

Formulation and Development of Matrix Tablets of Tramadol Using Katira Gum as Release Modifier

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The present study was aimed to study the drug release retardant property of katira gum in matrix tablets containing tramadol as a model drug. Katira gum was characterized in terms of pH, viscosity and swelling index. The tablets were evaluated for various physical tests *viz.* hardness, friability, tensile strength and drug content. *In vitro* dissolution studies were performed and different empirical models were applied to drug release data for evaluating the drug release mechanisms and kinetics. Owing to good swelling properties (swelling index 340% and 480% after 6 and 24 h hydration) of the gum, the *n* values (as computed from Korsmeyer-Peppas model) were found to be ranging between 0.453 to 0.710 indicating involvement of both polymeric hydration and relaxation in the diffusion of drug from the matrix tablet.

Key words—katira gum; direct compression; matrix tablet; Higuchi and Korsmeyer-Peppas model

INTRODUCTION

In the design of oral controlled release drug delivery systems, natural occurring materials like gums are being targeted by pharmaceutical scientists for their biocompatible nature, easy availability and nontoxic properties. On contact with water the hydrophilic natural gums hydrates and swell and these have been used for the preparation of controlled and/or sustained release dosage forms. Also, the natural gums have an economic importance in being cheaper than many processed synthetic gums. Formulation of matrix tablets by direct compression has attracted much attention due to its technological simplicity and industrial acceptability as it involves simple blending of all ingredients used in the formulations followed by compression. Moreover, it required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate.¹⁾

Tramadol is a centrally acting analgesic. The chemical name for tramadol is (±) cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol. Tramadol is marketed as a racemic mixture and at the receptor level has a weak affinity for the μ -opioid receptors (approximately 1/6th that of morphine).

The (+)-enantiomer is approximately four times more potent than the (–)-enantiomer in terms of μ -opioid receptor affinity and 5-HT reuptake, whereas the (–)-enantiomer is responsible for noradrenaline reuptake effects.²⁾ These actions appear to produce a synergistic analgesic effect, with (+)-tramadol exhibiting 10-fold higher analgesic activity than (–)-tramadol.³⁾

Katira gum, an insoluble gum derived from the bark of *Cochlospermum religiosum* and has been successfully used as a gelling agent in microbial tissue culture media.⁴⁾ The gum is sweet, thermogenic, anodyne, sedative and useful in cough, diarrhoea, dysentery, pharyngitis, gonorrhoea, syphilis and trachoma.⁵⁾ Katira gum is pale and semi-transparent, insoluble in water, but swells into a pasty transparent mass with water.⁶⁾ Owing to swelling property of katira gum, it could be investigated as potential drug release retardant from the dosage forms.

The present study was aimed to explore the drug release retardant activity of katira gum from matrix tablet dosage form. With this aim, various formulation combinations were developed by varying katira gum and binder compositions in the dosage form to study their effect on various physical parameters of the prepared tablets (*viz.* hardness, friability, tensile strength, and assay) and drug release kinetics. The drug release data were fitted into zero order, first

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order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell semi empirical models to elucidate the release kinetics. Accelerated stability testing was also carried out as per ICH guidelines (40°C/75% RH).

MATERIAL AND METHODS

Tramadol hydrochloride and PVP-K-90 were received as a gift sample from Indswift Ltd. Chandigarh, India. Vivapur-102 (micro crystalline cellulose, particle size 90 μm) and Vivapress CA-800 (precipitated calcium carbonate, particle size between 180–840 μm) were kindly received as gift samples from S. Zhaveri Pharmakem Pvt. Ltd., Mumbai, India. Katira gum was purchased from Yarrow Chem, Mumbai, India. Katira gum was powdered and passed through 60-mesh sieve for being used in the research work. Talc and magnesium stearate were procured from S. D. Fine Chemicals Ltd. Mumbai, India. All other chemical/reagents were of analytical grade and used as such.

Characterization of Katira Gum

Determination of pH The pH of 1% (w/v) katira gum was determined using a digital pH meter (EI products, India).

