Academíc Sciences

# International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491

Vol 4, Suppl 5, 2012

**Research Article** 

# *IN VITRO* EVALUATION OF ORAL TIMED RELEASE TABLET OF LOSARTAN POTASSIUM USING NATURAL GUM AND IT'S SOLID CHARACTERIZATION

# K LATHA<sup>\*1</sup>, M U UHUMWANGHO<sup>2</sup>, SA SUNIL<sup>3</sup>, MV SRIKANTH<sup>3</sup> AND KV RAMANA MURTHY<sup>3</sup>

<sup>1</sup>G. Pulla Reddy College of Pharmacy, Mehidipatnam, Hyderabad, 500 028, India, <sup>2</sup>Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Nigeria, <sup>3</sup>University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, India. Email: lathakukatil@gmail.com

#### Received: 17 Feb 2012, Revised and Accepted: 29 Mar 2012

# ABSTRACT

The purpose of this study is to investigate the release profile of a formulated oral timed- release tablet of losartan potassium using guar gum. Timedrelease tablets (TRT) containing losartan potassium in the core tablets were prepared by dry coating technique using different ratios of guar gum, PEG 6000,SSG mixture as the outer coating polymer. The following parameters are investigated: Tensile strength, friability, *in vitro* dissolution studies and drug content. The formulation was further characterized with powder X-ray diffraction (PXRD) and Fourier-Transform Infrared to investigate drug/or excipient modification and/or interaction. The results showed that the tensile strength values of all the TRT were between 1.06-1.08 MN/m<sup>2</sup> while their friability values were <0.34%. The TRT showed a lag time before burst release of losartan potassium. The lag time (less than 10% drug release) of TRT1, TRT2, TRT3, TRT4 and TRT5 were not definite. Of all the TRT formulations TRT6 showed a clear lag time of 6h before burst release of the drug (63.4%). Drug content of all the TRT was >99.5%. There was no physical and chemical interaction or complexation throughout the process of formulation and compression. Optimized chronotherapeutic drug delivery systems of losartan potassium (TRT6) using guar gum: PEG 6000: SSG with weight ratio 50:40:10 has been developed gave the required lag time of 5-7 hrs prior to the drug release. The dosage form administered before going to the bed and release was observed after 5-7 hrs of lag time that is in early hours of the morning where it needs to conteract the increased blood pressure due to the stimulation of angiotensin-aldosterone system. There was no modification and/ or interaction or complexation of the drug and added excipients throughout the process of formulation and compression.

**Keywords:** Losartan potassium, Guar gum, Polyethylene glycol 6000, Sodium starch glycollate, Powder X-ray diffraction, Fourier-Transform Infrared Spectroscopy.

#### INTRODUCTION

Losartan potassium is a highly specific, non-peptide angiotensin II antagonist indicated for treatment of hypertension [1]. It blocks the renin–angiotensin system by suppressing the effects of angiotensin II at its receptors [2]. It is a weakly acidic yellowish white crystalline powder with a  $pK_a$  of 4.9. It is a salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[2\_-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]

imidazole with a biological half life of 2-2.5h [2,3]. Its adult dose is 25mg, 50 mg and 100 mg once daily based on the requirement as prophylactic, for treatment and in severe conditions.

Oral timed–release tablets (TRT) are dosage forms used for chronotherapeutic drug delivery [4]. These systems consist of an inner core immediate release tablet embedded by an outer layer compartment, which contains either a hydrophilic, hydrophobic or a mixture of both polymers. The outer layer dissolves or disintegrates slowly to produce the drug after a predetermined lag time. The advantage of this production technique is that it is simple, inexpensive, capable to physically separate two incompatible drugs within the same dosage form, taste masking of bitter drugs and it is not hazardous to the environment, since it does not require the use of organic solvents in high amounts [5].

Guar gum is a nonionic polysaccharide obtained from the seeds of *Cyamopsis tetragonolobus, family Leguminosae*. Previously, it has been exploited as binder and disintegrant in solid dosage forms [6-8]. It has also been exploited as a hydrophilic matrix former in the formulation of an orally controlled release dosage forms [8-10]. Previously, Krishnaiah et al [11] has also investigated the influence of metronidazole and tinidazole on the usefulness of guar gum matrix tablets of albendazole as model formulation. It was reported that matrix tablets of albendazole containing 20% of guar gum has potential in targeting albendazole to colon in the treatment of helminthiasis.

