wet\ Weight - Remaining\ Dry\ Weight}{Remaining\ Dry\ Weight} \times 100 \quad (1)$$

$$Mass\ Loss\ (\%) = \frac{Remaining\ Dry\ Weight - Original\ Dry\ Weight}{Original\ Dry\ Weight} \times 100 \quad (2)$$

$$Erosion\ at\ Time\ t\ (\%) = Mass\ Loss\ (\%)\ at\ Time\ t - Drug\ Released\ (\%)\ at\ Time\ t \quad (3)$$

Three tablets were used per time point. At the predetermined times, the tablets were lightly patted with tissue paper to remove excess surface water. The wet weight of tablets was determined, and then they were dried at 70°C for 10 days, before reweighing. The remaining dry weight was determined, and placebo tablets consisting of pure polymer were treated in the same way.[16]

Data Analysis

Zero-order ($Q_t = Q_0 + K_0 t$), first-order ($ln\ Q_t = ln\ Q_0 + K_1 t$), Higuchi ($Q_t = K_H t^{1/2}$), Hixson-Crowell ($Q_0^{1/3} - Q_t^{1/3} = K_S t$),[17] and Korsmeyer-Peppas ($Q_t/Q_\infty = Kt^n$)models[18] were fitted to the dissolution data using linear regression analysis. A value of n = 0.5 indicates case I (Fickian) diffusion or square root of time kinetics, 0.5 < n < 1 anomalous (non-Fickian) diffusion, n = 1 Case-II transport and n > 1 Super Case-II transport.[19] Model independent approaches (ie, dissolution efficiency [DE])[20] and mean dissolution time (MDT)[21] were used to translate the profile differences into a single value.

$$DE_8\% = \frac{\int_0^t y\ dt}{y_{100}}\, t \times 100 \qquad (4)$$

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \qquad (5)$$

Where *i* is the dissolution sample number, *n* is the number of dissolution sample time, t_{mid} is the time at the midpoint between *i* and *i-1,* and ΔM is the amount of drug dissolved between *i* and *i-1*.[21]

The similarities between 2 dissolution profiles were assessed by a pair-wise model independent procedure such as similarity factor (f_2)[19]:

$$f_2 = 50\ Log\left\{\left[1 + \frac{1}{n\sum_{n=1}^{n=i}(R_t - T_t)^2}\right]^{-0.5} \times 100\right\} \qquad (6)$$

Where *n* is the number of pull points, w_t is an optional weight factor, R_t is the reference profile at time point *t,* and T_t is the test profile at the same time point; the value of f_2 should be between 50 and 100.[22] An f_2 value of 100 suggests that the test and reference profiles are identical and, as the value becomes smaller, the dissimilarity between release profiles increases.

Comparison among multiple means of prepared natural gum formulations and reference formulation (Topalgic LP) were made by 1-way analysis of variance ANOVA followed by least significant difference's (LSD) test at the 95% level of confidence (SPSS, Version 11, SPSS Inc, Chicago, IL).

Results and Discussion

Different combinations of natural gums (guar or xanthan) with HPMC and also a triple mixture of these polymers were used to provide matrix tablets for sustained release of water-soluble tramadol HCl. A total 64% of release retardant polymer(s) was used in the formulations. Each formulation was coded according to the ratio of polymers for example X_8G_2 is a formulation with X gum and G gum in the ratio of 8:2. The hardness of the tablets ranged from 41 to 69 N. All formulations satisfied the content uniformity of tramadol HCl and friability between 0.2% and 0.58% (Table 2).

As Figure 1 indicates, an initial burst release of the drug is observed with G and HPMC matrices, which is absent with X matrices. Such a burst effect was also observed by other investigators who suggested the addition of other hydrocolloids such as HPMC in relatively large amounts.[23]