Determination of Viscosity Viscosity of 1% (w/v) katira gum was measured (at $37 \pm 1^\circ\text{C}$) by using searle type viscometer, DV-2 +LV Brookfield Viscometer, USA with spindle number 61 at different rpm.

Swelling Capacity Swelling capacity of katira gum was determined by keeping 1 g of the gum in 20 ml water in a measuring cylinder for 24 h. Swelling index was determined as follows:

$$\text{Swelling index} = (V_2 - V_1) / V_1 \times 100$$

where V_1 and V_2 are initial volume of the material prior to hydration and volume of the hydrated material, respectively.

Preparation of Tablets Vivapur-102 and Vivapress CA-800 (directly compressible ingredients, as diluent), PVP-K-90 and powdered katira gum were mixed thoroughly followed by additional mixing of 1% w/w lubricants/glidant (talc and magnesium stearate). The tablet weight was kept 250 mg for all the batches and the final weight was adjusted by adding 2 : 1 ratio of diluent (vivapur : vivapress). The directly compressible mixture were then compressed single stroke mutipunch tableting machine (AK Industries, India) equipped with a 8.40 mm flat faced

punch and die set. The compression force and compression time were 5 ton and 30 sec respectively. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate.

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 min to ensure complete solubility of drug. The mixture was centrifuged (Remi, India) and 10 ml of the supernatant liquid was diluted 20 times with 0.1N HCl, and after centrifugation the absorbance was determined spectrophotometrically (Systronics 2202 model, India) at 272.5 nm.

Physical Properties of Tablets The formulated tablets were evaluated for diameter, thickness, hardness and friability.

Diameter and Thickness A calibrated vernier caliper was used for diameter and thickness evaluation of the tablets.

Hardness Ten tablets from each batch were examined using Monsanto hardness tester.

Friability For friability tests, ten tablets were weighed (W_1) and rotated at one hundred revolutions for 4 min in a Roche friabilator. The tablets were then reweighed (W_2) and the percentage of friability (%F) were calculated.

$$\%F = W_1 - W_2 / W_1 \times 100$$

Determination of Tensile Strength The tensile strength (T) of tablet which is a measure of the stress necessary to cause diametric fracture of the compact was determined from the mean data obtained from the hardness test carried out on the tablets ($n=10$) using the Monsanto hardness tester according to Brook and Marshal.⁷⁾ The T values were computed from equation below:⁸⁾

$$T = 2P / \pi Dt$$

where P is the load applied on the tablet that causes tensile fracture of the tablet of diameter, D, and t is the tablet thickness.

In Vitro Drug Release Studies The formulated tablets were subjected to the paddle type 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 $37^\circ\text{C} \pm 1^\circ\text{C}$. At predetermined time intervals, 5 ml samples were withdrawn and assayed spec-

trophotometrically at 272.5 nm. After each sampling, equal volume of fresh buffer solution with the same temperature was replaced. All experiments were run in triplicate.

Kinetic Studies The *in vitro* drug release data of the formulated batches of the tablets were fitted into the following models and respective plots were made: zero order kinetic model (cumulative percentage drug release vs. time); first order kinetic model (log cumulative of percentage drug remaining vs. time); Higuchi model (cumulative percentage drug release vs. square root of time); Korsmeyer-Peppas Model (log cumulative percentage drug release vs. log time) and Hixson-Crowell model (cube root of drug percentage remaining in matrix vs. time). The zero order model (Eq. 1) describes concentration independent drug release rate from the formulation whereas first order model (Eq. 2) describes concentration dependent drug release from the system. Higuchi (Eq. 3) described the release of drugs based on Fickian diffusion as a square root of time dependent process from swellable insoluble matrix whereas the Hixson-Crowell cube root law (Eq. 4) correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets.^{9,10} The Korsmeyer-Peppas Model (Eq. 5) describes the influence of polymeric hydration and swelling on drug release rate.¹¹

$$C = k_0 t \quad (1)$$

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

$$\text{Log } C = \text{Log } C_0 - k_1 t / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and k_1 is first order constant.

$$Q = k_H t^{1/2} \quad (3)$$

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

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (4)$$

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.

$$M_t / M_\infty = k_{KP} t^n \quad (5)$$

where, M_t / M_∞ is the fraction of drug release, k_{KP} is the release rate constant, n is the diffusional release exponent indicative of the drug release mechanism (Table 1), and t is the dissolution time.