Hence, the purpose of this study was to design an oral TRT of losartan potassium using guar gum in different weight ratios with PEG 6000 incorporated with a superdisintegrant in the outer coat in order to optimise the drug release in a predetermined lag time of 6 hrs. The influence of the PEG 6000 and superdisintegrant (SSG) in

modulating the rupture of the oral timed release tablet was investigated. The formulation was further characterized with powder X-ray diffraction (PXRD) and Fourier-Transform Infrared to investigate drug/or excipient modification and/or interaction.

# MATERIALS AND METHODS

#### Materials

Losartan potassium was received as a gift sample from Dr Reddy's Laboratory Pvt. Ltd, Hyderabad, India), Guar gum (LR grade) and sodium starch glycollate (SSG) were received as a gift sample from Aurbindo Pharma Ltd, Hyderabad, India. Avicel 112, Croscarmellose sodium (CCS), Polylvinylpovidone (PVP K30) were gift samples received from Aurbindo Pharma Ltd, Hyderabad, India. There were used as diluents, disintegrants and binders respectively, Polyethylene glycol 6000 (PEG 6000) was purchased from S.D. Fine Chemicals Ltd., Mumbai, India and used as channeling agent. Talc and magnesium stearate were purchased from S.D. Fine Chemicals Ltd., Mumbai, India 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. (P1 = ALSARTAN - 50mg, (Manufacturing date: May 2007 and Expiring date April 2010, Aristo Pharmaceuticals Ltd., India) and P2 = COVANCE-50 mg, Manufacturing date: August 2008 and Expiring date July 2011, Ranbaxy laboratories Ltd., India.)

#### Preparation of an optimised core tablet (OCT)

From preliminary studies in our laboratory, an optimized core tablet was formulated by using various concentrations and different types of diluents, disintegrants and binders. The drug, diluent, disintegrant and binder were weighed for a batch of 100 tablets as per formulae given in **Table 1** these were then passed through 710 nm transferred to a poly bag and blended for 5 minutes. To the homogeneous blend talc and magnesium stearate previously passed through 500 nm was added and blended for 2 minutes. The resulting blend was compressed with a rotary compression machine (Model Riddhi, Ahmedabad) to form a bi convex tablet with a diameter of 6mm, thickness 3.1±0.2mm and weight 106.5±0.5mg.

Latha et al.

Table 1: Composition of the core tablet

Ingredients	qty/tab	qty/100 tab
Losartan potassium	50 mg	5000 mg
Avicel 112	50 mg	5000 mg
CCS	2.5 mg	250 mg
PVP K 30	2.5 mg	250 mg
Mag.stearate	0.5 mg	50 mg
Talc	1 mg	100 mg
Total weight ( mg)	106.5 mg	10650 mg

# Table 2: Composition of the TRT

Ingredients (mg)	TRT1	TRT2	TRT3	TRT4	TRT5	TRT6
Guar gum	100	50	50	50	50	50
PEG 6000	0	50	46	44	42	40
SSG	0	0	4	6	8	10
Talc	1	1	1	1	1	1
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	208	208	208	208	208	208

TRT1-TRT6 were containing core tablet of losartan potassium 106.5 mg

# Preparation of timed-release tablets (TRT)

The required amount of PEG 6000 was melted in water bath at temperature of about  $60^{\circ}$ C which is higher than its melting point. Then required mixtures of guar gum and SSG were added to the molten PEG 6000 (See **Table 2**). This was allowed to cool and then screened through sieve size 500µm. Talc and magnesium stearate were added to the dried granules and passed through 125µm and blended for 2 minutes. Half the amount of polymer granules was placed into the die to make a powder bed. Then the core tablet was 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 (Model Riddhi, Ahmedabad) to form a bi convex tablet to a diameter of 9mm, thickness of  $4.1\pm0.2mm$  and average weights  $207\pm0.6mm$ .

### Physicochemical analysis of OCT, CB and TRT formulations

# Friability test

Ten tablets of each batch were placed in the drum of an Electro lab, Model EF2, Mumbai, India friabilator rotating at 25 rev per min for 4min. The percentage dust formed due to the impact was determined and taken as index of friability. The test was carried in triplicate.

#### **Disintegration test (DT)**

The method described in the Indian Pharmacopoeia [12] was followed using water maintained at  $37\pm2^{\circ}C$  as the disintegration fluid. Six tablets were placed in disintegration apparatus (Electro lab, Model, ED-2L Mumbai, India)) for each determination. It was carried out in triplicate and the mean results reported.

