

Comparative Study of Sustained Release Potential of a Newly Isolated *Senna tora* Seed Galactomannan with Commercially Available Polymers

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Abstract

The objective of the present research work was to study sustained release behavior and potential of galactomannans alone, in combination with xanthan gum and their comparison with commercially available semi-synthetic hydrophilic polymer. Once daily sustained release matrix tablets of losartan potassium were prepared using isolated *Senna tora* seed galactomannan, other galactomannan containing commercially available gums (guar gum and locust bean gum) alone and in combination with xanthan gum. The influence of different concentrations and nature of polymer was studied. The tablets were prepared by wet granulation method and evaluated for physical characteristics like hardness, weight variation, friability and drug content. The in-vitro drug release profile of matrix tablets prepared using galactomannan containing gums were compared with matrix tablet prepared using commercially available and widely used semi-synthetic polymer (Methocel K 100 M) at the same concentration level. All the physical characters of the fabricated tablet were found to be within acceptable limits. Drug-excipient interaction was evaluated by differential scanning calorimetry and FTIR. There was no drug excipient interaction. Galactomannans isolated from *Senna tora* seeds showed better sustained release potential as compared to other galactomannans used in the study when used alone. The tablets prepared using combination of guar gum and xanthan gum (F11) with drug to polymer ratio of 1:4 exhibited greater swelling index and better sustained release potential than other galactomannans in combination with xanthan gum. Hence, the batch F11 was considered as optimized formulation. Formulation F11 showed no change in physical appearance and dissolution profile upon storage at 40°C/75 % relative humidity for six months. Compared to conventional tablets, release of losartan potassium from these matrix tablets was prolonged, leading to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication. Formulation F11 was found stable at accelerated conditions 40 ± 5°C / 75% RH for a period of 6 months. The pharmacokinetic parameters C_{max} , T_{max} , and AUC of developed sustained release tablets were found to be improved with significant difference when compared with conventional immediate release tablets.

Keywords: *Senna tora*; Losartan potassium; Seed gum; Sustained release; Guar gum

Introduction

High patient compliance and flexibility in developing dosage forms made the oral drug delivery systems the most convenient mode of drug administration compared to other dosage forms [1].

In conventional oral dosage forms drug dosage must be taken several times which results in fluctuating drug levels in plasma. This drawback of conventional dosage form can be overcome by formulation of sustained release dosage forms which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with release profiles sustained by the special technological construction and design of the system.

The terms sustained or controlled drug release incorporates the element of prolongation of duration of drug action as well as the drug predictability and reproducibility in drug release kinetics [2]. Polymeric sustained drug delivery systems is the one which offer numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity and improved patient compliance [3,4].

The use of hydrophilic polymers for sustained drug delivery has attracted the attention of investigators in recent years. Among the hydrophilic polymers, natural polysaccharides are preferred due to their nontoxicity, biocompatibility, biodegradability and acceptance by the regulating agencies. Hydrophilic matrix tablets are among the most popular delivery systems for oral sustained release dosage forms

through the gastrointestinal route [5,6].

Seed galactomannans are vegetable, heterogeneous polysaccharides widely distributed in nature. Galactomannans are polysaccharides built up of a β -(1-4)-D-mannan backbone with single D-galactose branches linked α -(1-6). Because of their water absorption, swelling and gel forming ability, galactomannans are ideal polymeric matrices for mucoadhesive sustained release formulations [7].

Considerable research carried out on locust bean gum, guar gum, and tamarind gum reveals that polysaccharides can be isolated from their seeds or whole fruits [8-10]. *Senna tora* (L.) belongs to the same type containing pod type fruits with seeds rich in polysaccharide. *Senna tora* (L.) Roxb. (*S. tora*) belonging to the family fabaceae is an annual under shrub which grows all over the tropical countries (throughout India, Pakistan, Bangladesh and west China). It grows well in wasteland

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as a rainy season weed. It is also known as 'Chakramard' in Ayurveda [11,12]. It is an annual foetid herb about 30-90 cm high. Leaves are green in colour, pinnate, up to 6-8 cm long, leaflets are in 3 pairs, distinctly petioled, opposite, conical at one end, ovate, oblong and base oblique. Flowers are pale yellow in color usually in nearly sessile pairs in the axils of the leaves with five petals, upper one are very crowded. Pods are subteret or 4 angled, very slende, 6-12inch long, incompletely septate, membranous with numerous brown oblong, rhombohedral seeds [13,14]. Generally, its pods and seeds are considered as wastage and that too there is no work that has been carried out related to polysaccharide for sustained release formulation.

The aim of the present investigation is, therefore, to isolate natural polysaccharide from the seeds of *Senna tora* and evaluate it as sustained release carrier, using losartan potassium as a model drug. The isolated polysaccharide is named as *Senna tora* seed gum (*S.tora* gum, STG) by authors for further reference.

The polysaccharide isolated from seeds of *S. tora* has been reported to contain galactomannan. Hence, two more commercially available galactomannan containing gums (Guar gum and locust bean gum) have been selected in the present research work for comparative study. When associated with other polysaccharides such as xanthan gum and kappa-carrageenan, galactomannans can form gels with new properties.

In the current research work, once daily sustained release matrix tablets of losartan potassium were prepared using isolated *S. tora* gum, guar gum and locust bean gum alone and in combination with xanthan gum. The *in-vitro* drug release profile of matrix tablets prepared using galactomannan containing gums were compared with matrix tablet prepared using commercially available widely used semi-synthetic polymer (Methocel K 100 M) at the same concentration level.

Losartan potassium (BCS Class: III, High solubility and low permeability) is the first orally active angiotensin-II antagonist used in the treatment of hypertension either alone or in combination of hydrochlorothiazides. Losartan potassium is a potent, highly specific angiotensin-II type-1 receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and its plasma elimination half-life ranging from 1.5 to 2.5 hrs [15]. Accordingly, studies on regulation of drug release by formulating its sustained release systems would be advantageous as it would decrease the side effects and improve the patient compliance. To reduce the frequency of administration and to improve patient compliance; a once-daily sustained release formulation of losartan potassium is desirable.

Materials and Methods

Materials

The dried pods of *Senna tora* were collected from Kalyan (Maharashtra State, India) and the seeds were manually separated. Plant was authenticated by Dr. Rajendra D. Shinde, Associate Professor, Blatter Herbarium; St. Xavier's College, Mumbai and was identified as *Senna tora* (L.) Roxb (Herbarium Specimen no. 8361). Losartan potassium was obtained as a gift sample from Flamingo Pharmaceuticals Ltd., Talaja (India). Guar gum was procured from SD Fine Chemicals Limited, Mumbai, India. Xanthan gum EP and locust bean gum were purchased from Research Lab Fine Chem Industries, Mumbai, India. Methocel K 100 M and aerosil (colloidal silicon dioxide) were obtained from Colorcon, India. Microcrystalline Cellulose (Avicel PH 101) was received from FMC Biopolymer,

India. PVP K-30 (Polyvinylpyrrolidone) was procured from S.D. Fine Chemicals Ltd., Mumbai, India. All chemicals and reagents used were of analytical grade.

