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Applicability of Gum Karaya in the Preparation and *in Vitro* Evaluation of Losartan Potassium as Chronotherapeutic Drug Delivery System

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Abstract

The objective of this investigation is to study the applicability of gum karaya, the natural gum for the preparation and *in vitro* evaluation of losartan potassium, as Chronotherapeutic Drug Delivery System (ChDDS). The compression-coated timed-release tablets (CCT) containing losartan potassium in the core tablet were prepared by dry coating technique with different ratios of gum karaya as the outer coat. The parameters investigated were tensile strength, friability, *in vitro* dissolution studies and drug concentration. The optimized formulation was further characterized by powder XRD and FTIR to investigate interactions and no interactions observed. The tensile strength and friability of all the CCT were between 1.06-1.23 MN/m^2 and < 0.3% respectively. All the CCT showed a clear lag time before a burst release of drug. However, the lag time of drug release increased as the amount of gum karaya in the outer layer increased. For instance, the lag time of LGK1, LGK2, LGK3, LGK4, LGK5, LGK6 and LGK7 were 16, 10.5, 5.5, 3, 2, 1.5 and 0.5 hrs respectively. The drug content of all the CCT was >98%. Formulation LGK3 was taken as an optimized formulation which can be exploited to achieve ChDDS of losartan potassium for the treatment of hypertension.

Keywords: Losartan potassium; Compression coated timed release tablet; Gum karaya; Powder X-ray diffraction; Fourier-Transform Infrared Spectroscopy.

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1. Introduction

Maximum concentration of drug *(C_{max})* normally reaches within 1-2 hours for many of the conventional dosage forms, which may not match with the maximum intensity of the

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disease state. For effective therapy, it is always advisable to provide maximum drug concentration at maximum intensity of disease condition. Oral time-controlled drug release formulations have the unique characteristic that a drug is released from the formulation after a predetermined lag time before drug release [1]. Time-controlled release formulations could be an effective tool in chronopharmacotherapy because of the drug release is modulated in a manner that the C_{max} of the drug is reached at the point in the circadian cycle when clinical signs develop or increase. Drugs that treat cardiovascular diseases and asthma have been investigated for the chronopharmacotherapy because these symptoms follow circadian rhythms [2]. Hence, the purpose of this study is to design an optimized Chronotherapeutic Drug Delivery System (ChDDS) of losartan potassium using gum karaya in different ratios with a predetermined lag time [3].

Compression-coated tablets (CCT) are composed of an inner core immediate release tablets that contain an active pharmaceutical ingredient and excipients, surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. Advantage of this technique is simple, inexpensive and eco-friendly, since it does not require the high amount of organic solvent.

Losartan potassium is an angiotensin II antagonist. It is used in the treatment of hypertension particularly in diabetic patients for nephropathy. It is a weekly acidic drug with a pK_a of 4.9 and the biological half life is 2 to 2.5 h [4]. Adult dose is 25 mg, 50 mg and 100 mg once daily based on the requirement as prophylactic, treatment and in severe conditions respectively in combination with other antihypertensive drugs.

Gum karaya (GK), also called as *Sterculia* gum, is the dried exudation of the *Sterculia urens* tree and other species of *Sterculia*, which belong to the family *Sterculiaceae* [5, 6]. GK is a negative colloid and a high-molecular-mass complex acidic polysaccharide. The general utility of GK is based on its viscosity [7]. It was successfully evaluated for its suitability in the preparation of hydrophilic matrices [8], mini-matrices, microcapsules [9] and transdermal patches. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drugs is increasing [10]. However, the high viscosity [11] and hardness of these polymers might limit their application as carriers for dissolution enhancement.

2. Experimental

2.1. *Materials*

Losartan potassium was received as a gift sample from Dr Reddy's Laboratory Pvt. Ltd, Hyderabad, India), Gum karaya was purchased from Girijan co-operative corporation, Visakhapatnam, India. GK is a general food additive and generally recognized as safe (GRAS) in USA since 1961, was accepted temporarily (Annexure 11) as a food additive in 1974. Since then no adverse incident involving human health has been attributed to the ingestion of GK [12]. It has been found that LD_{50} values of GK in rats ranged from 2.6 to

18.0 g/kg [13]. Eastwood found that human subjects could tolerate an oral dosage of 10.5 g of GK [14].