# 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 [13] as:

#### $T = 2P/\pi Dt(1)$

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 [14]. The mean values of the fracture loads were used to calculate the T values for the various tablets.

#### In vitro drug release studies for OCT, CB formulations and TRT

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

varying ratios of guar gum: PEG 6000: SSG in polymer coating were subjected to in vitro drug release studies in different suitable dissolution media for 24 hours 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 hours was 900 ml of 0.1N HCl for the remaining period 6.8 pH Phosphate buffer was used for TRT. The temperature of dissolution medium was maintained at 37  $\pm$  0.2 °C. The required release of the drug after a predetermined lag time of 5-7 hrs, by the time drug might be reaching to the distal part of intestine where pH is 6.8. So, dissolution was carried for the optimized core tablets in pH 6.8.

The tablet was introduced into the basket, and then lowered such that the lower end of the basket was 25 mm above from the base of the beaker and it was rotated at 50 rpm. In all experiments, an aliquot of 5 ml sample was withdrawn at pre determined 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  $\lambda_{max}$ , 230 nm for the percentage drug release. One tablet was used for each determination and the experiment was performed in triplicates.

# Drug content of the OCT, CB formulations and TRT

In order to determine the content of losartan potassium present in all the tablets, 5 tablets were weighed and crushed to fine powdered. 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 to 100 ml with pH 6.8 phosphate buffer, the resulting solution was filtered with Whatman no 3 filter paper. From this 1 ml was taken and diluted to 10 ml with pH 6.8 phosphate buffer. The absorbance of the resulting solution was measured at  $\lambda_{max}$ , 230 nm and the drug content in the tablets was estimated from the regression equation.

#### Powder X-ray diffraction (PXRD)

PXRD was performed using a type XRD-7000 diffractometer (Shimadzu, Japan). The samples were exposed to CuKa radiation at 56 kV and 182 mA over the 20 range from 0° to 80° in increments of  $0.5^{\circ}$ /min every 0.04°.

### Fourier Transform Infra Red (FTIR)

The FTIR spectrum of the different samples were recorded in an Infra Red spectrometer (Shimadzu, Model 84005, Japan) using potassium bromide discs prepared from powdered samples. The spectrum was recorded in the region of 4000 to 400 cm<sup>-1</sup>

# **RESULT AND DISCUSSION:**

# Physicochemical parameters of the OCT, CB formulations and TRT of losartan potassium

#### Friability, tensile strength, disintegration 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 <0.53% while their tensile strength values were between 1.06–1.10MN/m<sup>2</sup>. 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 15mins (IP 2007). More so, their drug contents were  $\geq$  99% (See **Table 3**).

On the other hand, the friability, tensile strength and drug content values for all the TRT (TRT1 to TRT7) are shown in **Table 4**. It was observed that the friability values were <0.34% while their tensile strength values were between 1.06-1.08 MN/m<sup>2</sup>. There was also no statistically significant difference between these values (p>0.05). The drug content values for all the TRT were >99 % (See **Table 4**).

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

Different Formulations	Optimised core tablet	P1	P2
Drug content (%)(n=5)	99.1±1.5	99.3±0.35	99.0±0.13
Tensile strength (MN/m <sup>2</sup> )(n=10)	1.06±1.2	1.10±1.36	1.10±1.2
Friability (%)(n=10)	0.42±0.05	0.51±0.07	0.53±0.05
DT (Sec)(n=6)	20±0.02	90±0.4	85±1.0

Note where P1 = ALSARTAN (Manufacturing date: May 2007 and Expiring date April 2010.) and P2 = COVANCE Manufacturing date: August 2008 and Expiring date July 2011.) **Table 4: Physico-chemical parameters of TRT** 

Different Formulations	TRT1	TRT2	TRT3	TRT4	TRT5	TRT6
Drug content (%)(n=5)	99.5±1.2	99.6±1.4	100±1.2	99.7±1.35	99.9±1.1	99.8±1.4
Tensile strength (MN/m <sup>2</sup> )(n=10)	1.06±0.27	$1.06 \pm 0.21$	1.08±0.32	1.06±0.12	$1.06 \pm 0.17$	$1.08 \pm 0.25$
m∞ (%)(n=5)	94.65±1.51	96.85±1.74	95.99±1.51	92.97±1.35	92.63±1.27	94.19±1.42
Friability (%)(n=10)	0.29±0.03	0.29±0.04	0.32±0.05	0.34±0.05	0.33±0.05	0.32±0.05
*						