Table 3 shows data analysis of release profiles according to different kinetic models. When HPMC is the only retarding agent, drug release profile better fits with a Higuchi model and Peppas equation also indicated the Fickian diffusion (Table 3). This polymer showed less mass loss (Figure 2) and water uptake (Figure 3) compared with natural gums. The hydration rate of this synthetic polymer relates to its hydroxypropyl substitutes percentage. HPMC-K100M contains the greatest amount of these groups and produces strongly viscose gel that plays an important role in drug release especially at the beginning of the release profile. Therefore, the quick hydration and subsequent gel formation is a foremost and important property of an excipient for it to be used in sustained-release formulations.[24] Table 3 also shows when X is used as the only retarding hydrophilic polymer, drug release significantly follows a zero-order kinetic model ($P < .05$) (Table 3). On the other hand, X shows the highest erosion and water uptake among the studied formulations (Figures 2, 3). This finding suggests 3 mechanisms (ie, swelling, erosion, and diffusion fronts) synchronize and the thickness of gel layer was constant, so a zero-order release was observed.[25] Our previous studies[26] with X gum, a natural derivative of cellulose, showed that the drug release from this microbial exocellular polysaccharide follows zero-order or almost time-independent release kinetics, which is in accordance with the finding of others.[27-29] In high concentrations of X (X_8H_2 and X_6H_4), considering the high level of erodability of X (Figure 2), a

Table 2. Physical Characteristics (drug content, hardness, and friability) and Release Parameters of Tramadol From Different Matrices (n = 3)*

Formulation	Average drug content (mg) ± SD	Hardness (N) ± SD	Friability (%)	MDT (min) ± SD	DE_8% ± SD	f_2
Topalgic-LP	99.5 ± 3.6	68.5 ± 2.3	0.37	161 ± 1.0	60.0 ± 0.96	-
H	98.8 ± 2.0	58.6 ± 1.2	0.20	225 ± 6.2	49.6 ± 3.02	54
X	100.1 ± 3.8	68.8 ± 2.3	0.37	172 ± 1.3	57.1 ± 1.05	76
G	97.4 ± 3.0	40.8 ± 1.0	0.48	120 ± 7.4	70.6 ± 3.80	44
H_8G_2	99.0 ± 4.1	50.0 ± 3.5	0.32	159 ± 3.3	54.8 ± 1.74	78
H_6G_4	98.6 ± 3.9	48.0 ± 2.7	0.40	153 ± 4.9	58.6 ± 1.32	75
H_2G_8	100.1 ± 4.5	43.6 ± 2.2	0.42	138 ± 7.1	64.2 ± 22.7	55
X_8H_2	100.0 ± 5.0	66.7 ± 2.9	0.32	182 ± 3.0	53.5 ± 1.72	61
X_6H_4	97.6 ± 3.2	60.0 ± 3.5	0.30	175 ± 2.1	56.8 ± 1.36	66
X_2H_8	101.0 ± 4.2	58.9 ± 3.6	0.28	160 ± 4.8	61.2 ± 1.13	57
X_8G_2	97.4 ± 3.0	59.0 ± 5.2	0.42	159 ± 1.5	58.0 ± 1.32	74
X_6G_4	102.0 ± 5.5	49.0 ± 4.2	0.56	153 ± 8.0	60.0 ± 3.55	68
X_2G_8	98.8 ± 3.3	43.6 ± 2.2	0.58	138 ± 7.2	63.2 ± 2.22	58
$H_6X_2G_2$	102.0 ± 3.7	52.0 ± 4.1	0.50	143 ± 4.3	61.4 ± 3.20	69
$X_6G_2H_2$	94.9 ± 2.4	61.8 ± 4.6	0.40	168 ± 7.2	50.5 ± 4.04	66
$G_6X_2H_2$	96.0 ± 4.2	41.8 ± 1.3	0.58	129 ± 5.3	71.3 ± 3.33	61

*MDT indicates mean dissolution time; DE_8%, dissolution efficiency up to 8 hours of release test; and f_2, similarity factor).

Hixson-Crowell release kinetic is concluded (Table 3). As there is no significant difference between r^2 of the zero-order and Hixson-Crowell kinetic in X_8H_2 (Table 3), it may be concluded that drug is released both by erosion and by diffusion within the matrix and often approximates zero-order for a significant part of total release time. Decreasing the X gum concentration in X_2H_8 shifts the drug release kinetic to Higuchi model (Table 3). When G gum is used as the only retarding polymer, a first-order release kinetic (Table 3) is observed. In an effort to obtain some evidence for the relationship between release mechanism and water uptake and matrix mass loss kinetics, additional studies were conducted. As Figure 2 indicates also, G gum matrices have negligible mass loss (~2%), and a high water uptake (~507%) after 8 hours (Figure 3). Three processes of water penetration, gelatinization, and diffusion rate have also been reported previously as the rate-limiting steps for the release of water-soluble drugs with first-order release kinetics for guar matrices by Ughini et al[30] Al-Saidian et al[31] reported a first-order kinetics via Fickian-diffusion for diltiazem HCl release from G gum matrix tablets. In all formulations of the combination of HPMC and G gum, drug release kinetics is predominantly Higuchi model kinetics ($P < .05$) via Fickian diffusion (Table 3). As HPMC and G gum are both hydrophilic colloids and water-soluble, they dissolve and form pores filled with liquid in which drug can thereafter diffuse.[25]