Stability Studies Accelerated stability testing was carried out as per ICH guidelines (40°C/75% RH). One hundred tablets of each batch were secure-

Table 1. Formulation Code Table of the Prepared Tablets

Batch No.	Katira gum (mg)	PVP-K-90 (mg)	Drug (mg)	Diluent (mg)	Lubricant (mg)
I	50	5	50	140	5
II	75	5	50	115	5
III	100	5	50	90	5
IV	50	10	50	135	5
V	75	10	50	110	5
VI	100	10	50	85	5
VII	50	15	50	130	5
VIII	75	15	50	105	5
IX	100	15	50	80	5

ly packed in HDPE bottles and were kept in a stability chamber. Tablets were evaluated at 0 days, 6 weeks, 3 months and 6 months for hardness, friability and assay.

RESULTS AND DISCUSSION

Katira gum solution (1% w/v) exhibited a pH of 6.2. The katira gum swelled rapidly over the first one hour to about 120%, 340% (first six hour) of its initial volume, and to a maximum of about 480% over a time period of 24 h. Viscosity of 1% w/v solution of katira gum, using spindle number 61 of brookfield viscometer, was found to be 4.12, 6.54, 10.20, 9.56 and 7.60 mPa s at 20, 40, 60, 80 and 100 rpm, respectively (Fig. 1). Katira gum forms a viscous colloidal hydrophilic gel when it comes in contact with water. This hydrated swollen gel of katira gum is responsible for the release retardant property of the gum when incorporated in the tablet dosage form. Viscosity, pH and swelling studies were performed for characterizing the katira gum.

All the batches of matrix tablets were formulated under similar conditions to avoid variation in processing variables. The prepared tablets were evaluated for various physical parametric tests (Table 2). The diameter and thickness of the prepared tablets were found to be 8.43 ± 0.02 mm 4.75 ± 0.05 mm, respectively.

The amounts of katira gum along with PVP K-90 were found to have a significant effect on friability, hardness and tensile strength of the formulated tablets ($p > 0.05$). Friability is an important factor in tablet formulation to ensure that the tablet can stay

Table 2. Physical Parameters of the Formulated Tablets

Batch No.	Diameter (mm) <i>n</i> =10	Thickness (mm) <i>n</i> =10	Friability (%) <i>n</i> =10	Hardness (kg/cm ²) <i>n</i> =10	Tensile strength (MN/m ²) <i>n</i> =10	Assay
F I	8.40±0.02	4.75±0.04	1.14±0.05	2.60±0.54	0.415±0.02	99.1±0.85
F II	8.42±0.01	4.78±0.02	1.20±0.08	2.65±0.27	0.419±0.06	98.6±0.29
F III	8.42±0.02	4.76±0.01	1.10±0.03	2.80±0.72	0.444±0.13	98.9±1.03
F IV	8.43±0.05	4.75±0.03	0.72±0.04	2.54±0.36	0.397±0.07	98.2±0.55
F V	8.40±0.01	4.78±0.01	0.65±0.05	3.19±0.21	0.491±0.15	99.0±0.11
F VI	8.42±0.02	4.80±0.04	0.66±0.09	3.75±0.64	0.590±0.04	97.5±0.70
F VII	8.45±0.01	4.75±0.02	0.45±0.02	5.47±0.30	0.856±0.10	98.2±0.15
F VIII	8.43±0.03	4.78±0.03	0.40±0.06	5.50±0.82	0.869±0.08	98.6±0.48
F IX	8.41±0.04	4.77±0.02	0.25±0.07	6.25±0.69	0.993±0.05	97.9±0.87