Isolation, purification and evaluation of *Senna tora* seed galactomannan (gum)

The dried seeds were subjected to mechanical treatment to separate endosperm from husk and germs followed by milling and screening of the endosperm. The gum was isolated from endosperm using method reported in literature [16]. The obtained crude gum was dissolved in warm water, re-precipitated using ethanol (1:1), dried at 40°C, powdered and stored in airtight container at room temperature. The process of dissolution in water and precipitation with alcohol was repeated until an almost white precipitate was obtained. The dried polysaccharide was milled and sifted with a 60 mesh for further use. The obtained gum was evaluated for various parameters such as solubility, pH, loss on drying (% w/w), ash content (% w/w), swelling index (%), specific gravity, surface tension and flow property.

Preformulation study (Compatibility study)

Fourier transform infrared (FTIR) spectroscopic studies were performed on the drug, physical mixture of drug and excipient (1:1) and optimized formulation using FTIR (FT-IR spectrophotometer Affinity 1, Shimadzu, Japan). The samples were analyzed in the region of 4000 cm⁻¹ and 400 cm⁻¹. The procedure consisted of dispersing a sample in excess of potassium bromide (KBR) nearly at the ratio 1:100, mixed well and pellet were prepared for IR analysis.

The drug and the optimized formulation were subjected to Differential Scanning Calorimetry (DSC) to confirm the compatibility. The powder samples were hermetically kept in the aluminum pan and heated at constant rate (°C/min), over a temperature range of 10°C to 300°C in an atmosphere of nitrogen.

Preparation of sustained release matrix tablets

Sustained-release tablets of losartan Potassium were prepared by using different gums/polymers at varying concentration [Using Drug-Polymer ratio 1:2, 1:4 and 1:6]. Microcrystalline cellulose (Avicel 101) was used as diluents (Filler) and PVP K-30 as binder. All the ingredients were passed through 40 mesh sieve before mixing. Accurately weighed ingredients were blended before granulation and sufficient quantity of isopropyl alcohol was used as a granulating agent. The slug was passed through sieve no.12 and granules were allowed to dry in oven. The dried granules were then passed through sieve no.16 and weight of fines was kept to 5% of granules. Magnesium stearate and aerosil in the concentration of 1% w/w and 0.5% w/w respectively, were added to the dried granules prior to compression. The granules were compressed using 12 mm punch on a single stroke tablet compression machine at an appropriate compression force. The weight of the tablet was kept to 406 mg. Tablet composition (% w/w) of different formulations of losartan potassium sustained release tablets developed are shown in Table 1.

The compressed tablets were evaluated for weight variation, thickness, hardness, friability, drug content, % swelling and *in vitro* drug release. The effects of the polymer concentration and the various fillers on the physicochemical and *in vitro* drug release behavior were studied.

Evaluation of matrix tablets

Pre-compression: The granules were evaluated for various pre-

Batch Code	Ingredients (mg/tablet)										
	Losartan Potassium	<i>S.tora</i> gum	Guar Gum	Locust Bean Gum	Xanthan Gum	Methocel K100 M (HPMC)	MCC	PVP K 30	Magnesium Stearate	Aerosil	Isopropyl alcohol
F-1	50	100					230	20	4	2	Q.S.
F-2	50	200					130	20	4	2	Q.S.
F-3	50	300					30	20	4	2	Q.S.
F-4	50	50			50		230	20	4	2	Q.S.
F-5	50	100			100		130	20	4	2	Q.S.
F-6	50	150			150		30	20	4	2	Q.S.
F-7	50		100				230	20	4	2	Q.S.
F-8	50		200				130	20	4	2	Q.S.
F-9	50		300				30	20	4	2	Q.S.
F-10	50		50		50		230	20	4	2	Q.S.
F-11	50		100		100		130	20	4	2	Q.S.
F-12	50		150		150		30	20	4	2	Q.S.
F-13	50			100			230	20	4	2	Q.S.
F-14	50			200			130	20	4	2	Q.S.
F-15	50			300			30	20	4	2	Q.S.
F-16	50			50	50		230	20	4	2	Q.S.
F-17	50			100	100		130	20	4	2	Q.S.
F-18	50			150	150		30	20	4	2	Q.S.
F-19	50				100		230	20	4	2	Q.S.
F-20	50				200		130	20	4	2	Q.S.
F-21	50				300		30	20	4	2	Q.S.
F-22	50					100	230	20	4	2	Q.S.
F-23	50					200	130	20	4	2	Q.S.
F-24	50					300	30	20	4	2	Q.S.

Q.S.: Quantity sufficient, MCC : Microcrystalline cellulose, PVP K 30: Polyvinyl pyrrolidone

Table 1: Tablet composition of different formulations of losartan potassium sustained release tablets

compression parameters like bulk density, tapped density, Hausners ratio, Carr's index and angle of repose as per the standard procedures reported in literature [17-19].

Post-compression: The tablets were characterized for weight variation, friability, hardness; drug content (Assay) and uniformity of dosage units. Thickness of a tablet was measured using vernier caliper. Ten tablets from each batch were used and the average values were calculated.

The hardness and friability were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Electrolab, Mumbai, India), respectively.

Drug content of the tablets was also determined by using 20 tablets. Twenty tablets were weighed and crushed in a mortar. An accurately weighed quantity of the powdered tablets (equivalent to 50 mg Losartan potassium) was extracted with pH 6.8 phosphate buffer solution and the solution was filtered through 0.45 μ membrane. The absorbance was measured at the 225nm (λ_{max} of Losartan potassium) after suitable dilution by UV visible spectrophotometer [20]. Uniformity of dosage unit was determined by analyzing 10 tablets individually. It was made clear that none of the ingredients used in the matrix formulations interfered with the absorbance of the drug.

Swelling studies: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in a petridish containing pH 6.8 phosphate buffer. At the end of 1hr, the tablet was withdrawn, soaked with tissue paper, and weighed [21]. Then for every 2 hr, weights of the tablet were noted, and the process

was continued till the end of 24 h. % weight gain by the tablet was calculated by formula: $S.I. = \left\{ \frac{(Mt - Mo)}{Mo} \right\} \times 100$

Where,

S.I. = swelling index,

Mt = weight of tablet at time's' and Mo = weight of tablet at time t = 0

Morphological examination of the swollen tablets was carried out using digital camera. Photographs of hydrated tablets were taken at different time intervals.