# Table 5: Dissolution parameters $\{m_{\omega} (\%), t_{\omega}(min), m_{\omega} / t_{\omega}(\%min^{-1})\}$ for OCT and two CB

Different Formulations	Optimised core tablet	P1	P2
m∞ (%)	93	84	79
t∞(min)	45	45	45
m <sub>∞</sub> / t <sub>∞</sub> (%min <sup>-1</sup> )	2.01	1.87	1.76

# 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**. 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 ( $m_{\infty}$ ), 93%, 84%, 79% respectively while the time to attain maximum release ( $t_{\infty}$ ) was the same for all the formulations (i.e. 45 mins). The dissolution rate ( $m_{\infty}/t_{\infty}$ ) was observed to be 2.01% min<sup>-1</sup>, 1.87% min<sup>-1</sup>, 1.76% min<sup>-1</sup> for OCT, P1 and P2 respectively.



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

# Drug release profile for all the formulated TRT of losartan potassium

The drug release profiles of all the formulated TRT (TRT1–TRT6) of losartan potassium are presented in **Fig 2**. TRT1-TRT5 formulations did not show any clear lag times followed by a burst release of the losartan potassium. It was observed that the clear definite lag time followed by burst release was observed only when the disintegrant concentration was 10% w/w. The percentage amount of drug release in predetermined lag time of 6h duration was observed to be 12.3, 29.5, 38.5, 39, 48.1 and 63.5 for TRT1, TRT2, TRT3, TRT4, TRT5 and TRT6 respectively (See **Fig 2**). The reason for incorporating the PEG 6000 which is a water soluble polymer used previously to create channels in drug delivery systems [15], was to

enhance the wetting of the TRT and also modifying the barrier properties of the guar gum used as outer coating layer. The reason for incorporating the PEG 6000 which is a water soluble polymer used previously by researchers to create channels in drug delivery systems[16], was able to enhance the wetting of the TRT and also modified the barrier properties of the guar gum used as outer coating layer.

The incorporation of the PEG 6000 in the outer coat with guar gum improved the drug release by two fold but was not able to achieve the lag time with immediate release. Hence, super disintegrant (SSG) was incorporated in the other batches formulated (TRT3–TRT6). A clear predetermined lag time of 5 hrs followed by immediate release maximum up to 98% was observed 10% SSG to the guar gum-PEG.



Fig. 2: Dissolution profiles of the different Timed-release coated tablets formulation with weight different ratios of guar gum: PEG 6000: SSG as outer coat.

Hence, superdisintegrant (SSG) were incorporated in the other batches formulated (TRT3 - TRT6). At low concentrations of disintegrant a definite lag time was not achieved. A clear predetermined lag time of 6h followed by a burst release was observed only when the concentration of SSG was 10%w/w, with a maximum release of 98%. This burst release could be due to the presence of high concentration of the SSG (10%w/w) which resulted in the rupture of the TRT during dissolution test. Previously, Katikaneni et al., (1995)[17] had reported that increase in tablet tensile strength results in decrease in drug release rate from tablet formulations, due to a decrease in tablet porosity. Since there was no significant changes in the tablet tensile strength (p>0.05) of all the TRT formulations, hence the lag time of losartan potassium before burst release may be attributable to the different weight ratios of the outer coating layer. The aim of the present study was the release of the drug after a predetermined lag period of 5-7 hrs. This is required in certain disease conditions that follow circadian rythms. This formulation is administered at bed time and need to be delivered the drug after a lag time of 5-7 hrs to conteract the increased blood pressure due to the stimulation of angiotensin-aldosterone system at early hours of day.

Guar gum showed suitability for chronotherapeutic drug delivery system due to its high retarding effect for the drug release. Modulation of the release control up to 5-6 hrs followed by the immediate release within 1 hr was obtained with guar gum. As the concentration increased drug release was found to be decreased, whereas with low concentration it could not maintain the required lag time.

#### **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  $2\theta$  angles of 10.8°, 13.6°, 18.5° and 24.2° (Fig 3a). However, in the guar gum the intensity was markedly reduced which show that it was amorphous (Fig 3b). These peaks were seen at the same position in the optimized TRT (Fig 3c). From these observations we can conclude that the crystalline nature of the drug was maintained.