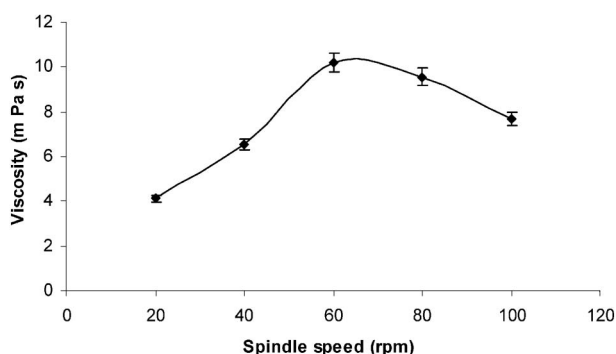


Fig. 1. Viscosity of 1% w/v Solution of Katira Gum at 37 ± 1 °C

Data show mean values ± S.D. (*n*=6).

intact and withhold its form from any outside force of pressure. The percentage friability was found to decrease from 1.14–1.10 (F I–F III), 0.72–0.66 (F IV–F VI) and 0.45–0.25 (F VII–F IX), indicating the dependence of friability upon the concentration of gum and binder. Hence it could be deduced that katira gum is instrumental in providing additional binding strength, along with the presence of binder, to the prepared tablets. Tablet hardness or tablet breaking force a measure of the mechanical integrity of the tablet, was found to increase from 2.60–2.80 (F I–F III), 2.5–3.75 (F IV–F VI) and 5.40–6.25 (F VII–F IX), demonstrating the effect of the selected variables on hardness. Hence, both katira gum and binder concentrations were found to have direct affect on hardness and friability of the prepared tablets. As hardness was found to be effected by the two variables, similarly, tensile strength (hardness derived parameter) was also affected by the same. The ranges

of the tensile strength were 0.415–0.444 (F I–F III), 0.397–0.590 (F IV–F VI) and 0.856–0.993 (F VII–F IX). The formulated tablets were evaluated for hardness, friability and tensile strength as per the methods described for assessing physical properties of the tablets.

The drug content was found to be in the range of 97.5 ± 0.70 to 99.1 ± 0.85% amongst the formulated batches. The drug content determinations were performed spectrophotometrically as described in drug content determination section of material and methods.

The rate and extent of drug release from the formulated tablet batches was found to be affected by different proportions of katira gum (release retardant) and PVP-K-90 (binding agent). The increase in polymer contents was found to reduce the drug release from the matrix tablets. Batches F III, F VI and F IX having 40% w/w katira gum content were showing 61.0%, 55.76% and 71.14% drug release in 120 min respectively contrary to nearly 100% drug release in F I, F IV and F VII having 20% w/w composition of the natural gum. The reduction in drug release with increase in katira gum concentration may be attributed to decrease in total porosity of the matrices and increase in tortuosity and drug diffusion path length of the polymeric matrix. PVP-K-90 in concentrations of 2, 4 and 6% w/w in the matrix tablets was evaluated for its effect on drug release. F VII, F VIII and F IX (6% PVP-K-90) were showing drug release after 120 minutes to be 98.31, 87.52 and 71.15% respectively as compared to 99.68, 68.53 and 55.76% drug release in case of F IV, F V and F VI respectively. This may be

due to the fact that excesses PVP-K-90 (above 4%) being soluble in water might increase the solubility of the Katira-PVP matrix and may interfere with the swelling of the katira gum. Hence, optimum concentration of PVP-K-90 in the formulation of matrix tablets using katira gum was found to be 4% w/w. *In vitro* drug release studies were performed using paddle type dissolution method.

