

DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLET OF TRAMADOL HYDROCHLORIDE USING NATURAL GUMS

¹MS. LATA A. PANCHAL, ²DR. PRAGNA K. SHELAT, ³DR. MAITREYI N. ZAVERI

¹Department of Pharmaceutics, K.B. Institute of Pharmaceutical Education & Research, ²Department of Pharmaceutics, K.B. Institute of Pharmaceutical Education & Research, ³Department of Pharmacognosy, K.B. Institute of Pharmaceutical Education & Research, Kadi Sarva Vishwavidyalaya University, Gandhinagar. Email: latapanchal@yahoo.co.in, khandharmaitreyi@gmail.com

Received: 07 Mar 2012, Revised and Accepted: 19 Apr 2012

ABSTRACT

The objective of this study was to study the individual effect of Tamarind gum (TG), Locust bean gum (LB) and xyloglucan extracted out from tamarind gum (XG) as a release modifier in the design and development of sustained release matrix tablets of highly water-soluble drug Tramadol hydrochloride. Advantages offered by these natural excipients are that they are non-toxic, less expensive and freely available. Matrix tablets of tramadol hydrochloride were produced by direct compression and wet granulation method. The prepared tablets were evaluated for various physicochemical parameters. To analyze the release mechanism zero-order, first-order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas model were used. Similarity factor f_2 was also calculated to compare prepared matrices with the synthetic release retardant HPMC as well as market product Contramal SR (Piramal Healthcare Limited, 100 mg). Xyloglucan of tamarind gum and locust bean gum exhibit higher release retarding ability than tamarind gum.

Keywords: Sustained release matrix, Tramadol hydrochloride, Tamarind gum, Locust bean gum, Xyloglucan.

INTRODUCTION

Generally, controlled drug delivery are formulated with primary objectives of ensuring safety and improving efficacy of drugs as well as patient compliance, which can be achieved by better control of plasma drug levels and less frequent dosing¹. Physical blending of drug with polymer matrix, followed by direct compression, compression molding, injection molding, extrusion, or solvent casting are the most convenient way to achieve controlled release of active agent which results either in monolithic device or in swellable hydrogel matrix²⁻⁶. In fact, matrix is defined as a well composite of one or more drugs with a gelling agent i.e. hydrophilic polymer. Extensive use of the natural materials in the field of drug delivery have been owed to their ready availability, cost-effectiveness, eco-friendliness, capability of undergoing multitude of chemical modifications, potential degradability and compatibility due to their natural origin⁷. Past research therefore studied and acknowledged various natural gums like agar, konjac, guar gum, chitosan, xanthan gum, sodium alginate and locust bean gum for potential pharmaceutical and biomedical applications⁸. Hydrophilic matrices containing swellable polymers are referred to as swellable controlled release systems or hydrophilic matrix tablets.^{3,7}

Hydrophilic natural gums are high molecular weight substances, usually insoluble in alcohol, but can be made to dissolve, swell or disperse in water to give viscous or mucilaginous solutions. When solutions of hydrophilic gums are mixed, they interact with each other; this can result in an increase in viscosity, which becomes greater than the viscosity of each solution.

Tamarind gum (*Tamarindus indica* Linn., Family Leguminosae) consists of a main chain of cellulose with frequent branching at the O-6 positions with short side chains of one or two D-xylopyranosyl capped with D-xylopyranosyl, D-galactopyranosyl or L-arabinofuranosyl units.

Locust bean gum⁹ or Carob bean gum (*Ceratonia siliqua* Family Leguminosae) is a plant seed galactomannan, composed of a 1-4-linked β -D-mannan backbone with 1-6-linked α -D-galactose side groups¹⁰. The physico-chemical properties of galactomannan are strongly influenced by the galactose content¹¹ and the distribution of the galactose units along the main chain. Longer galactose side chains produce a stronger synergistic interaction with other polymers and greater functionality¹². LBG is also used to treat elevated plasma cholesterol levels in healthy subjects¹³.

Xyloglucans are a major class of structural polysaccharides found in the primary cell walls of higher plants. Xyloglucan polysaccharide

has the same skeleton, α -1, 4 D-glucan, as cellulose and therefore is not digested by human digestive enzymes (it acts as dietary fiber)¹⁴. Isolation of xyloglucan the polysaccharide from tamarind kernel powder was carried out by aqueous extraction-non aqueous precipitation method¹⁵. Polysaccharide based matrix tablets were prepared by many researchers¹⁶⁻¹⁷.