Avicel 112, croscarmellose sodium (CCS), polylvinylpyrrolidone (PVP K30) were received as gift samples from Aurbindo Pharma Ltd, Hyderabad, India. These were used as diluent, disintegrant and binder respectively, Talc and magnesium stearate (S.D. Fine Chemicals Ltd., Mumbai, India) were used as glidant and lubricant respectively. All other reagents used were of analytical grade. Two different commercial brands (CB)) of immediate release formulations of losartan potassium were purchased from the market. Where P1= ALSARTAN (Manufacturing date: May 2007 and Expiring date April 2010, Aristo Pharmaceuticals Ltd., India) and P2 = COVANCE (Manufacturing date: August 2008 and Expiring date July 2011, Ranbaxy laboratories Ltd., India).

2.2. *Preparation of an optimized core tablet (OCT)*

From preliminary studies in our laboratory, an optimized core tablet was formulated by using various concentrations and different types of diluents, disintegrates and binders. The drug, diluent, disintegrant and binder were weighed for a batch of 100 tablets as per formulae given in Table 1 and were then passed through 500 μm sieve, transferred to a polybag and blended for 5 min. To the above homogeneous blend, talc and magnesium stearate was added and blended for 2 min. The resulting blend was compressed with a rotary compression machine (Model Rimek, India) to form a biconvex tablet with a diameter of 6 mm. The weights of the tablets were 106.5 ± 0.5 mg.

Table 1. Optimized core tablet composition.

Ingredients	Mass/tab (mg)
Losartan potassium	50
Avicel 112	50
CCS	2.5
PVP K 30	2.5
Magnesium stearate	0.5
Talc	1.0
Total mass	106.5

2.3. *Preparation of compression-coated timed-release tablets (CCT)*

The gum karaya and microcrystalline cellulose (MCC) were accurately weighed as required for a batch of 100 tablets as per formulae given in Table 2 and granulated using 5% PVP solution in mixture of isopropyl alcohol and water in the ratio of 70:30. Then the wet screening was done by passing through 710 μm sieve, and it was dried for 2 h at 45°C in a hot air oven. Then the dried mass was screened. Talc and magnesium stearate were added to the dried granules and passed through 500 μm and blended for 2 min. Half the amount of polymer granules was placed into the die to make a powder bed. The core tablet was then placed at the centre on the polymer bed while the remaining half of the polymer granules was filled into the die. The content was compressed with a rotary

compression machine to form a biconvex tablet with a diameter of 9 mm. The weights of the tablets varied depending on the formulation (Table 2).

Table 2. Coat tablet composition of gum karaya

Ingredients (mg)	LGK1	LGK2	LGK3	LGK4	LGK5	LGK6	LGK7
Gum karaya	100	80	60	50	40	20	0
MCC	0	20	40	50	60	80	100
Talc	1	1	1	1	1	1	1
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5

2.4. *Physicochemical analysis of optimized core tablet (OCT), commercial brand (CB) and compression coated tablet (CCT) formulations*

2.4.1. *Friability test*

Ten tablets (1.065 g) were placed in the drum of a friabilator (Electro labs, Model EF2, Mumbai, India) rotating at 100 revolutions for 4 min. The percentage dust formed due to the impact was determined and taken as index of friability. The test was carried in triplicate.

2.4.2. *Disintegration test (DT)*

The method described in the British Pharmacopoeia [15] was followed using water maintained at 37±2 $^{\circ}$C as the disintegration fluid. Six tablets were placed in disintegration apparatus (Electrolabs, Model, ED-2L Mumbai, India)) for each determination. It was carried out in triplicate and the mean results reported.

2.4.3. *Determination of tablet tensile strength (T)*

This is the stress needed to fracture a tablet by diametral compression. It is given by Fell and Newton [16] as:

$$T = 2P / \pi Dt \quad \text{----------} \quad (1)$$

Where, *P* is the fracture load that causes tensile failure of a tablet of diameter, *D* and thickness, *t*. The fracture load (kg) of ten tablets was determined individually with the Monsanto hardness tester (Tab Machines, Mumbai, India), following Brook and Marshal [17]. The mean values of the fracture loads were used to calculate the *T* values for the various tablets.