Different semi-empirical kinetic equations (zero-order (Fig. 2), first-order, Higuchi's equation (Fig. 3), Korsmeyer-Peppas (Fig. 4) and Hixson Crowell) were applied to interpret the release rate from various batches of tablets formulated using katira gum in the matrix system. The model that best fitted the release data was evaluated by correlation coefficient (R^2). R^2

values for all formulations in various models are given in Table 3. All prepared batches of the tablets were found obeying Higuchi model indicating the square root time dependency of the drug release from the formulated matrix tablets using katira gum as release retardant. Based on Korsmeyer-Peppas model, the magnitude of the release exponent "n" (based on $M_t/M_\infty=0.6$) corresponds to the release mechanism (Fickian diffusion, case II transport or anomalous transport). For instance $n=0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n=0.89$ (indicates a case II relaxational release transport; non-Fickian, zero-order release). Values of n between 0.45 and 0.89 can be regarded as an indicator of anomalous transport behavior of drug

Table 3. Kinetic Parameters of the Formulated Tablets

Batch No.	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	r^2	k_0 (h^{-1})	r^2	k_1 (h^{-1})	r^2	k_H (h^{-2})	r^2	N value	k_{KP} (h^{-n})	r^2	k_{HC} ($h^{-1/3}$)
F I	0.996	1.483	0.949	-0.017	0.987	17.15	0.992	0.710	0.753	0.968	-0.045
F II	0.926	0.197	0.964	-0.003	0.985	4.754	0.990	0.411	0.956	0.957	-0.009
F III	0.933	0.188	0.956	-0.004	0.989	4.827	0.993	0.453	0.837	0.965	-0.009
F IV	0.964	1.468	0.957	-0.026	0.988	17.26	0.988	0.759	0.679	0.938	-0.087
F V	0.929	0.185	0.991	-0.003	0.989	4.448	0.995	0.362	1.080	0.917	-0.009
F VI	0.988	0.228	0.964	-0.002	0.992	5.342	0.986	0.5	0.701	0.877	-0.010
F VII	0.912	0.505	0.890	-0.010	0.957	9.071	0.960	0.602	0.691	0.976	-0.026
F VIII	0.966	0.533	0.966	-0.006	0.986	9.457	0.985	0.698	0.462	0.937	-0.025
F IX	0.979	0.376	0.954	-0.004	0.967	7.381	0.9571	0.5962	0.5649	0.888	-0.017

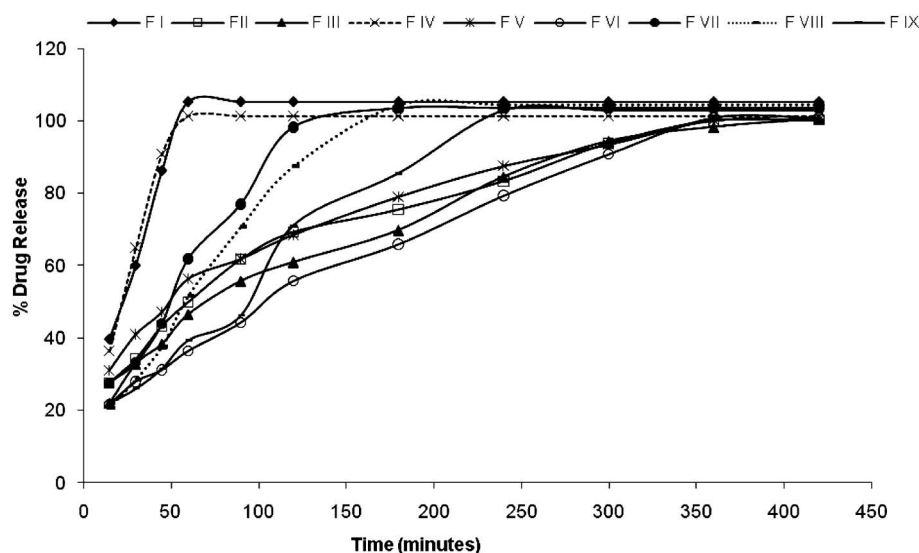


Fig. 2. Zero Order Release Model of Tramadol from Katira Gum Matrix Tablets

from the formulation. The *n* values were found to be ranging between 0.453 to 0.710 (except for batches F II and F V) indicating involvement of both polymeric hydration and relaxation in the diffusion of drug from the matrix tablet and that the difference between the penetration of the diffusion front and the erosion front is not too high. Hence drug release from the matrix tablets prepared utilizing katira gum could be seen as a two stage process involving the hydration of the polymeric system by the surrounding solvent leading to the water-induced relaxation of the polymeric matrix followed by diffusion of the drug from the pores/channels created during relaxation of the poly-