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 orally¹⁸. Tramadol hydrochloride is used in the treatment of osteoarthritis when nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief. After oral administration, tramadol hydrochloride 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 and requires dosing every 6 hours in order to maintain optimal relief of chronic pain¹⁹⁻²⁰. Consequently, once-daily extended-release tablets have been formulated (tramadol hydrochloride ER). Long-term treatment with sustained-release tramadol hydrochloride once daily is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated²¹. It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance²². 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. The objective of this study was to develop matrix sustained-release tablets of tramadol hydrochloride using natural gums (tamarind gum, locust bean gum and xyloglucan of tamarind gum) as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (i.e., hydroxy propyl methylcellulose [HPMC]/ carboxymethyl cellulose [CMC] with respect to in vitro drug release rate) and hydration rate of the polymers.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was obtained from Saga laboratories (Ahmedabad, Gujarat). Microcrystalline cellulose (MCC) PH 101, polyvinyl pyrrolidone (PVP)-K-30, dicalcium phosphate (DCP) and talc

were obtained as a gift from Suvik Hitek Private Limited (Gandhinagar, Gujarat). Tamarind gum was obtained as a gift from H.B. Gum Industries Pvt. Ltd. (Kalol, North Gujarat). Locust bean gum was obtained as a gift from Lucid Colloids Ltd. (Mumbai). Magnesium stearate, Sodium hydroxide (NaOH), and Potassium phosphate monobasic (KH_2PO_4) were obtained from S.D. Fine chemicals Ltd. and Contramal-SR was obtained from retail pharmacy and used as reference product. All other chemicals were pure and of analytical grade.

Methods

Isolation of xyloglucan (XG) from tamarind gum

The isolation of xyloglucan was performed in the following manner. Twenty gram of tamarind kernel powder was added to 200 ml of cold distilled water and slurry prepared. The slurry was slowly poured into 800 ml of boiling distilled water and further boiled for 20 min under stirring condition on a water bath. The resulting mixture was kept overnight and then it was centrifuged at 5000 revolutions per minute (RPM) for 20 min. The supernatant liquid was separated and poured into twice the volume of absolute alcohol by continuous stirring to precipitate the polysaccharide. The precipitate was washed with 200 ml of absolute ethanol and then dried at 50°C for 10 h in hot air oven (Nova Instruments Pvt. Ltd.). The dried polymer was powdered and stored in zip-bag until further use¹⁵.

Preformulation studies

Preformulation parameters of the tamarind gum and locust bean gum were evaluated in the form as procured from the manufacturer. Similarly, isolated xyloglucan was also evaluated.

Swelling index

The official method²³ was used i.e. 1.0g each of the sample was placed in each of 15ml plastic centrifuge tubes and the volume occupied was noted. 10ml of distilled water was added and stoppered. The contents were mixed thoroughly for 2min. The mixture was allowed to stand for 10min and immediately centrifuged at 1000RPM for 10 min on a bench centrifuge (Labtronik, Ahmedabad). The supernatant was carefully decanted and the volume of sediment was measured. The swelling index was computed using the following equation:

$$S = V_2 / V_1 \dots\dots\dots(1)$$

Where; S = Swelling index

V_1 = Volume occupied by the gum prior to hydration

V_2 = Volume occupied by the gum after to hydration

Loss on drying

The method adopted was that specified for gum acacia²³⁻²⁴. 1.0g each of the samples was transferred into each of several petridishes and then dried in hot air oven at 105°C until a constant weight was obtained. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.

pH determination

This was done by shaking a 1%w/v dispersion of the sample in water for 5 min and the pH determined using a pH meter (Electrolab, Mumbai).

Angle of repose

The static angle of repose θ was measured according to the fixed funnel and free standing cone method^{23, 25-26}. A funnel was clamped with its tip 2cm above a graph paper (h) placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base (D) of the powder cones were

determined and the tangent of the angle of repose ($\tan \theta$) calculated using the following equation:

$$\tan \theta = 2h/D \dots\dots\dots(2)$$

Where, h is the height powder cone from base to the apex.

Bulk and tap densities

2g quantity each of the powder sample was placed in a 10ml measuring cylinder and the volume V_0 , occupied by each of the samples without tapping was noted. After 100 taps on the table, the occupied volume V_{100} was read. The bulk and tap densities were calculated as the ratio of weight to volume (V_0 and V_{100} respectively)²⁷.

Hausner Ratio

This was calculated as the ratio of tapped density to bulk density of the samples.

Compressibility Index (C.I. %)

This was calculated using the equation:

$$\text{Compressibility} = (\text{Tapped density} - \text{bulk density}) / \text{Tapped density} \times 100 \dots\dots\dots(3)$$

Viscosity (cps)

Viscosity of 1% w/v solution was determined using Brookfield viscometer (Model LVDV-II), spindle number 61.

Preparation of Tramadol hydrochloride Matrix Tablets

Preparation of Tramadol hydrochloride Matrix Tablets by direct compression method (DC)

Matrix tablets of tramadol hydrochloride (dose 100 mg) were prepared by direct compression method and wet granulation method. For direct compression (DC), concentrations of gums used were 30 to 70%. All ingredients were sieved through an ASTM #60 sieve (250 μm size), and then weighed quantity of drug was physically mixed with all auxiliary excipients by geometric addition using a glass mortar and pestle for about 10 min. Then magnesium stearate and talc were added as the lubricant/ glidant and thoroughly mixed (zip bag) for 5min. This was the Granules Ready for Compression (GRC). From the GRC, the homogeneous powder mixture for a single matrix was weighed, fed manually into the die of an eight station automatic rotary tablet machine (Karnavati Engineering Ltd., Kadi) equipped with biconcave die-punch set of 8mm diameter and compressed to a target weight of 400mg and an average hardness of 5–6 kg/cm² for all tablets. The obtained matrices were subjected to various pharmacopoeial and physical properties evaluation like weight variation, thickness (Vernier calipers), hardness (Monsanto hardness tester, Campbell electronics), Friability (Roche Friabilator, Labtronik), drug content, in vitro drug release and swelling behavior of the matrix tablets.