In-vitro release study: A calibrated dissolution apparatus (USP II) was used with paddles at 50 rpm and bath temperature maintained at $37 \pm 0.5^\circ\text{C}$. Nine hundred milliliter freshly prepared and degassed pH 6.8 Phosphate buffer solution was used as the dissolution medium [22,23]. Dissolution samples were collected at 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr, 16hr, 20hr and 24hr time interval. At each time point, a 5 mL sample was removed from each vessel and filtered through a nylon filter (0.45 μm, 25 mm) into labeled glass tubes. The dissolution samples were analyzed using previously developed and validated HPLC method.

Kinetic study: The *in-vitro* release data was subjected to zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson Crowell mathematical model in order to establish the drug release mechanism and kinetics of drug release from the matrix tablets [24-28].

Similarity factor analysis (f_2): To determine the similarity factor, *in-vitro* release profile of all the batches of tablets was compared with the theoretical release profile, which was calculated earlier. If $f_2 > 50$, it

is considered that two products share similar drug release behaviors. The data were analyzed by the following formula [29].

$$f_2 = 50 \log \left\{ 1 + \frac{1}{N} \sum (R_i - T_i)^2 \right\} - 0.5 \times 100$$

Where, N = number of time points, Ri and Ti = dissolution of reference and test products at time i

Stability study

Accelerated stability studies were carried out for the optimized formulation as per ICH guidelines [30]. The optimized matrix tablets were packed in screw capped high density polyethylene containers (HDPE) and were isothermally stressed to study the stability under accelerated temperature and relative humidity (RH) conditions (40°C and 75% RH) in stability chamber (Lab Aids, Mumbai, India) for 6 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month and at the end of 6 months and subjected to various tests, including visual inspection for any appreciable change on the tablet surface, assay, hardness, friability and dissolution. f_2 (Similarity values) values were calculated to verify the similarity of the dissolution profiles.

Bioavailability studies of the optimized formulation in Albino white rabbits

Five healthy male albino rabbits having body weight ranging between 1.5 to 2.5 kg were taken for the study. The rabbits were divided into 2 groups. First group (N=3) received compounded immediate release tablets of losartan Potassium. Second group (N=2) received sustained release matrix tablet (Optimized formulation F11) of losartan potassium. The tablet was put behind the tongue to avoid biting by rabbit. Food was withdrawn from the rabbits 12 h before drug administration and until 24 h post dosing. All rabbits have access to water during the study period. The Institute Animal Ethical Committee of Ultra College of Pharmacy, Madurai has approved the study protocol (Protocol No.: UCP/IAEC/2013/068).

The dose for the rabbits was selected based on the surface area ratio of rabbit and man. The formulations administered to the animals orally. After administration of the dosage form to the animals, blood samples were withdrawn from the marginal ear vein at time intervals of 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours using a sterilized syringe. The blood samples were collected in the vial containing the anti-coagulant. Plasma was immediately separated by centrifugation and was frozen until further analysis. Estimation of drug in plasma sample by RP-HPLC was carried out using optimized chromatographic conditions.

Plasma concentration time profile for the test and reference formulation was plotted and various pharmacokinetic parameters were determined. The results were analyzed statistically.

Results and Discussion

solution and evaluation of *Senna tora* seed gum

The isolated gum from *Senna tora* seeds was an amorphous free flowing powder with dull brown color. The results of physicochemical evaluation are summarized in Table 2.

The pH values of 1% solution of the *S. tora* gum was found to be slightly acidic or near neutral, which indicated that the gum is non-irritating to the mucous membrane of buccal cavity and gastrointestinal tract, and could be used for the development of buccal and oral drug delivery systems. The bulk density, tapped density and angle of repose data reveals that *S. tora* gum has good flow properties. The water absorption and swelling index of *S. tora* gum are high. *S. tora* gum can, therefore, maintain the aqueous equilibrium between the dosage form and the surrounding medium. Further, the surface tension of *S. tora* gum is higher than that of water, which may facilitate sustained release of drugs from dosage forms. Based on the physicochemical studies, *S. tora* gum was selected as a sustained release polymer for preparation of matrix tablet.

Preformulation study

The identification of drug was confirmed by comparing IR spectrum of drug with reported spectrum of losartan potassium. The FTIR spectrum of losartan potassium (Figure 1A) showed characteristic bands (Table 3) similar to that of reported in literature [31].

FTIR of losartan potassium and its physical mixture with excipient in the ratio 1:1 exhibited the peak for Losartan potassium at similar places (Figure 1). This indicated that there is no interaction between the losartan potassium and excipients.

DSC thermograph of the losartan potassium exhibited a sharp endothermic peak at 184.5°C corresponding to its melting point (Figure 2A). There was no appreciable change in the melting endotherms of the physical mixture of excipients (Optimized formulation) compared to pure drug (Figure 2B). This indicated that there was no interaction between the losartan potassium and excipients.

Formulation and evaluation of sustained release matrix tablet

Polymer selection: Galactomannans are neutral polysaccharides

Parameter	Result
Solubility	Soluble in hot water forming viscous colloidal solution but insoluble in methanol, ethanol, acetone, DMSO and ether.
pH	6.5 to 7.3 (Near to neutral, less irritating and hence suitable for uncoated tablets)
Loss on drying (% w/w)	6.7
Total Ash content (% w/w)	1.2
Specific gravity (1% w/v solution)	1.007
Surface tension, 0.1% w/v (dyne/cm)	97.59
Swelling Index (%)	84
Bulk Density (g/mL)	0.51
Tapped Density (g/mL)	0.60
Hausner's Ratio	1.17
Carr's Index	14.29
Angle of repose	29°44'

Table 2: Physicochemical evaluation of *S. tora* seed gum

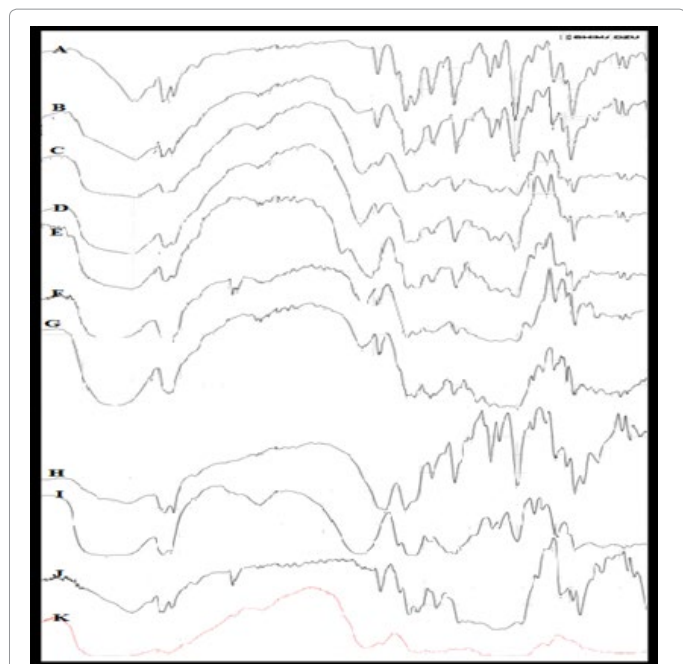


Figure 1: FTIR spectrum of (A) losartan potassium (B) losartan potassium + *S. tora* gum (C) losartan potassium + guar gum (D) losartan potassium + locust bean gum (E) losartan potassium + xanthan gum (F) losartan potassium + methocel K 100 M (G) losartan potassium + MCC (H) losartan potassium + magnesium stearate (I) losartan potassium + PVP K-30 (J) losartan potassium + aerosil (K) Optimised formulation [F11].