2.5. *In vitro drug release studies for OCT, CB formulations and CCT*

The OCT and two different CB formulations were subjected to *in vitro* drug release in a 900 mL of 6.8 pH phosphate buffer for 90 min. On the other hand, the different coated

tablets with varying ratios of polymer coating were subjected to *in vitro* drug release studies in different suitable dissolution media for 24 h to assess their ability in providing the desired lag time before drug release. The *in vitro* drug release studies were performed using a USP Type I dissolution apparatus. The dissolution medium for the first two h was 900 mL of 0.1 N HCl for the remaining period 6.8 pH phosphate buffer was used. The temperature of dissolution medium was maintained at 37±0.2°C. The tablet was introduced into the basket and was rotated at 50 rpm. In all experiments, an aliquot of 5 mL sample was withdrawn at predetermined time intervals and replaced with an equal volume of the fresh dissolution medium to maintain the sink condition. The samples were filtered and analyzed spectrophotometrically at λ_{max} of 230 nm for the percentage drug release. One tablet was used for each determination and the experiment was performed in triplicates.

2.6. *Drug concentration of the OCT, CB formulations and CCT*

In order to determine the concentration of losartan potassium present in all the tablets, 5 tablets were weighed and crushed to fine powder. The powder equivalent to 50 mg of drug was weighed out. The equivalent weight of drug was transferred into a 100 mL of volumetric flask and diluted with 6.8 pH phosphate buffer, the resulting solution was filtered. 1 mL was taken and diluted 10 times with 6.8 pH phosphate buffer. The absorbance of the resulting solution was measured at 230 nm and the drug concentration in the tablets was estimated from the regression equation.

2.7. *Compatibility studies*

Physical and chemical interaction or complexation throughout the formulation and compression process was carried out by the PXRD and FTIR.

2.7.1. *Powder X-ray diffraction (PXRD)*

PXRD was performed using a type D/Max-2400 diffractometer (Rigaku Instrument, Japan). The samples were exposed to CuKa radiation at 56 kV and 182 mA over the 2θ range from 3˚ to 45˚ in increments of 0.5˚/min every 0.04˚.

2.7.2. *Fourier Transform Infra Red (FTIR) spectroscopy*

The FTIR spectra of the different samples were recorded in an Infra Red spectrometer (Shimadzu, Japan) using KBr discs prepared from powdered samples. The spectrum was recorded in the region of 4000 to 400 cm^{-1}.

3. Results and Discussions

3.1. *Physicochemical parameters of the OCT, CB formulations and CCT of losartan potassium*

3.1.1. *Friability, hardness, disintegration time and drug content*

The results of the friability, tensile strength and disintegration test for OCT and the two CB of losartan potassium are presented in Table 3. Friability index is a measure of the ability of the tablet to withstand abrasion during packaging, handling and transportation. It was observed that the friability values for the OCT and the two CB formulations were < 0.6% while their tensile strength values were between 1.06-1.23 MN/m^2. However, there was no significant difference between these values ($p>0.05$). The DT values for the OCT and the two CB were less than 2 min. as against the stipulated official time of 15 min. (BPC 2002). More so, their drug concentrations were > 97% (Table 3).

Table 3. Physico-chemical parameters of core tablet and commercial tablets.

Formulations	Optimized core tablet	P1	P2
Drug concentration[a] (%)	99.1±1.5	99.3±0.35	99.0±0.13
Tensile strength[b] (MNm^{-2})	1.06±0.2	1.23±0.37	1.23±0.25
Friability[c] (%)	0.42±0.05	0.5±0.07	0.5±0.05
Disintegration time[d] (s)	20±0.02	90±0.4	85±1.0

a: mean ± s.d., n=5; b: mean ± s.d., n=5; c: mean ± s.d., n=10; d: mean ± s.d., n=6

Table 4. Physico-chemical parameters of compression coated tablets.

Formulations	LGK1	LGK2	LGK3	LGK4	LGK5	LGK6	LGK7
Drug concentration[a] (%)	101.1±1.5	99.8±1.1	101.5±0.9	99.8±0.60	100.5±0.55	98.9±1.40	100.6±1.20
Tensile strength[b] (MN/m^2)	1.06±0.5	1.14±0.10	1.23±0.15	1.06±0.70	1.14±0.30	1.14±0.25	1.23±0.55
Friability[c] (%)	0.28±0.01	0.11±0.05	0.12±0.06	0.2±0.02	0.26±0.05	0.17±0.02	0.19±0.05
Lag time[d] (h)	16.0±0.33	10.5±0.57	5.5±0.25	3.0±0.67	2.0±0.33	1.5±0.57	0.5±0.33

a: mean ± s.d., n=5; b: mean ± s.d., n=5; c: mean ± s.d., n=10; d: mean ± s.d., n=3

On the other hand the friability, hardness and drug content values for all the CCT (LGK1 to LGK7) are shown in Table 4. It was observed that the friability values were < 0.3% while their hardness values were between 1.06-1.23 MN/m^2. There was also no statistically significant difference between these values ($p>0.05$). The drug content values for all the CCT were > 98%.