Formulation codes (Batch F1 and F2) and composition of the batches are shown in Table 1.

Preparation of Tramadol hydrochloride Matrix Tablets by wet granulation method (WG)

For wet granulation method, mucilage of gums were prepared and added to the mixture of previously sifted and weighed quantity of drug and other auxiliary excipients to make a wet mass using a glass mortar and pestle; then passed through sieve to prepare granules; dried in hot air oven at 60°C for 30 min; then magnesium stearate and talc were added as the lubricant/ glidant and thoroughly blended for 5min and were sieved through ASTM sieve #20 sieve (841 μm) and retained on #40 sieve (420 μm). This was the Granules Ready for Compression (GRC). The rest of the procedure was same as used for direct compression.

Formulation codes (F3 to F8) and composition of the batches are shown in Table 1.

Table 1: Composition of batches prepared to produce matrix tablets of tramadol hydrochloride*

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol hydrochloride	100	100	100	100	100	100	100	100
TG	160	-----	-----	-----	-----	-----	-----	-----
XG	-----	160	160	160	-----	-----	-----	-----
LB	-----	-----	-----	-----	160	160	160	-----
HPMC K100M	-----	-----	-----	-----	-----	-----	-----	160
PVP K-30	128	128	-----	-----	-----	-----	-----	128
DCP	-----	-----	128	-----	128	-----	64	-----
MCC	-----	-----	-----	128	-----	128	64	-----
Talc	8	8	8	8	8	8	8	8
Mg.Stearate	4	4	4	4	4	4	4	4
Total	400	400	400	400	400	400	400	400

*All quantity are in mg.

Determination of Drug Content

The tramadol hydrochloride 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 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 1800, Shimadzu) at 271 nm.

In Vitro Drug Release Studies

As per USP monographs for extended-release dosage forms, the percent of drug released after more than one time point is required. Therefore, the percent of drug release after every hour up to 12 h (Q_t) was selected as the response variables (Figure 1). The dissolution of the developed matrix formulations was carried out in USP type II (paddle) apparatus model TDT-60T (Electrolab, Mumbai) using phosphate buffer pH 6.8 at 100 RPM and 37 ± 0.5 °C up to 12 h. Five milliliter dissolution medium was withdrawn at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h, filtered and analyzed spectroscopically. After each sampling, equal volume (5 ml) of fresh buffer solution with the same temperature was replaced. All experiments were run 3 times and the calibration curve specifications $y = 0.0105x - 0.0161$ and $R^2 = 0.9994$ were obtained after plotting absorbance(y) vs. conc.(x) graph adding trend line through regression to obtain straight line equation of the type $y = mx + c$; where y is the value of y variable, x is the value of x variable, m is the slope of the straight line and c is the intercept of the line on y axis; and R^2 is the correlation coefficient indicative of accuracy of the data obtained. The release behavior of the matrix tablets (batch F1 to F7) was compared with batch F8 and the market product CONTRAMAL SR (reference product).

Study of Release Kinetics

To compare the release profile of the prepared matrices with the market product, similarity factor f_2 was calculated using the following equation²⁸:

$$f_2 = 50 \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{i=1}^n (T_i - R_i)^2}{n}}} \right] \dots \dots \dots (4)$$

Where, T_i and R_i show the average percents dissolved from test and reference products at the time point(i), and n is the number of time points.

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate equation (Eq.) (5) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (6) describes the release from system where release rate is concentration dependent²⁹. Higuchi Eq. (7)³⁰ described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The Hixson-Crowell cube root law Eq. (8) describes the release from systems where there is a change in surface area and diameter of particles or tablets³¹. Korsmeyer and Peppas Eq.(9)³² for mechanism of drug release

$$Q = k_0 t \dots \dots \dots (5)$$

Where, k_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\log Q_0 = \log Q (k t / 2.303) \dots \dots \dots (6)$$

Where, C_0 is the initial concentration of drug and k is first order constant.

$$Q_t = k t^{1/2} \dots \dots \dots (7)$$

Where, k is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \dots \dots \dots (8)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and k_{HC} is the rate constant for Hixson-Crowell rate equation.

$$Q_t / Q_\infty = k t^n \dots \dots \dots (9)$$

Here, Q_t and Q_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant which incorporates structural and geometric characteristics of the device, and n is the drug release exponent (DRE), indicative of the mechanism of drug release. The values of DRE assigned to a cylinder are 0.45 for Fickian diffusion and $0.45 < n < 0.89$ for non-Fickian diffusion, respectively.