#### Fourier Transform Infra Red

In order to investigate if there is any interaction between added excipients and losartan potassium in the TRT, the FTIR of the losartan potassium, guar gum, and the optimised TRT were determined (See Fig 4a, b and c respectively). All the characteristic peaks observed for both drug and excipient remained unchanged and the spectra data was superimposed. This observation ruled out the possibility of chemical interaction and modification between the losartan potassium and added excipients during the production process.







Fig. 4: FTIR of (a) Losartan potassium, (b) Guar gum and (c) optimised TRT.

# CONCLUSION

Optimized chronotherapeutic drug delivery system of losartan potassium using guar gum: PEG 6000: SSG with weight ratio

50:40:10 has been developed gave the required lag time of 5-7 hrs prior to the drug release. The dosage form administered before going to the bed and release was observed after 5-7 hrs of lag time that is in early hours of the morning where it needs to conteract the

increased blood pressure due to the stimulation of angiotensinaldosterone system. There was no modification and/ or interaction or complexation of the drug and added excipients throughout the process of formulation and compression.

#### REFERENCES

- Carini DJ, Christ DD, Duncia JV, Pierce ME, In: Borchardt RT, Freidinger RM, Sawyer TK, Smith PL, (Eds.), Integration of Pharmaceutical Discovery and Development: Case Histories, Plenum Press, New York.1998, 29–56.
- 2. Randal AS, Ballard JM, Hwang TL, Sullivan CM, Photosensitized degradation of losartan potassium in an extemporaneous suspension formulation, J of Pharm and Biomed Analysis. 2006, 42: 411–422.
- 3. Indian Pharmacopoeia. Monograph of losartan potassium, volume 2, Government of India, Ministry of Health and Family Welfare published by the Indian Pharmacopoeia Commission, Ghaziabad, 2007, p1319.
- Vikram S, Srikanth K,Sheelpriya R, Abhay M, The essentials of chronopharmacotherapeutics, Int J Pharm Pharm Sci, 2012, 4(3): 1-8
- 5. Hadfield PJD, Holmes S, Yarwood RJ, The potential use of compression coating in the blinding of clinical trial supplies. Drug Dev Ind Pharm. 1987, 13: 877-1190.
- Wassel GM, Omar SM, Ammar NM, Application of guar flour and prepared guaran in tablet manufacture. J. Drug. Res. 1989, 18:1-8.
- 7. Rowe RC, Sheskey PJ, Weller PJ. Guargum. In: Hand Book of Pharmaceutical Excipients. 4th ed. London: Pharmaceutical Press and AAPS Pharm Sci Tech 2003, 271-273.

- 8. Baweja JM, Misra AN, Modified guar gum as a tablet disintegrant. Pharmazie. 1997, 52: 856-859.
- 9. Misra AN, Baweja JM, Modified guar gum as hydrophilic matrix for controlled release tablets. Indian Drugs. 1997, 34: 216-223.
- 10. Rajya LK, Indira MY, Vijaya KV, Design and evaluation of colon specific drug delivery of naproxen sodium using guar gum and crosslinked guar gum, Int J Pharm Pharm Sci, 2012, 4(1): 284-288.
- Krishnaiah YSR, Devi AS, Rao LN, Reddy PRB, Karthikeyan RS, Satyanarayana V, Guar gum as a carrier for colon specific delivery; influence of metronidazole and tinidazole on *in vitro* release of albendazole from guar gum matrix tablets, J Pharm Pharmaceut Sci. 2001, 4(3): 235-243.
- Indian Pharmacopoeia. Monograph of losartan potassium, volume 2, Government of India, Ministry of Health and Family Welfare published by the Indian Pharmacopoeia Commission, Ghaziabad, 2007, p1320.
- 13. Fell JT, Newton JM, Determination of tablet strength by diametral test. J Pharm. Sci. 1970, 59: 688-689.
- 14. Brook DB, Marshall K, Crushing strength of compressed tablets 1: comparison of testers. J Pharm Sci. 1968, 57: 481- 484.
- 15. Emeje MO, Kunle O, Ofoefule SI, Compaction Characteristics of Ethylcellulose in the Presence of Some Channeling Agents: Technical Note. AAPS Pharm Sci Tech. 2006, 7 (3): E1 E4.
- Wassel GM, Omar SM and Ammar NM. Application of guar flour and prepared guaran in tablet manufacture. J Drug Res. 1989, 18:1-8
- Katikaneni PR, Upadrashta SM, Neau SH, Mitra AK, Ethylcellulose matrix controlled release tablets of a watersoluble drug. Int J Pharm. 1995, 123: 119-125.