3.2. *Drug release profile for the OCT and the two CB of losartan potassium*

The drug release profiles of the OCT and the two CB of losartan potassium are presented in Fig. 1. The release parameters obtained from these curves are also shown in Table 5. However, it can be observed that OCT gave a comparable release profile with the two CB. The value of the release parameters for OCT and the two CB (P1 and P2) are maximum release (m_∞), 93%, 84% and 79% respectively, while the time to attain maximum release (t_∞) was the same for all the formulations (i.e. 45 min). However, the dissolution rate (m_∞/t_∞) was observed to be 2.01, 1.87, 1.76 min^{-1} for OCT, P1and P2 respectively.

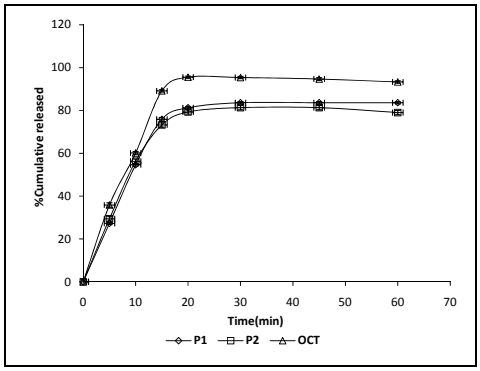

Fig. 1. Cumulative percentage of losartan potassium released from different tablets from phosphate buffer pH (6.8) where OCT is core tablet, P1 is Alsartan and P2 is Covance.

Table 5. Dissolution parameters {m_∞ (%), t_∞(min), m_∞ /t_∞(%min^{-1})} for OCT and two CB

Different Formulations	Optimized core tablet	P1	P2
m_∞ (%)	93	84	79
t_∞(min)	45	45	45
m_∞ / t_∞ (%min^{-1})	2.01	1.87	1.76

3.3. *Drug release profile for all the formulated CCT of losartan potassium*

The drug release profiles of all the formulated CCT (LGK1–L GK7) of losartan potassium are presented in Fig. 2. All the formulations had different lag times followed by a burst release of the losartan potassium. It was observed that the lag time for drug release from the compression coated tablets was increased as the concentration of the gum karaya: MCC was increased in the outer coat. For instance, at a polymer ratio of 100:0 (LGK1), 80:20 (LGK2), 60:40 (LGK3), 50:50 (LGK4), 40:60 (LGK5), 20:80 (LGK6) and as well as 0:100 (LGK7) their corresponding lag time values were 16, 10.5, 5.5, 3, 2, 1.5 and 0.5 h. There was a statistically significant difference between the lag time as the coating polymer increased ($p<0.05$). Previously, Katikaneni *et al*., [18] had reported that increase in tablet tensile strength is accompanied by a decrease in release rate, due to a decrease in

tablet porosity [18]. However, since there is no significant change in the tablet tensile strength of all the CCT formulations with increased concentration of the gum karaya as compression coating material (Table 4), hence the lag time of losartan potassium before burst release may not be due to tablet tensile strength. It may be attributable to the different ratio of the polymer coating used as outer layer for the preparation of the compression coated tablets.

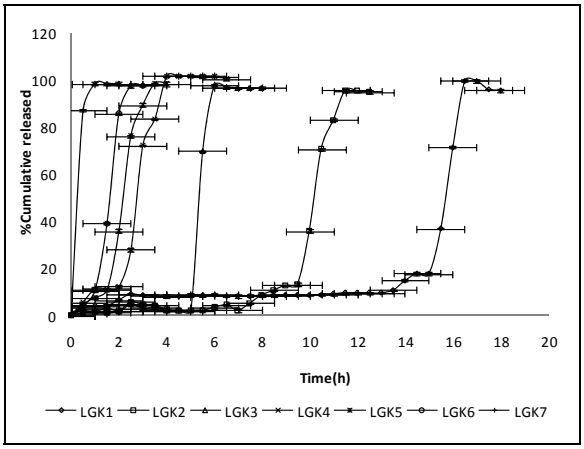

Fig. 2. Dissolution profile of the different compression coated tablets formulated with different ratios of karaya gum polymer as coating agent.