The best fit model was found out by comparing the correlation coefficient values for batches, while the mechanism of drug release was decided on the basis of DRE (n).

Study of swelling behavior

Measurement of hydration and erosion rates of batch F2, F5, F8 and reference product were carried out, after the immersion of the tablets in the test medium⁸, to correlate the observed drug release phenomena with the rates of polymer hydration. One tablet for each time point from each formulation was kept in petridish containing phosphate buffer pH 6.8. At the end of 1, 2, 3, 4, 5, 6, 7 and 8h tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula. The wet samples were then dried in an oven at 110–120°C for 24 h, allowed to cool in desiccators 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:

$$Q = (W_w - W_f/W_f) \times 100 \dots \dots \dots (10)$$

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

$$E = (w_i - W_f/W_f) \times 100 \dots \dots \dots (11)$$

where W_i is the initial weight of the dry sample.

Table 2: Physicochemical parameters for the gums used in preparation of matrices

Source	Swelling Index (%)	Loss on Drying (%)	pH (1%w/v soln.)	Angle of Repose (o)	Bulk density (gm/ml)	Tapped density (gm/ml)	H.R.	C.I. (%)	Viscosity (cps) (1%w/v soln.)
TG	1.5-1.8	4.4	6-7	28	0.45	0.77	1.71	42	800
LB	6.2-6.4	5	5.5-7	25	0.42	0.68	1.62	38	2235
XG	80	5.5	5-7	13	0.28	0.36	1.29	22.2	50

Preparation of Tramadol hydrochloride Matrix tablet

Optimization of sustained release formulation

Many Batches were prepared by direct compression method using 30, 40, 50, 60 and 70% of gums. Release retarding ability was very poor in case of 30% while more than 50% gum was unable to compress by DC. Wet granulation method was not effective in producing sustained release tablet in case of TG. Table 1 shows only the optimized batches containing 40% of the gum. In DC method PVP-K-30 was used as filler and dry binder while in wet granulation method MCC and/ or DCP were used as filler and mucilage of gum was incorporated as binder. The optimization of the batch was done on the basis of hardness and friability of the tablet obtained and in vitro release behavior.

Table 3: Physicochemical parameters of tramadol hydrochloride matrices prepared by direct compression and wet granulation method*

Formulation	Average drug content (mg) ± SD	Hardness (Kg/Cm2) ± SD	Friability (%)	weight(mg) (mean±SD)
Contramal SR	98.5 ± 2.6	5.8±0.5	0.57	399.40 ± 1.14
F1	99.8 ± 1.2	5.8±0.6	0.4	399.61 ± 1.18
F2	100.5 ± 2.8	5.8±0.8	0.57	400.48 ± 0.29
F3	99.3 ± 2.0	5.0±0.8	0.68	399.28 ± 0.34
F4	99.5 ± 4.0	5.0±0.3	0.35	399.99 ± 0.75
F5	96.8 ± 2.8	5.8±0.2	0.6	401.2 ± 0.88
F6	100.0 ± 3.4	5.3±0.6	0.62	399.76 ± 0.84
F7	100.1 ± 4.5	5.6±0.7	0.52	399.53 ± 0.75
F8	100.05 ± 1.2	6.0 ± 0.1	0.45	399.95 ± 0.67

*n=3

In Vitro Drug Release Studies

In vitro release profile of the prepared matrices and market product of tramadol hydrochloride are shown in Figure 1. Comparison of the prepared matrices were carried out with the reference product, for %cumulative release after 1,2,3,4,5,6,7,8,9,10,11 and 12 h. Compared to the market product, an initial burst release (>30%) of the drug was observed with almost all matrices except batch F2, F5 and F8. Such a burst effect was also observed by other investigators who suggested the addition of other hydrocolloids such as HPMC in relatively large amounts³³. It was also reported that increasing the concentration of either HPMC K-4M or HPMC K-100M is expected to decrease the drug release. Such delay in drug release may be because of the release rate is conditioned by the concentration of the polymer³⁸. When exposed to the dissolution fluid, the hydrophilic polymer matrix gradually hydrates from the periphery towards the core to form a gelatinous layer. The diffusion of drug from the matrix to the aqueous medium depends on the thickness of gel layer. In the initial stage, the drug release was due to the dissolution of the drug present on the tablet surface and the lag time required for polymer hydration to form viscous gel layer³⁴. Batch F4 and F6 in which MCC

RESULTS AND DISCUSSION

Physicochemical characterization of the gums

Various physicochemical parameters for the gums were tested and are shown in Table 2. It was observed that XG has higher swelling index and less viscosity than TG and LB. Total bacterial count of the gums and tests for pathogens were carried out from time to time as prescribed in BP under the heading "Microbiological testing of nonsterile pharmaceuticals"²³. The result of the TBC was found within the limit and all gums were free from pathogens.