Wavelength (cm ⁻¹)	Functional group
761.88	C-Cl bond
1577.77	N=N stretching
1460.11 and 1577.77	C=C bond
3194.12	Stretching vibration of O-H

Table 3: FTIR assignments for losartan potassium

obtained from the endosperm of seeds of some Leguminosae plant and they have several functions, including reserve of carbohydrates [32]. Galactomannans are polysaccharides built up of a β -(1-4)-D-mannan backbone with single D-galactose branches linked α -(1-6). Their mannose/galactose (M/G) ratios differ according to the species [33]. They are water soluble hydrocolloids which form highly viscous, stable aqueous solutions [34]. The main difference between galactomannans from different plant sources lies in the galactose content as well in its distribution along the mannopyranosyl backbone [32,35].

The three major galactomannans of commercial importance in food and non-food industries are guar gum (GG, *Cyamopsis tetragonoloba*, M/G ratio: 2:1), tara gum (TG, *Caesalpinia spinosa*, M/G ratio: 3:1) and locust bean gum (LBG, *Ceratonia siliqua*, M/G ratio: 3.5:1 [36].

Chemical investigation of *S. tora* seed gum (STG) revealed that it contains galactomannans. Hence, two more commercially available polysaccharides i.e. guar gum and locust bean gum were selected from the same category for comparing its sustained release properties.

To study and compare the sustained release potential of naturally occurring galactomannans with commercially available semisynthetic hydrophilic polymer, high viscosity grade hydroxypropylmethyl cellulose (Methocel K 100 M) was selected in the present investigation.

Galactomannans can synergistically interact with xanthan gum resulting in improved product quality and reduced production costs. Different models have been proposed to explain the intermolecular binding mechanism between xanthan gum and galactomannans.

Xanthan is an extracellular polysaccharide secreted by *Xanthomonas campestris* composed by pentasaccharide repeating units, with a β -1,4 linked cellulosic backbone, attached with a charge trisaccharides side chain docked on alternated glucose residue [37,38].

Viscometric studies on mixing xanthan gum with galactomannans reported synergistic effect due to stronger interactions in aqueous systems. The results showed the formation of a gel-like structure with hysteresis between increasing and decreasing shear rate [39].

Hence, xanthan gum (XG) was selected as one more polymer to study and investigate its effect of interaction with different galactomannan containing polysaccharides on rate of release of drug in matrix tablet formulation when used in combination.

Formulation development: Losartan potassium matrix tablets (Total number of batches: 24) were prepared using isolated *S. tora* gum, guar gum, locust bean gum alone and their combination with xanthan gum. Losartan potassium tablets were also prepared using different concentrations of xanthan gum and hydroxy propyl methyl cellulose (Methocel K100M).

Sustained release matrix tablets of Losartan potassium were prepared using *S. tora* gum, guar gum, locust bean gum alone and in combination with xanthan gum. Microcrystalline cellulose (Avicel 101) was used as diluents, magnesium stearate was used as lubricant and aerosil was used as glidant. PVP K-30 was used as binder and isopropyl alcohol was used as granulating fluid.

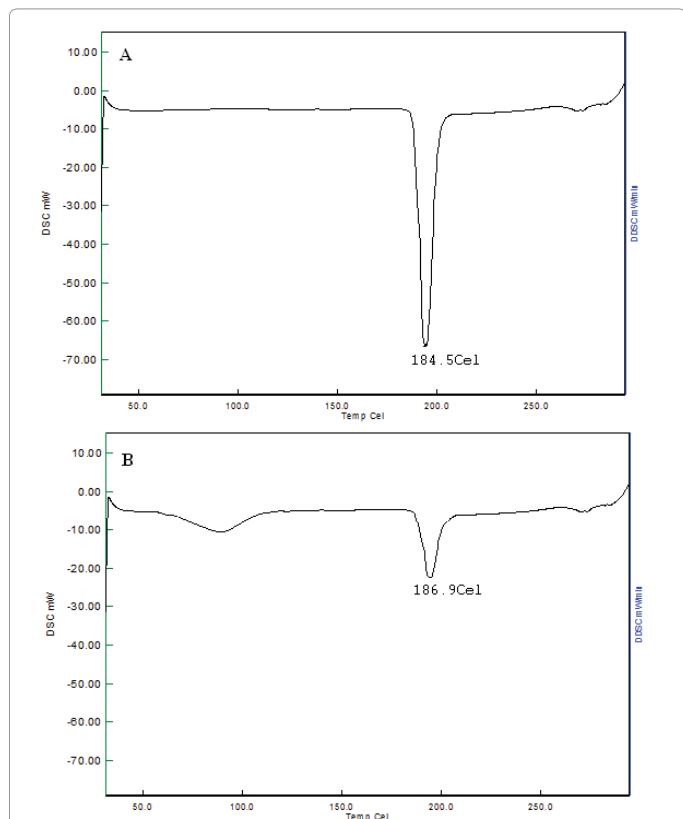


Figure 2: DSC of (A) losartan potassium (B) losartan potassium sustained release tablet (Optimized formulation)

Evaluation

Pre-compression and post-compression: The pre-compression studies indicated that all the prepared granules are having good flow capacity. These properties were assisted to uniform fill weight and avoided some problems during the tablet compression. Each batch shows limited moisture content and good Carr's index. The granule properties of different formulations of losartan potassium sustained release tablets evaluated are shown in Table 4.

All the compressed tablets were round, flat with smooth surface in both sides. Colour of the tablets was varied with gum/galactomannans used in the formulation and their concentration. In a weight variation test, the Pharmacopoeial limit of percentage deviation for tablets whose weight is more than 250 mg is $\pm 5\%$ [40]. The average percentage deviation of all the tablets was found within the limit. The friability values for all the prepared tablets were within acceptable range. Optimum tablet hardness has been maintained by compression force and thickness; hence, the tablets have enough strength for shipping. The drug content was also found uniform and within the prescribed limit. The tablet properties of different formulas of losartan potassium sustained release tablets developed are given in Table 5.

Swelling study: The swelling behavior of a hydrogel matrix system is an important property for uniform and prolonged release of drug. The swelling behavior depends upon nature of polymer, concentration of polymer and pH of the medium. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The outermost hydrophilic polymer layer hydrates/swells first and as the hydrated layer progressively dissolves or disperse, the swelling process will continuous towards new exposed surfaces thus maintaining the integrity of dosage form. It was observed that the concentration of polysaccharide has a significant impact on the drug release. The drug release was decreased when the concentrations of the polymer in the formulation increased.