mer. The contact of aqueous fluids with the gum matrix embeddings results in water uptake and the glassy polymer so formed further undergo a relaxation process observed macroscopically as gelation and swelling. This progressive swelling of the polymer with in the matrix tablet may be leading to considerable structural changes including the change of the mobility of the macromolecular chains, macromolecular relaxations, and changes of the porous structure including alteration of the shape and size distribution of the pores (effecting porosity and tortuosity of the swollen matrix).¹²⁾ These changes of the polymer during swelling may be responsible for

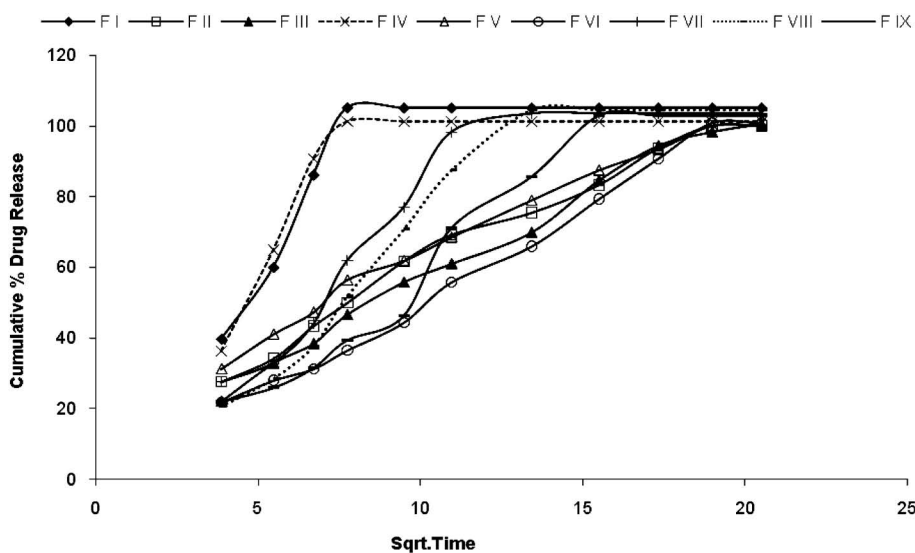


Fig. 3. Higuchi Release Model of Tramadol from Katira Gum Matrix Tablets

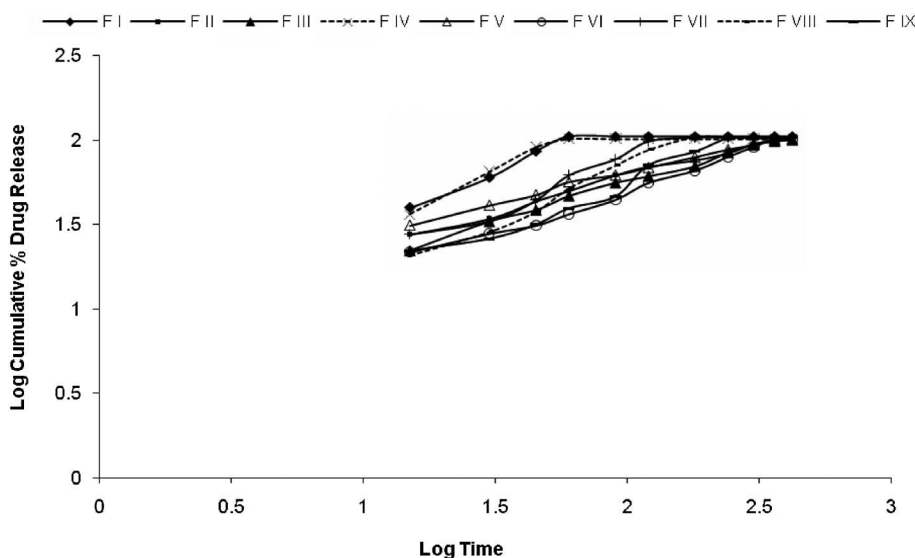


Fig. 4. Korsmeyer-Peppas Model for Mechanism of Drug Release from Katira Gum Matrix Tablets