Physicochemical Investigation of prepared matrix tablets

The prepared matrices were evaluated for thickness, weight variation, hardness, friability, drug content (Table 3) and release rate (Figure 1). All the tablets were of 8mm diameter and biconcave in shape. The data are shown in Table 3.

The hardness of the tablets was ranged from 5-7 Kg/Cm². All formulations satisfied the content uniformity of tramadol hydrochloride and friability between 0.4% and 0.8%.

Determination of Drug Content

All formulations passed the drug content uniformity as per official specification (Table 3).

PH 101 was included, not showed desired controlled release, may be due to its hydrophilic nature. While batch F5 in which DCP was included, able to control the drug release upto 12h in the desired pattern. Locust bean gum as such was not able to give sustained release beyond 4h so DCP was included in batch F5 and F7, and MCC was included in batch F6 and F7. Inclusion of MCC also affected the release pattern as evident from the in-vitro drug release study of batch F6 (Figure 1).

Study of Release Kinetics

To compare the release profile and release behavior of the prepared matrices of tramadol hydrochloride with the market product, similarity factor f_2 was calculated (Table 4). The two dissolution profiles are considered significantly similar when the f_2 value is in the range of 50 to 100. Here, all batches except batch- F4 showed similarity factor value above 50. Analysis of release profiles were also carried out using zero order, first order, Higuchi, Korsemeyer-Peppas and Hixon-Crowell models. Drug release exponent (DRE) i.e. 'n' was taken into consideration to decide the mechanism of drug release. Data analysis of release profiles according to different kinetic models is shown in Table 4.

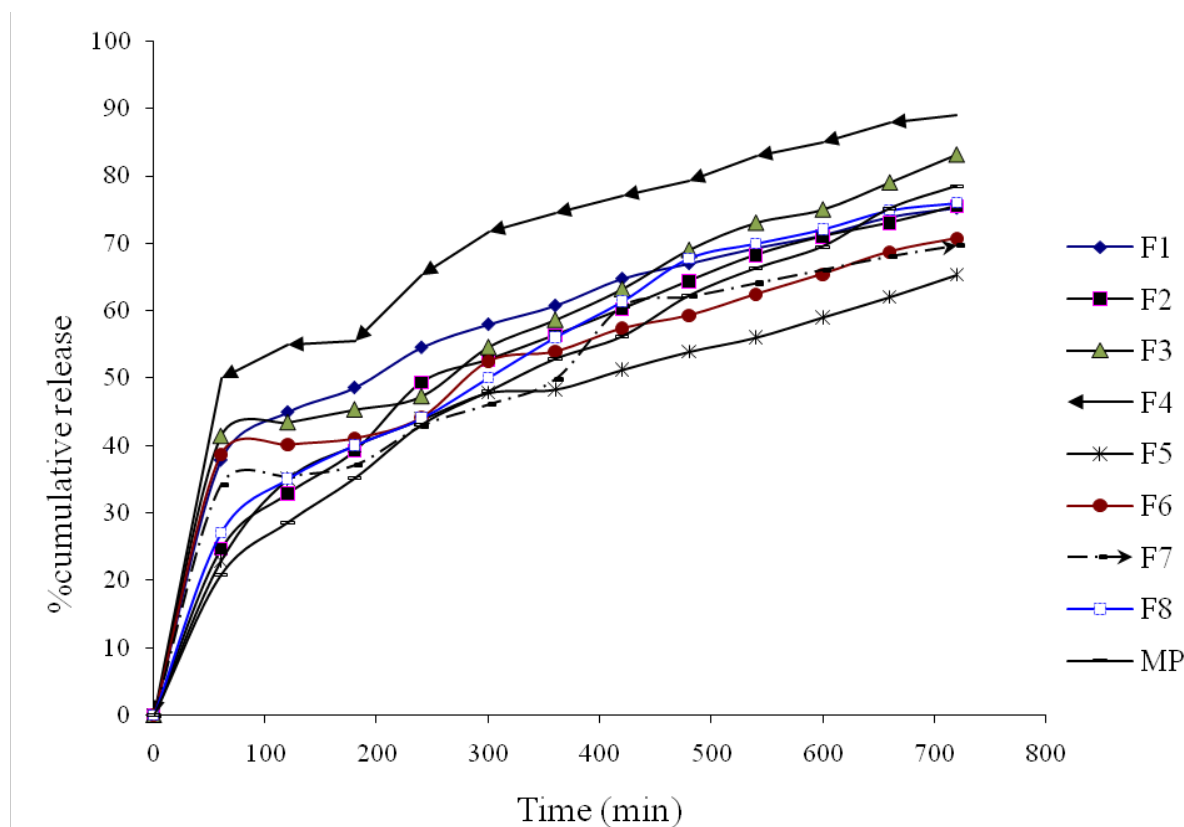


Fig. 1: In-vitro release profiles of the sustained release matrices of tramadol hydrochloride

Table 4: Similarity factor (f_2) and Drug Release Exponent (n), Regression Coefficient (r_2) and best fit model for Tramadol hydrochloride matrix tablets After model fitting ($n = 3$)