The swelling study of prepared matrix tablets was performed in pH 6.8 phosphate buffer and the results are presented as percentage weight change with respect to time. The results of swelling behavior of losartan potassium sustained release tablets are depicted in Figure 3.

Photographs of hydrated tablet of optimized formulation F11 taken at different time interval are shown in Figure 4.

In vitro dissolution studies: The *in vitro* dissolution studies for different batches of losartan potassium sustained release tablets were carried out in pH 6.8 phosphate buffer using optimized dissolution conditions.

The drug content in the dissolution samples were determined by previously developed and validated HPLC method. HPLC analysis was carried out using Agilent Zorbax XDB (150 mm \times 4.6 mm, 5 μ m) C-18 column. The good performance with rapid elution was achieved in mobile phase consisting of orthophosphoric acid (0.1% v/v) and acetonitrile (55:45, v/v) at a flow rate of 1.0 mL/min. Better peak response and less placebo interference was observed at 225 nm. The representative chromatogram of sample is shown in Figure 5.

Drug release from hydrophilic matrices is known to be a complex interaction involving swelling, diffusion and erosion mechanisms [41-44]. The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the periphery towards the center, 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

Formulation Code	Bulk Density*	Tapped Density*	Carrs Index	Hausner Ratio	Angle of repose	Moisture Content (%)
F-1	0.371 \pm 0.017	0.461 \pm 0.010	1.24	19.52	27°87'	1.56
F-2	0.384 \pm 0.019	0.459 \pm 0.027	1.20	16.34	25°13'	1.72
F-3	0.402 \pm 0.012	0.456 \pm 0.019	1.13	11.84	28°12'	1.81
F-4	0.373 \pm 0.016	0.462 \pm 0.011	1.24	19.26	26°49'	1.42
F-5	0.386 \pm 0.022	0.468 \pm 0.015	1.21	17.52	24°11'	1.53
F-6	0.409 \pm 0.026	0.472 \pm 0.021	1.15	13.35	23°91'	1.66
F-7	0.392 \pm 0.031	0.485 \pm 0.024	1.24	19.18	29°42'	1.72
F-8	0.421 \pm 0.023	0.491 \pm 0.009	1.17	14.26	27°57'	1.80
F-9	0.433 \pm 0.014	0.497 \pm 0.014	1.15	12.88	26°61'	1.51
F-10	0.385 \pm 0.009	0.471 \pm 0.026	1.22	18.26	24°29'	1.39
F-11	0.391 \pm 0.017	0.461 \pm 0.016	1.18	15.18	23°39'	1.48
F-12	0.406 \pm 0.018	0.456 \pm 0.007	1.12	10.96	22°83'	1.54
F-13	0.374 \pm 0.019	0.464 \pm 0.018	1.24	19.40	28°99'	1.69
F-14	0.382 \pm 0.028	0.459 \pm 0.013	1.20	16.78	27°30'	1.38
F-15	0.401 \pm 0.021	0.452 \pm 0.019	1.13	11.28	25°72'	1.87
F-16	0.367 \pm 0.026	0.451 \pm 0.030	1.23	18.63	27°11'	1.63
F-17	0.383 \pm 0.024	0.461 \pm 0.029	1.20	16.92	25°58'	1.47
F-18	0.397 \pm 0.010	0.452 \pm 0.012	1.14	12.17	24°89'	1.36
F-19	0.378 \pm 0.032	0.470 \pm 0.009	1.24	19.57	29°36'	1.51
F-20	0.381 \pm 0.013	0.462 \pm 0.015	1.21	17.53	28°88'	1.42
F-21	0.391 \pm 0.014	0.454 \pm 0.017	1.16	13.88	26°63'	1.68
F-22	0.313 \pm 0.029	0.381 \pm 0.019	1.22	17.85	25°97'	1.61
F-23	0.326 \pm 0.008	0.377 \pm 0.026	1.16	13.53	24°51'	1.37
F-24	0.334 \pm 0.023	0.373 \pm 0.029	1.12	10.46	23°16'	1.43

*The values represent mean \pm SD (n = 3)

Table 4: Granule properties of the different formulations of losartan potassium sustained release tablets.

the drug. The drug release from different matrices is as discussed below:

a: Release from formulations containing individual gum matrices: The results of release obtained from individual use of STG (Formulation F1-F3), GG (Formulation F7-F9), LBG matrices (Formulation F13-F15) and XG matrices (Formulation F19-F21) are shown in Figure 6.

GG, LBT and XG gum failed to sustain the drug release up to 24 h even at very high concentration (drug polymer ratio of 1: 6). Tablets containing low concentration (1: 2) of individual gum showed complete erosion, while the others demonstrated fast hydration and swelling in contact with the dissolution medium. The satisfactory release for 24

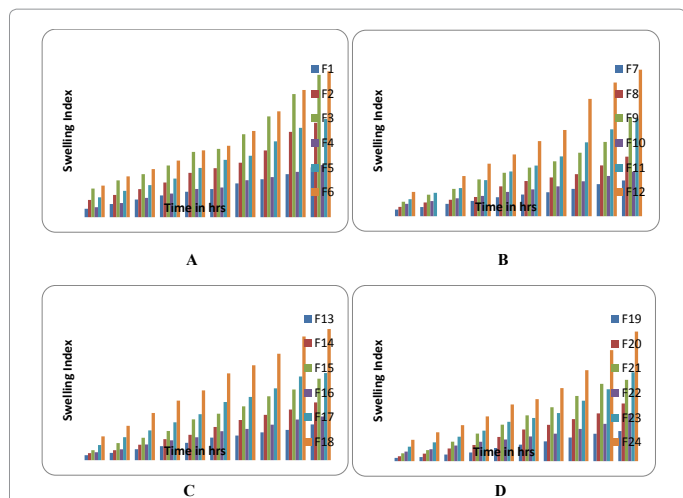


Figure 3: Graphical comparison of swelling index of various formulations of losartan potassium sustained release tablets (A)F1-F6(B)F7-F12(C)F13-F18(D)F19-F24.

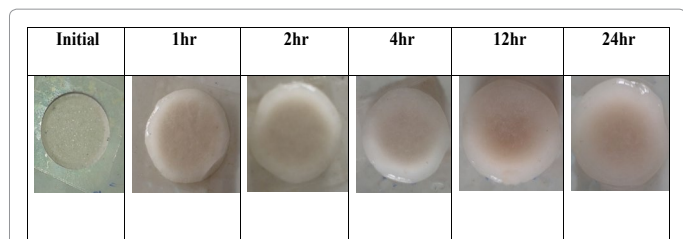


Figure 4: Photographs of hydrated tablets of optimized formulation F11.