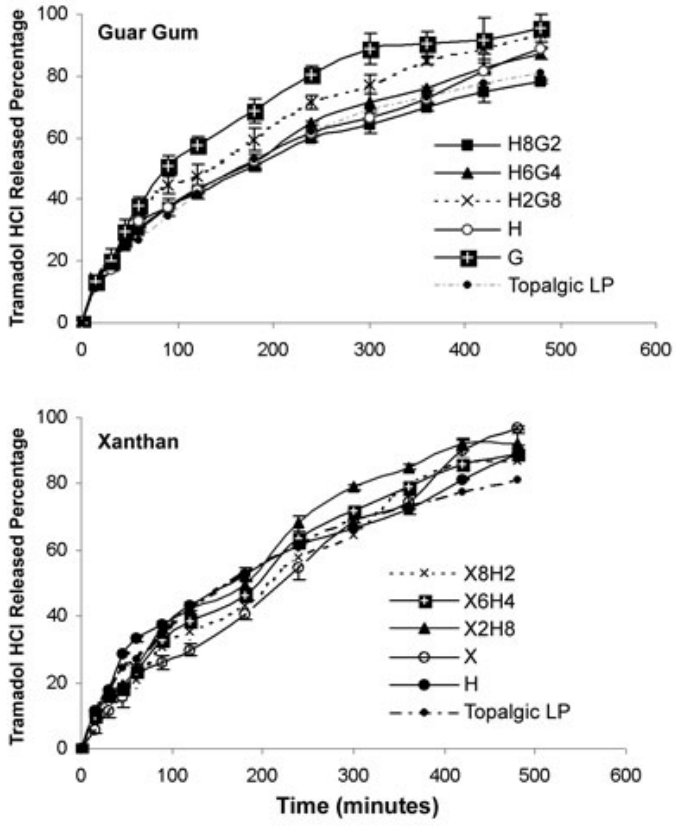

Figure 1. Release profiles of tramadol HCl from the matrices containing different percentages of guar gum and xanthan in phosphate buffer solution (n = 3).

The overall rate of release of tramadol from G matrices is significantly higher than that from X matrices ($P < .05$) (Figure 4), which is confirmed by smaller MDT (120.1 ± 7.4 minutes) for G gum and higher MDT (225.0 ± 6.2 minutes) for X matrices (Table 2). These results are clear indication that X has higher drug retarding ability than G gum. Bhalla and Sanzgiri[23] reported also that G gum is not able to retard sulbutamol release alone. However, Altaf et al[32] showed G-gum-based matrix tablets represent sustained-release properties for diltiazem. HPMC also showed the most similar MDT to Topalgic-LP (Table 2).

Table 3. Diffusion Exponent (n) of Peppas Model and Regression Coefficient (r^2) of Tramadol Release Data From Studied Matrices According to Different Kinetic Models (n = 3)