Formulation	f_2	n	r_2	Best fit model
F1	51.19	0.2847	0.9951	Korsmeyer-Peppas
F2	73.19	0.4618	0.9947	Korsmeyer-Peppas
F3	53.94	0.3099	0.8902	Korsmeyer-Peppas
F4	37.99	0.2555	0.9578	Korsmeyer-Peppas
F5	75.22	0.3802	0.977	Korsmeyer-Peppas
F6	59.92	0.2722	0.9029	Korsmeyer-Peppas
F7	67	0.3402	0.9042	Korsmeyer-Peppas
F8	68.08	0.4423	0.9872	Korsmeyer-Peppas
Market Product	Reference	0.5414	0.9975	Korsmeyer-Peppas

For all batches prepared, drug release profile better fits with Korsmeyer and Peppas equation. Further, mechanism of release was decided on the basis of value of DRE which was indicative of the anomalous diffusion in case of batch F2 which was comparable to that of market product (Table 4). XG plays an important role in drug release especially at the beginning of the release study as evident from drug release profile of batch F2. This was owing to its high swelling index as apparent from Table 2. 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 as reported³⁵. The overall rate of release of tramadol hydrochloride from batch F2, F5 and F8 was significantly similar to the release obtained from the market product (Figure 1). These results are clear indication that XG and LB has higher drug retarding ability than TG. Also it can be concluded that HPMC is in the similar line to that of natural gums in release retarding ability. Reference product followed a Peppas model indicating anomalous diffusion of the drug (Table 4). Initial burst release (>30% in the first hour) from the matrices could probably be attributed to the dissolution of drug from the surface of the tablet. Furthermore, The hydrophilic matrix system could control the release only up to 14 hours as reported for Hydrophilic matrix of HPMC which could not control the tramadol hydrochloride release effectively beyond 12 hour³⁶.

Water uptake and erosion studies

The swelling process of batch F5 containing LB was not uniform and the zones of high LB concentration appeared more swollen. In the case of LB matrix, a rapid erosion of the hydrated layer was observed, releasing most of the drug content after 4 h. This is because LB does not exhibit a controlled release effect but has a synergistic action with the DCP and/or MCC as in batch F5, F6 and F7 to produce a controlled release effect. Among which batch F5 showed more controlled release as evident from f_2 value of batch F5 (Table 4).

The swelling behavior 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 (Figure 2). Batch F2 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 dissolution medium. 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 (Figure 3) and was about 50%.