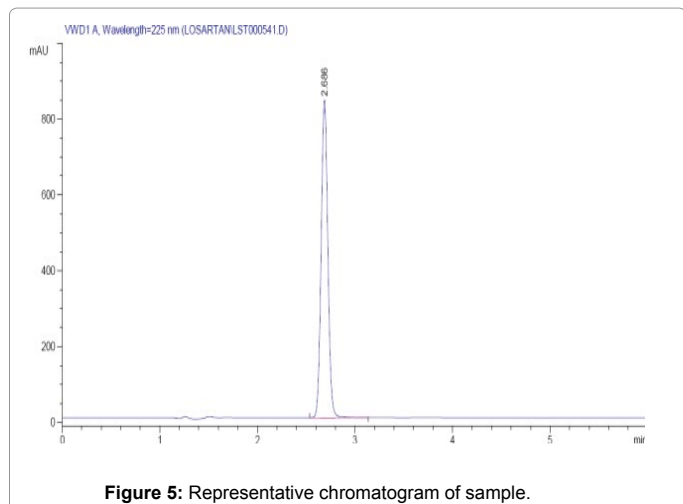


Figure 5: Representative chromatogram of sample.

hours was obtained with only STG gum among all the galactomannans at drug polymer ratio of 1:6. This may be explained by the swelling of tablet after it absorbed water. A higher amount of gum absorbs more water and causes greater swelling, thus increasing the length of drug diffusion path leading to decrease in the amount of drug. There must be sufficient polymer to gum ratio in a matrix system to form a uniform barrier for drug release. This barrier protects the drug from immediate releasing in the dissolution medium.

b: Drug release from HPMC matrices: Drug release from the

HPMC-drug matrix involves solvent penetration into the dry matrix, gelatinization of the polymer, dissolution of the drug and diffusion of the solubilized drug through the gel layer. Concomitantly, outer layers of the tablet become fully hydrated and dissolve, a process generally referred to as erosion.

Increasing the HPMC concentration in the tablet or using higher viscosity grades increases the strength of the gel layer and retards the penetration of water into the dry glassy core [45]. This results in a decrease in release of both water-soluble and water-insoluble drugs.

Low viscosity grade HPMC (Methocel K15M and Methocel K30M) were tried but the drug release was fast, indicating that a higher viscosity grade of Methocel would be required to retard drug release. HPMC of higher viscosity grade swells to a greater extent as it has a greater intrinsic water uptake property than that of a lower viscosity grade [45]. Hence, Methocel K100M was selected for further studies to retard drug release.

Different ratios of Methocel K100M studied were 1:2, 1:4 and 1:6 with respect to the drug. The results of release obtained from use of Methocel K100M (Formulation F22-F24) are shown in Figure 6D.

Drug release was fast with of Methocel K100M 1:2 with 90% drug released in 6 hr. The overall drug release is affected by the rate of water uptake and the diffusion rate of the drug through the swollen gel. High polymer content results in a greater amount of gel being formed. This gel increases the diffusional path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result, a reduction in drug release rate was obtained. Methocel K100M in the ratio 1:6 with respect to the drug (F24) provided the desired sustained release profile for a period of 24 h.

c: Release from formulations containing combination of gum matrices: The results of release of losartan potassium obtained from use of STG (Formulation F4-F6), GG (Formulation F10-F12), LBG (Formulation F16-F18) in combination with XG are shown in Figure 6.

The drug release was almost same from the matrices with XG-STG

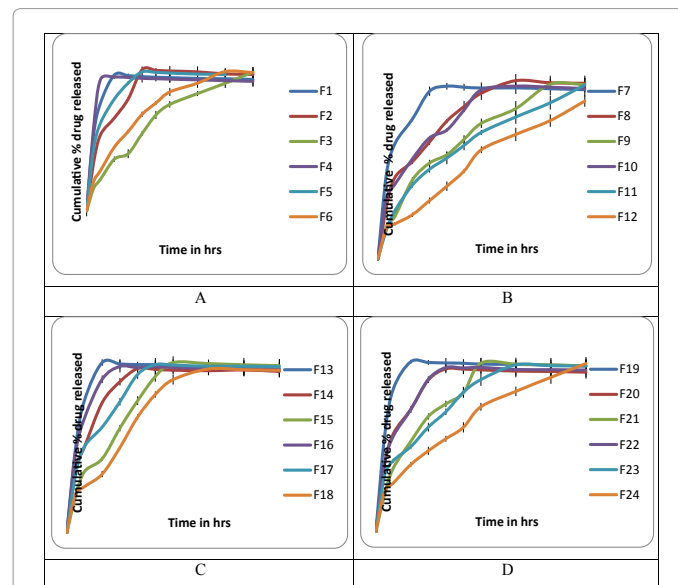


Figure 6: *In vitro* release of losartan potassium from the matrix tablets containing (A) STG and its combination with XG (F1-F6) (B) GG and its combination with XG (F7-F12) (C) LBG and its combination with XG (F13-F18) (D) XG and Methocel K100 M (F19-F24)

combination as compared to individual STG matrices with the same total polymer concentration. This indicated that there is no significant interaction between the galactomannans of *S.tora* polysaccharide and xanthan gum and has no impact on release pattern.

The tablets with XG-GG resulted in more uniform drug release matrices than GG alone, due to the synergistic interaction of the two biopolymers to produce a strong and elastic gel in the presence of a ternary component (MCC). XG produced more marked sustained effect in combination with GG than GG matrices alone. GG alone matrices failed to produce sustained release up to 24 h even at higher drug to polymer concentration of 1:6 but XG-GG matrix with same total polymer concentration extended release of drug more than 24 h. XG-GG matrix at drug to polymer concentration 1:4 showed successful drug release up to 24 h. The drug release was slower from the matrices with XG-GG compared with GG matrices with the same total polymer concentration. This is possibly due to slower erosion of GG and or XG and may be due to the increased viscosity of GG in the presence of XG which might have helped to keep the hydrated gel intact thus releasing the drug for 24 h.

The drug release was slower from the matrices with XG-LBG combination as compared to individual LBG matrices with the same total polymer concentration. This indicated that there is some interaction between the galactomannans of LBG and xanthan gum. This may be due to slower erosion of LBG and may be due to the increased viscosity of LBG in the presence of XG.

Thus, the drug release followed the rank order of using alone polymers as **XG> LBG> GG>STG** and combination polymers as **XG-STG>XG-LBT>XG-GG**.

Optimization

Among all the formulations prepared and evaluated for losartan potassium sustained release matrix tablet, formulation containing combination of guar gum and xanthan gum with the drug: guar gum : xanthan gum ratio 1:2:2 (Formulation F11), showed better release pattern with sustained release up to 24hrs in comparison with other formulations. It also showed better similarity factor (f_2) value with respect to release profile of matrix tablet prepared using Methocel K100M (F24). Hence, this batch was considered as optimized batch and was subjected to bioavailability and stability studies.