Formulation	n	Zero-order	First-order	Higuchi	Hixson-Crowell
Topalgic-LP	0.535	0.922 ± 0.002	0.972 ± 0.003	0.995 ± 0.005	0.960 ± 0.010
X	0.830	0.992 ± 0.004	0.869 ± 0.004	0.961 ± 0.005	0.960 ± 0.003
H	0.547	0.931 ± 0.004	0.971 ± 0.010	0.994 ± 0.008	0.960 ± 0.007
G	0.509	0.856 ± 0.003	0.986 ± 0.002	0.971 ± 0.005	0.943 ± 0.009
H_8G_2	0.529	0.909 ± 0.004	0.959 ± 0.004	0.996 ± 0.008	0.944 ± 0.007
H_6G_4	0.538	0.935 ± 0.003	0.964 ± 0.007	0.998 ± 0.008	0.959 ± 0.004
H_2G_8	0.542	0.916 ± 0.005	0.971 ± 0.008	0.994 ± 0.003	0.969 ± 0.006
X_8H_2	0.682	0.983 ± 0.006	0.960 ± 0.008	0.967 ± 0.008	0.989 ± 0.004
X_6H_4	0.651	0.964 ± 0.007	0.961 ± 0.008	0.987 ± 0.001	0.990 ± 0.006
X_2H_8	0.636	0.953 ± 0.003	0.961 ± 0.004	0.989 ± 0.004	0.966 ± 0.008
X_8G_2	0.605	0.937 ± 0.790	0.998 ± 0.004	0.994 ± 0.005	0.970 ± 0.008
X_6G_4	0.559	0.936 ± 0.009	0.995 ± 0.007	0.997 ± 0.006	0.962 ± 0.007
X_2G_8	0.525	0.911 ± 0.001	0.994 ± 0.004	0.991 ± 0.007	0.966 ± 0.004
$H_6X_2G_2$	0.540	0.960 ± 0.007	0.990 ± 0.008	0.980 ± 0.008	0.995 ± 0.006
$X_6G_2H_2$	0.504	0.900 ± 0.003	0.970 ± 0.008	0.980 ± 0.003	0.978 ± 0.009
$G_6X_2H_2$	0.511	0.890 ± 0.004	0.973 ± 0.005	0.993 ± 0.004	0.973 ± 0.004

Formulations of the mixture of 3 polymers (Figure 4) are capable of retarding drug release considering their MDT, and all of them show f_2 of greater than 50 compared with Topalgic-LP, which shows their capability to sustain the release of tramadol. $X_6H_2G_2$ showed greater MDT compared with the other triple mixture of polymers ($P < .05$) (Table 2). However, there doesn't seem to be any synergism effect between them as there are other formulations with 2 polymers or even one that showed greater MDT and f_2 values (Table 2). X gum also showed the least $DE_8\%$, while G gum showed the greatest $DE_8\%$ ($P < .05$) among the tablets with just one of the retarding polymers (Table 2).

Comparing the MDT and $DE_8\%$ of tablets with double combination of polymers (natural and/or synthetic) with a 2-way ANOVA test showed that the type of the combination of 2 polymers, the ratio of the 2 polymers and also their interaction effects had main effect on MDT and $DE_8\%$ ($P < .05$). This test shows that the combination of a natural gum with HPMC leads to a greater MDT compared with 2 natural gums (Table 2), so that XH > HG > XG. The 2-way

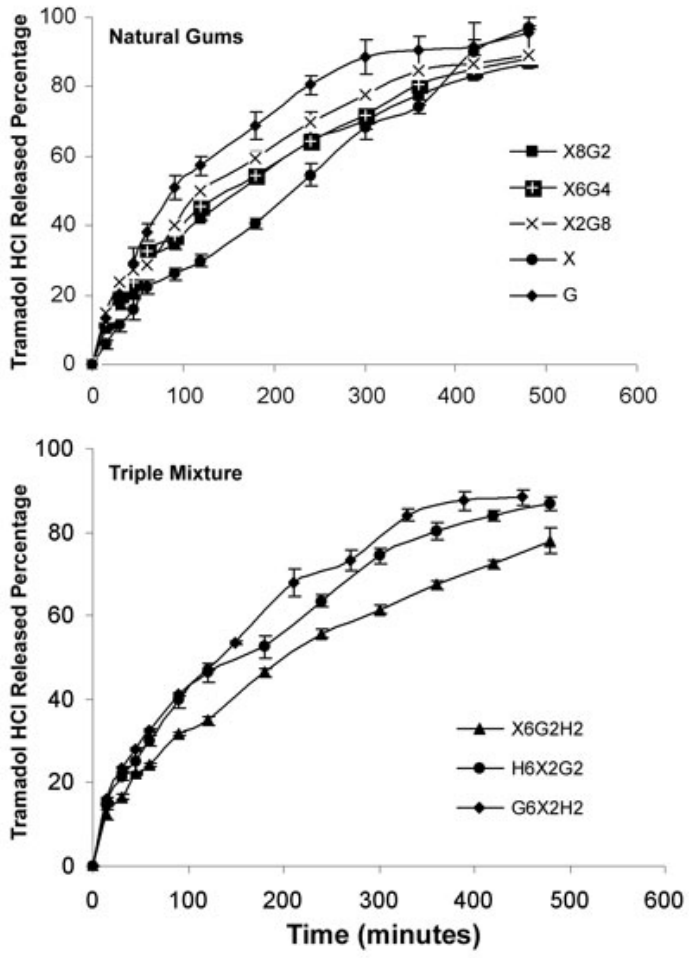

Figure 2. Mass loss percentage with time of some formulations of matrix tablets of tramadol (n = 3).