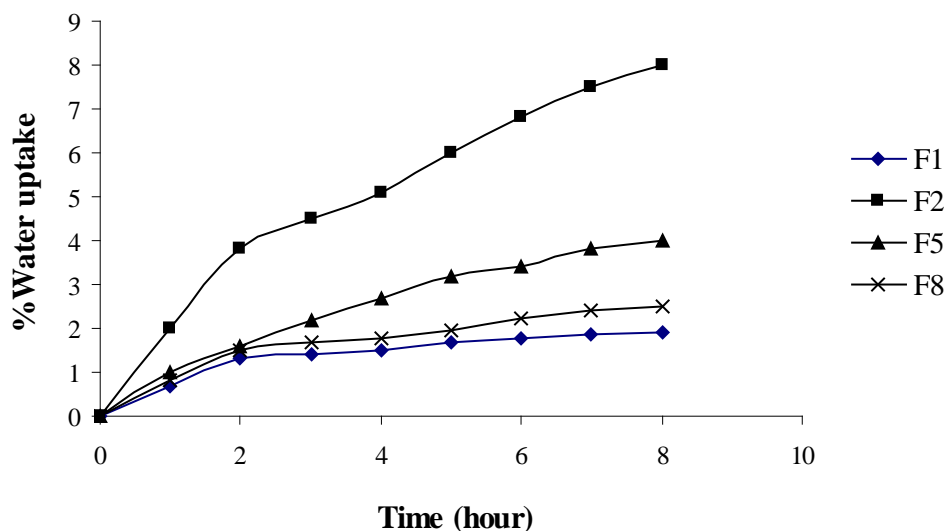


Fig. C. 2: % Water uptake study of the selected batches

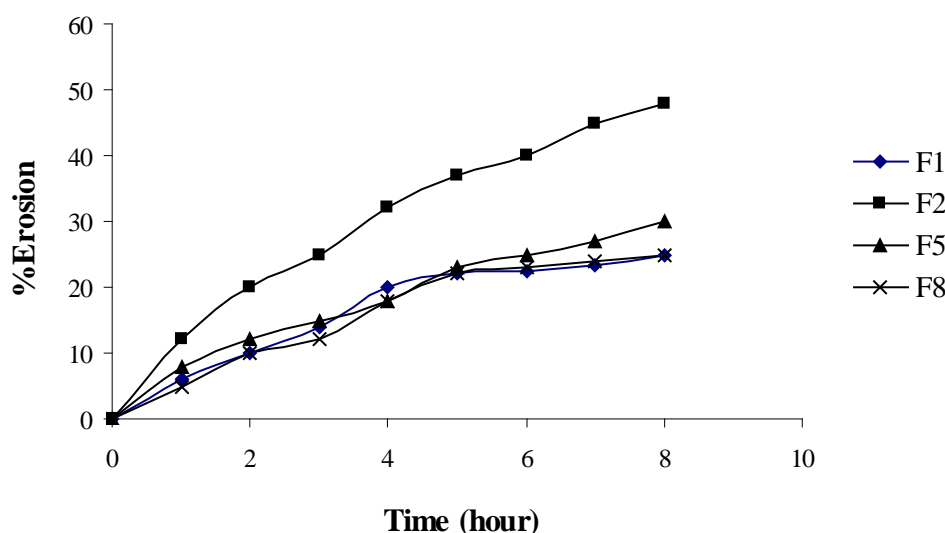


Fig. C. 3: % Erosion study of the selected batches

CONCLUSION

It can be concluded from our study that gums alone cannot efficiently control drug release, particularly in the beginning of dissolution study. Xyloglucan and locust bean gum has higher drug retarding ability than tamarind gum. However, according to similarity factor f_2 , batch F2, F5 and F8 are the most similar formulations to Reference product. Natural gum was able to give comparable sustained release as synthetic polymer like HPMC. It was also reported that combination of the hydrophilic polymers were effective than when used alone. Therefore we can include natural gums in combination in the formulation of sustained release matrix tablets as that of synthetic release retardants.

ACKNOWLEDGEMENT

We are thankful to Saga laboratories, Suvik Hitek Private Limited, H.B. Gum Industries Pvt. Ltd., Lucid Colloids Ltd. for providing drug and gums used in the study.

REFERENCES

- Li VHK, R.J., Lee VHL, ed. Influence of drug properties and routes of drug administration of the design of sustained and controlled release systems. 2nd, ed. Controlled Drug Delivery-Fundamentals and Applications, (Drugs and the Pharmaceutical Sciences), ed. I. Marcel Dekker. Vol. 29. 1987, J.R. Robinson: New York. 4-94.
- Al-Saidan, S.M., Krishnaiah, Y. S., Satyanarayana, V., Bhaskar, P., Karthikeyan, R. S., Pharmacokinetic evaluation of guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug. *European Journal of Pharmaceutics and Biopharmaceutics*, 2004. 58(3): p. 697-703.
- Heller, J., ed. Use of polymers in controlled release of active agents. 2nd ed., ed. I. Marcel Dekker. Vol. 29. 1987: New York. 179-212.
- Santos, H., Veiga, F., Pina, M. E., Sousa, J. J., Compaction, compression and drug release characteristics of xanthan gum pellets of different compositions. *European Journal of Pharmaceutical Sciences*, 2004. 21(2-3): p. 271-81.
- Shlieout, G.Z., Investigation of ethyl cellulose as a matrix former and a new method to regard and evaluate the compaction data. *Drug Development and Industrial Pharmacy*, 1996. 22: p. 313-319.
- Tobyn, M.J., Staniforth, J.N., Baichwal, A.R., McCall, T.W. , Prediction of physical properties of a novel polysaccharide controlled release system. *International Journal of Pharmaceutics*, 1996. 128: p. 113-122.
- Bhardwaj, T.R., Kanwar, M., Lal, R., Gupta, A., Natural gums and modified natural gums as sustained-release carriers. *Drug*