Kinetic study (Computation of release mechanism)

Among all the prepared formulations for losartan potassium, Formulation F11 showed expected release of 24 hours with highest correlation value (R^2) of 0.9962 for Higuchi model. The value of n as estimated by linear regression of $\log Mt/M_\infty$ vis $\log t$ of formulation F11 was 0.5956 indicates drug release mechanism from matrix tablets involving a combination of both diffusion and chain relaxation mechanisms. Therefore, the release of losartan potassium from the prepared tablets is controlled by the swelling of the polymer followed by drug diffusion through the swelled polymer and slow erosion of the tablet. The kinetic release of optimized formulation (F11) using different kinetic model is depicted in Figure 7.

Stability study

The results of stability studies of the optimized batches of losartan potassium sustained release tablets are shown in Table 6. The accelerated stability studies indicated that the developed matrix tablets were unaffected after 6 months storage under accelerated conditions. There were no signs of visually distinguishable changes

in the appearance, texture and color of the formulation. The data on drug content and friability were comparable with those of the control samples and are within the limits. f_2 values of 50-100 indicate similarity between the dissolution profiles. On the basis of these results, it may be concluded that the formulations developed are stable under accelerated conditions for 6 months.

Pharmacokinetic evaluation

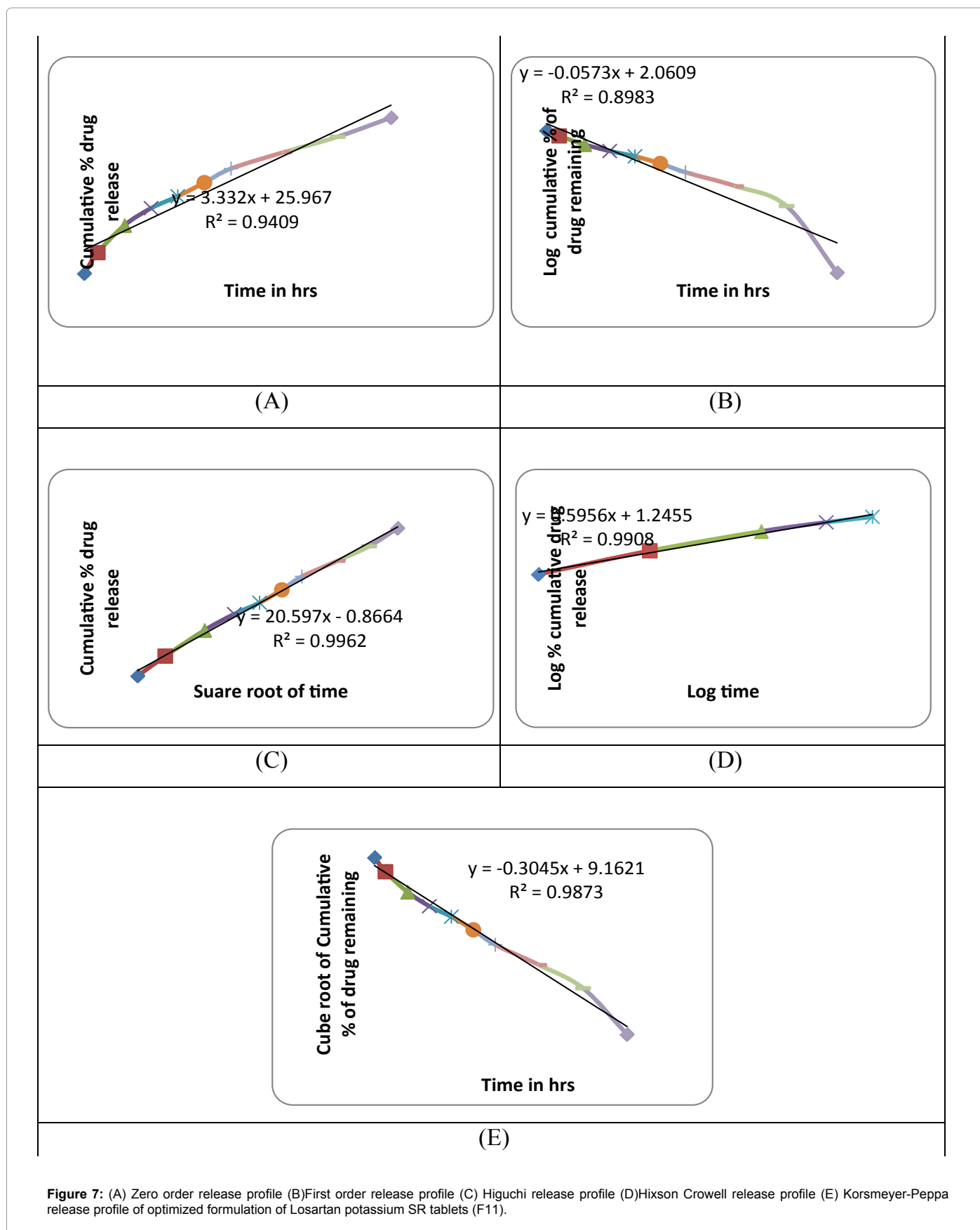
The results of the mean pharmacokinetic profiles calculated for the optimized matrix tablets (F11) and the conventional immediate release tablet (Reference product) are presented in Table 7.

The comparative plasma profiles of Losartan potassium conventional formulation (R) with losartan potassium sustained release formulation (T) is shown in Figure 8.

The results showed very rapid drug absorption from the reference product as revealed by a T_{max} of 1.5 h as compared to a T_{max} of 8h for sustained release matrix tablets. The developed matrix tablets gave a plasma concentration–time profile typical of the prolonged dissolution characteristic of the sustained release formulation. The optimized formulation F11 thus demonstrates a longer time to reach the peak concentration than the reference product and appear to be more consistent in its overall performance as indicated by a lower variation in plasma concentrations, longer time to peak and lower peak plasma concentration. The data obtained further reveal the absence of a burst-effect in formulation F11 in fasted, healthy animals. There is significant difference in the extent of absorption as seen from the AUC_{0-24} values. However, the $AUC_{0-\infty}$ value for sustained release tablets is 3.2 times higher than the reference thus, indicating more efficient and sustained drug delivery capable of maintaining plasma drug levels better. This is also evident from the lower elimination rate constant (0.0567 ± 0.04) and higher $t_{1/2}$ values (12.26 ± 0.89) for sustained release tablets. The drug release from the GG is thus sustained and could maintain the drug level in blood plasma. The *in vivo* concentration–time profile thus shows that the tablets maintain their integrity while traversing the stomach. There was a statistically significant ($P < 0.0001$) difference that occurred at the time of 1 h and continued to be significant up to 24 h when compared to reference.