3.4. *Powder X-ray diffraction*

The powder X-ray diffraction patterns of the drug and excipients as well as the OCT are presented in Fig. 3. In spite of a series of smaller peaks, losartan potassium has distinct crystalline peaks at 2θ angles of 10.8˚, 13.6˚, 18.5˚ and 24.2˚ (Fig. 3a). However, in the gum karaya the intensity was markedly reduced which show that it was amorphous (Fig. 3b). These peaks were seen at the same position in the OCT (Fig. 3c). These observations concluded that no physical interaction between drug and polymer as well as the crystalline nature of the drug was unaltered.

3.5. *Fourier Transform Infra Red spectroscopy*

The FTIR spectra of the losartan potassium, gum karaya and the OCT are shown in Fig. 4. The characteristic -C-O-C stretch for losartan potassium at 1006 cm^{-1}, -C-Cl at 1259, 1357 cm^{-1}, -C=C stretch at 1605, 1494, 1460 cm^{-1}, -N=N stretch at 1576 cm^{-1}, -C-H stretch at 2871, 2929, 2956 cm^{-1} and -O-H stretch at 3205 cm^{-1} are observed. For gum karaya the characteristic alcoholic stretch at 3450 cm^{-1}, -C=O stretch peaks at 1731 cm^{-1}, –C=CH_2 at 1620 cm^{-1}, –C-O-C- asymmetric at 1254 cm-^{1}, symmetric at 1042 cm^{-1} due to acetyl groups of karaya polysaccharide are appeared. The absorptions at 1616 and 1423 cm^{-1} are

due to carboxylate groups of the uronic acid residues. All the characteristic peaks observed for both drug and excipient remained unchanged in LGK3. This observation ruled out the possibility of chemical interaction and complex formation between the losartan potassium and added excipient (such as gum karaya) during the production process.

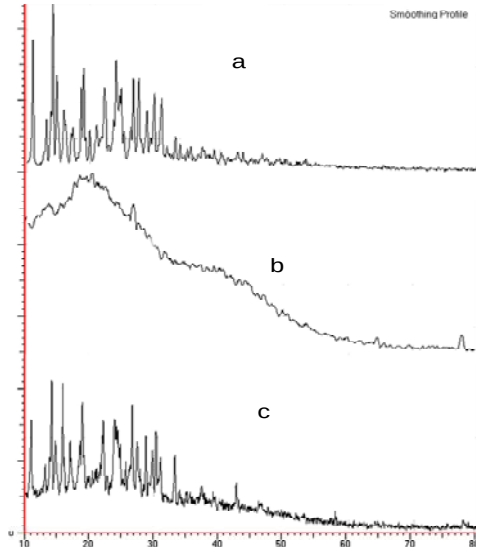

Fig. 3. Powder X-ray diffraction patterns of (a) losartan potassium (b) gum karaya and (c) CCT.

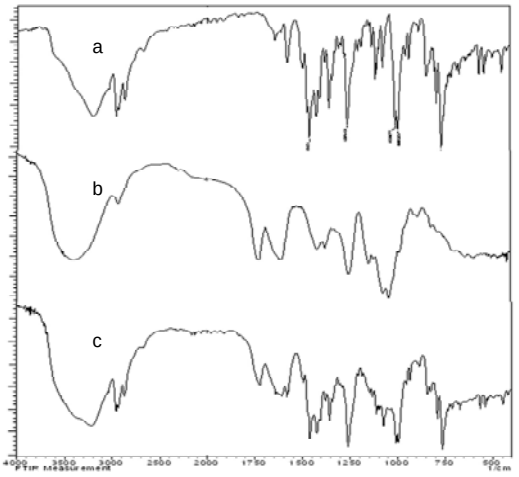

Fig. 4. FTIR of (a) Losartan potassium (b) gum karaya and (c) CCT.

4. Conclusions

Optimized chronotherapeutic drug delivery systems of losartan potassium using gum karaya with the ratio of 60:40 (gum karaya: MCC) has been developed. Formulation LGK3 with a predetermined lag time of 6 h before burst release of the drug from a press coated tablet was taken as the optimized formulation and it was observed that no modification and/ or chemical interaction throughout the process of formulation. Hence from the above study it was concluded that gum karaya is suitable for the development of chronotherapeutic drug delivery systems with losartan potassium.

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