- Development and Industrial Pharmacy, 2000. 26(10): p. 1025-38.
8. Efentakis, M., Koutlis, A., Release of furosemide from multiple-unit and single-unit preparations containing different viscosity grades of sodium alginate. *Pharmaceutical Development and Technology*, 2001. 6(1): p. 91-8.
 9. Venkataraju, M.P., Gowda, D. V. , Rajesh, K. S. , Shivakumar, H. G. , Xanthan and locust bean gum (from *Ceratonia siliqua*) matrix tablets for oral controlled delivery of propranolol hydrochloride. *Asian Journal of Pharmaceutical Sciences*, 2007. 2(6): p. 239-248.
 10. I. C. M. Dea, A.M., ed. Chemistry and interactions of seed galactomannans. *Adv. Carbohydrate chemistry and biochemistry*. Vol. 31. 1975. 242-312.
 11. Morris, E.R., ed. Mixed polymer gels. *Food gels*, ed. P. Harris. 1990, Elsevier Applied Science: London. 291-360.
 12. Launay, B., Doublier, J. R., Cuvelier, G., ed. Flow properties of aqueous solutions and dispersions of polysaccharides. *Functional properties of food macromolecules*, ed. J.R.M.a.D.A. Ledward. 1986, Elsevier Applied Science: London. 1-78.
 13. Haskell, W.L., Spiller, G. A., Jensen, C. D., Ellis, B. K., Gates, J. E., Role of water-soluble dietary fiber in the management of elevated plasma cholesterol in healthy subjects. *American Journal of Cardiology*, 1992. 69(5): p. 433-9.
 14. Picout, D.R., Ross-Murphy, S. B., Errington, N., Harding, S. E., Pressure cell assisted solubilization of xyloglucans: tamarind seed polysaccharide and detarium gum. *Biomacromolecules*, 2003. 4(3): p. 799-807.
 15. Rao, P.S., Ghosh, T.P., Krishna, S., extraction and purification of tamarind seed polysaccharide. *Journal of Scientific and Industrial Research*, 1946 4: p. 705-710.
 16. Tugcu-Demiroz, F., Acarturk, F., Takka, S., Konus-Boyunaga, O., In-vitro and in-vivo evaluation of mesalazine-guar gum matrix tablets for colonic drug delivery. *Journal of Drug Targeting*, 2004. 12(2): p. 105-12.
 17. Krishnaiah, Y.S., Veer, R.P., Dinesh, K.B., Bhaskar, P., Satyanarayana, V., Development of colon targeted drug delivery systems for mebendazole. *Journal of Controlled Release*, 2001. 77(1-2): p. 87-95.
 18. Krishnaiah, Y.S., Karthikeyan, R.S., Satyanarayana, V., A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. *International Journal of Pharmaceutics*, 2002. 241(2): p. 353-66.
 19. Raber, M., Hoffman, S., Junge, K., Momberger, H., Kuhn, D., Analgesic efficacy and tolerability of tramadol 100 mg sustained release capsules in patients with moderate to severe chronic low back pain. *Clinical Drug Investigation* 1999. 17: p. 415Y423.
 20. Staff, M.E., ed. *Physicians' Desk Reference*. 2003, Thomson MicromedexGreenwood Village.
 21. Malonne, H., Coffiner, M., Sonet, B., Sereno, A., Vanderbist, F., Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter, randomized, double-blind, placebo-controlled study. *Clinical Therapeutics*, 2004. 26(11): p. 1774-82.
 22. Babul, N., Noveck, R., Chipman, H., Roth, S. H., Gana, T., Albert, K., Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *Journal of Pain and Symptom Management*, 2004. 28(1): p. 59-71.
 23. *The British Pharmacopoeia*. 2004, Her Majesty's Stationary Office: London.
 24. Chen, S., Zhu, J., Ma, F., Fang, Q., Li, Y., Preparation and characterization of solid dispersions of dipyridamole with a carrier "copolyvidonum Plasdone S-630". *Drug Development and Industrial Pharmacy*, 2007. 33(8): p. 888-99.
 25. Copper, J., Gunn, C., ed. *Tutorial Pharmacy*. ed. E. Carter S.J. (1986) C.B.S. Publishers and Distributors: New Delhi, India. 211 - 233.
 26. *Cooper & Gunn's Tutorial Pharmacy*, 6e. 2005: CBS Publishers & Distributors.
 27. Martin, A., ed. *Physical pharmacy*. ed. 1st. 2001, Lipponcott Williams & Wilkins. 423-454.
 28. Moore, J.W., Flanner, H.H. , Mathematical comparison of dissolution profiles. , 20: 64-74. . *Pharmaceutical Technology*, 1996. 20: p. 64-74.
 29. Bourne, J.A., Tweedale, R., Rosa, M. G., Physiological responses of New World monkey V1 neurons to stimuli defined by coherent motion. *Cerebral Cortex*, 2002. 12(11): p. 1132-45.
 30. Higuchi, T., Mechanism of Sustained-Action Medication. *Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices*. *Journal of Pharmaceutical Sciences*, 1963. 52: p. 1145-9.
 31. Hixson, A.W., Crowell, J. H. , Dependence of reaction velocity upon surface and agitation *Industrial & Engineering Chemistry*, 1931. 23(8): p. 923-931.
 32. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N. A., Mechanisms of potassium chloride release from compressed, hydrophilic, polymeric matrices: effect of entrapped air. *Journal of Pharmaceutical Sciences*, 1983. 72(10): p. 1189-91.
 33. Bhalla, H.L., Sanzgiri, Y.D., An improvised controlled release tablet of salbutamol sulphate. *Indian Journal of Pharmaceutical Sciences*, 1987 49(1): p. 22-25.
 34. Prasad, Y.V., Krishnaiah, Y. S., Satyanarayana, S., In vitro evaluation of guar gum as a carrier for colon-specific drug delivery. *Journal of Controlled Release*, 1998. 51(2-3): p. 281-7.
 35. Veiga, F., Salsa, T., Pina, M. E., Oral controlled release dosage forms. II. Glassy polymers in hydrophilic matrices. *Drug Development and Industrial Pharmacy*, 1998. 24(1): p. 1-9.
 36. Kibbe, A.H., ed. *Handbook of Pharmaceutical Excipients*. 3rd ed. 2000, Pharmaceutical Press: London, UK. 94-95.
 37. Kale R., Bajaj A., Mathew D., Development of matrix diffusion controlled drug delivery system of Pentoxifylline. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2010. 2(1): p.122-130.
 38. Patel R., Baria A., Formulation development and process optimization of Theophylline sustained release matrix tablet. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2009. 1(2): p.30-42.