Table 4. Results of Accelerated Stability Studies of Katira Gum Tablets

Batch No.	Hardness (Kg/cm ²)				Friability (%w/w)				Assay (%)			
	0 D	6 W	3 M	6 M	0 D	6 W	3 M	6 M	0 D	6 W	3 M	6 M
FI	1.25±0.54	1.25±0.8	1.25±0.7	1.30±0.8	1.84±0.01	1.89±0.06	1.82±0.03	1.85±0.01	98.4±0.06	98.6±0.10	98.8±0.07	99.1±0.09
FII	2.25±0.41	2.25±0.4	2.20±0.9	2.20±0.8	1.61±0.01	1.63±0.05	1.61±0.02	1.57±0.03	99.3±0.06	99.1±0.08	99.7±0.07	98.8±0.09
FIII	2.50±0.9	2.45±0.5	2.45±0.7	2.50±0.8	1.19±0.03	1.23±0.02	1.22±0.04	1.26±0.03	97.5±0.03	98.1±0.07	97.7±0.05	96.7±0.08
FIV	1.85±0.12	2.00±0.3	1.90±0.5	2.00±0.2	1.64±0.02	1.67±0.01	1.69±0.03	1.58±0.07	98.3±0.02	98.7±0.09	98.3±0.10	98.0±0.08
FV	2.00±0.21	2.00±0.2	2.05±0.4	2.05±0.3	0.72±0.03	0.78±0.05	0.73±0.04	0.74±0.05	98.6±0.02	98.6±0.08	98.4±0.04	98.5±0.02
FVI	4.10±0.57	4.00±0.4	4.10±0.4	4.10±0.6	0.45±0.02	0.45±0.01	0.45±0.06	0.48±0.04	97.9±0.03	97.6±0.05	97.3±0.11	98.4±0.08
FVII	2.75±0.59	2.65±0.4	2.70±0.6	2.70±0.5	1.14±0.05	1.16±0.04	1.11±0.06	1.12±0.05	98.5±0.02	98.2±0.09	98.4±0.05	99.1±0.08
FVIII	5.50±0.64	5.55±0.6	5.55±0.5	5.60±0.7	0.77±0.02	0.78±0.05	0.78±0.04	0.77±0.05	102.4±0.03	102.2±0.07	101.8±0.04	100.8±0.05
FIX	6.10±0.48	6.20±0.5	6.20±0.4	6.20±0.4	0.41±0.01	0.43±0.03	0.43±0.02	0.40±0.02	99.2±0.05	99.8±0.13	99.3±0.10	98.5±0.06

the drug release from the katria gum matrix tablets. The *in vitro* drug release data of the tablets were fitted into various empirical models for studying the mechanism and kinetics of drug release from the formulation.

Table 4 shows the effect of accelerated storage conditions on the hardness, friability and assay of various batches of katira gum tablets. It is evident from the stability testing results that there was no significant change in the hardness, friability and drug content of any batch of the prepared tablets ($p < 0.05$).

CONCLUSION

From the results of the present study it could be concluded that katira gum could be effectively used as a drug release retardant in matrix tablet formulations. Being natural, hydrophilic and excellent swelling abilities adds to the pharmaceutical applicability of the katira gum. The drug release mechanism from katira gum incorporated matrix tablets was found to be involving the hydration and subsequent relaxation of the polymeric chains of the gum followed by diffusion of the drug from the pores/channels created during relaxation of the polymer.

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