Conclusion

S. tora gum, guar gum and locust bean gum (Natural polymers) were significantly affects mechanical properties, decreases porosity and sustains the drug release due to its swelling properties. Therefore, one can assume that the galactomannans (Such as *S. tora* gum, guar gum and locust bean gum) are promising natural biopolymers used in pharmaceutical dosage forms by providing sustained release drug delivery systems. It has been concluded that the polysaccharide isolated from *S. tora* seeds exhibit good sustaining properties similar to that of the widely used polymer, namely, HPMC when used alone. In combination with xanthan gum, guar gum shows better sustaining property as compared to other two galactomannan containing gums i.e. *S. tora* gum and locust bean gum. The developed sustained release tablets have acceptable pharmaco-technical properties which indicate that the process can be used for the scale up studies and the drug release can be modulated significantly by varying the components of the matrix. A comparative bioavailability study of the developed sustained release tablets and the conventional immediate release tablets indicated that the sustained release tablets of the selected drug, losartan potassium, are well absorbed and the extent of absorption is higher than that of the conventional immediate release tablets. The sustained



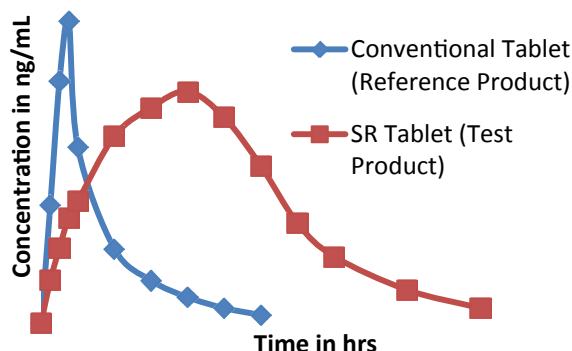


Figure 8: Comparative plasma profiles of losartan potassium conventional formulation (R) with losartan potassium sustained release formulation (T)

Formulation Code	Thickness (mm)*	Average Weight (mg)	Hardness (Kg/cm ²)*	Friability (%)	Drug Content (%)**	Content Uniformity (%)
F-1	2.944 ± 0.04	404.82	9.4 ± 0.29	0.37	98.96	99.61
F-2	3.112 ± 0.05	410.71	8.3 ± 0.20	0.68	102.11	101.48
F-3	3.083 ± 0.01	406.92	9.0 ± 0.35	0.41	100.92	99.12
F-4	2.901 ± 0.04	405.43	9.3 ± 0.45	0.44	98.96	98.04
F-5	3.043 ± 0.02	407.94	8.5 ± 0.33	0.63	100.74	98.85
F-6	3.171 ± 0.03	409.17	9.1 ± 0.48	0.59	101.78	99.16
F-7	2.985 ± 0.02	406.81	9.4 ± 0.41	0.51	99.21	98.77
F-8	3.115 ± 0.06	409.85	8.5 ± 0.23	0.74	102.49	101.04
F-9	3.034 ± 0.01	407.98	9.2 ± 0.45	0.66	100.56	98.93
F-10	3.054 ± 0.03	406.88	9.5 ± 0.36	0.25	99.19	98.13
F-11	3.133 ± 0.04	408.51	8.4 ± 0.17	0.43	101.64	99.72
F-12	2.903 ± 0.02	403.78	9.2 ± 0.13	0.32	97.93	98.95
F-13	3.092 ± 0.03	408.92	9.3 ± 0.41	0.62	102.3	100.74
F-14	2.972 ± 0.02	405.81	8.5 ± 0.32	0.72	98.51	99.79
F-15	3.121 ± 0.04	409.33	9.1 ± 0.38	0.69	102.85	101.09
F-16	3.104 ± 0.01	408.24	9.4 ± 0.53	0.55	101.14	99.83
F-17	3.068 ± 0.03	406.11	8.5 ± 0.33	0.64	100.83	99.39
F-18	2.984 ± 0.06	404.53	9.2 ± 0.25	0.59	98.93	100.40
F-19	3.142 ± 0.02	409.13	9.3 ± 0.29	0.58	102.71	101.23
F-20	2.993 ± 0.04	406.08	8.4 ± 0.30	0.76	99.49	98.07
F-21	3.107 ± 0.02	409.55	9.0 ± 0.34	0.65	102.27	101.72
F-22	3.043 ± 0.05	406.11	9.5 ± 0.51	0.44	98.99	99.48
F-23	3.105 ± 0.01	407.58	9.1 ± 0.42	0.47	99.52	100.36
F-24	3.164 ± 0.03	408.79	9.3 ± 0.32	0.41	101.66	99.01

*The value represents Mean ± SD, n=10 **n=3

Table 5: Tablet characteristics of the different losartan potassium sustained release tablets

Parameter	Initials	1 Month		2 Month		3 Month		6 Month	
		Control*	Accelerated**	Control*	Accelerated**	Control*	Accelerated**	Control*	Accelerated**
Physical Appearance	Off White	Off White	Off White	Off White	Off White	Off White	Off White	Off White	Off White
Thickness (mm)	3.066 ± 0.03	3.078 ± 0.04	3.071 ± 0.03	3.079 ± 0.02	3.083 ± 0.05	3.068 ± 0.04	3.081 ± 0.01	3.065 ± 0.05	3.071 ± 0.06
Hardness (Kg/cm ²)	9.3 ± 0.32	9.2 ± 0.45	9.3 ± 0.37	9.3 ± 0.25	9.4 ± 0.40	9.2 ± 0.28	9.4 ± 0.36	9.4 ± 0.39	9.5 ± 0.41
Friability (%)	0.32	0.46	0.52	0.50	0.61	0.57	0.56	0.44	0.68
Drug Content (%)	99.91 ± 0.41	99.41 ± 0.55	98.82 ± 0.34	98.96 ± 0.38	98.61 ± 0.61	98.71 ± 0.48	98.55 ± 0.44	98.45 ± 0.33	98.04 ± 0.36
F2 Value*** (Similarity Factor)	---	94.61	94.66	93.02	92.64	93.89	89.73	91.95	86.98

Table 6: Tablet properties of the developed Losartan potassium sustained release tablets after storage in stability studies

Pharmacokinetic parameters	Conventional tablets (R)	Developed SR tablet
C_{max} (ng/ml)	1027 ± 29.09	789 ± 14.85
T_{max} (h)	1.5 ± 0.00	8 ± 0.00
AUC ₍₀₋₂₄₎ (ng h/ml)	2974 ± 14.59	9595 ± 142.66
k_{el} (h ⁻¹)	0.2937 ± 0.01	0.0567 ± 0.04
$t_{1/2}$ (h)	2.36 ± 0.10	12.26 ± 0.89
AUC _(0-∞) (ng h/ml)	3013 ± 21.37	9667 ± 131.43

Values are reported as Mean ± Standard deviation

Table 7: Pharmacokinetic parameters of the conventional immediate release tablets and optimized sustained release tablets in healthy animals.

and efficient drug delivery system developed in the present study could maintain plasma drug levels better which can overcome the drawbacks associated with the conventional therapy. In the future this study can be continued by conducting clinical trials for the formulations showing promising results.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interests regarding the publication of this article.

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