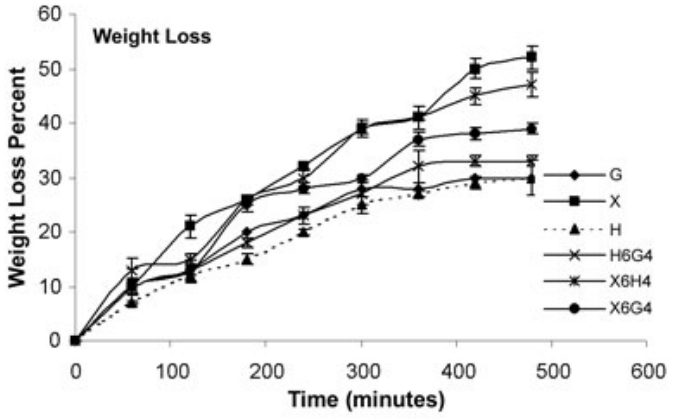

Figure 3. Water uptake percentage (× 0.1) with time of some formulations of matrix tablets of tramadol (n = 3).

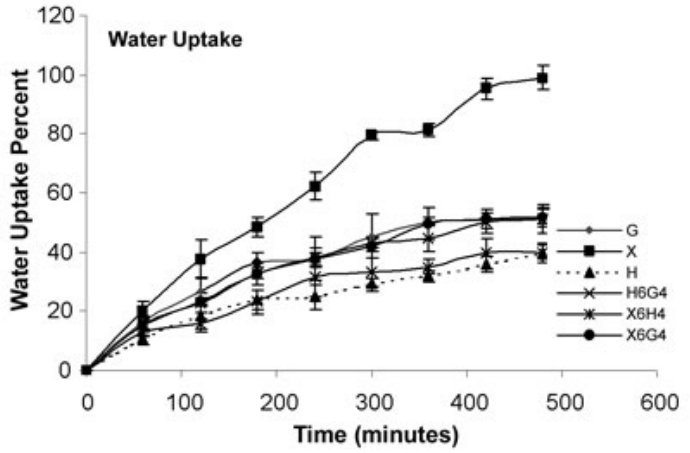

Figure 4. Release profiles of tramadol HCl from the matrices containing combination of natural gums or triple mixture of natural gums with HPMC in phosphate buffer solution (n = 3).

ANOVA test also shows that the higher the ratio of the polymers, the greater the MDT of tramadol: 80:20 > 60:40 > 20:80 (Table 2). A reverse order of the effect of double combination of polymers was seen on the DE_8% (ie, XG > HG > XH and 80:20 < 60:40 < 20:80) (Table 2). Except for G gum, other formulations had an f_2 factor between 50 and 100, while the greatest f_2 was seen for H, H_8G_2, H_6G_2, and X_8G_2 (Table 2), indicating the most similar formulations to Topalgic-LP. As Table 2 indicates, the greatest MDT relates to X that shows a great capacity of retarding effect of this natural gum compared with G gum that shows the least MDT compared with other formulations ($P < .05$) (Table 2).

Tablets prepared by HPMC:X like those prepared with X alone show a non-Fickian or anomalous mechanism (Table 3). Guar gum alone or in combination with HPMC (like HPMC alone) shows a Fickian-release diffusion. In a combination of X with G except X_8G_2, which shows a non-Fickian diffusion, other combinations of these polymers and also triple mixtures of X gum, G gum, and HPMC show a Fickian diffusion. Topalgic-LP that was used as a reference formulation followed a Higuchi release model indicating a Fickian diffusion of the drug (Table 3).

Conclusion

Guar gum alone cannot efficiently control drug release, and X gum has higher drug retarding ability than G gum. The combination of each natural gum with HPMC leads to a greater retarding effect compared with a mixture of 2 natural gums. No synergistic effect was seen for triple mixtures of polymers. All combinations of guar gum and/or xanthan with HPMC or xanthan alone can retard tramadol HCl release. However, according to f_2, pure HPMC and H_8G_2 are the most similar formulations to Topalgic-LP.

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