Tropical Journal of Pharmaceutical Research October 2011; 10 (5): 551-558

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v10i5.3

Research Article

Development of an Optimised Losartan Potassium Press-Coated Tablets for Chronotherapeutic Drug Delivery

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Abstract

Purpose: *To develop an optimised press-coated tablets of losartan potassium using an admixture of a hydrophilic polymer, hydroxypropylmethylcellulose (HPMC) and microcrystalline cellulose (MCC) in order to achieve a predetermined lag time for chronotherapy.*

Methods: *The press-coated tablets (PCT) containing losartan potassium in the inner core were prepared by compression-coating with HPMC 100KM alone and admixed with MCC as the outer layer in different ratios. The effect of the outer layer on the lag time of drug release was investigated. The parameters determined were tablet tensile strength, friability, drug content and in vitro dissolution. The optimised formulation was further characterized with Fourier-transform infrared spectroscopy (FTIR) and powder X-ray diffractometry (PXRD) to investigate any drug/excipient modifications/interactions.*

Results: *The tensile strength values of all the PCT were between 1.12 and 1.23MNm-^{2} and friability was < 0.36 %. The release profile of the press-coated tablet exhibited a distinct lag time before burst release of losartan potassium. Lag time was dependent on the ratio of HPMC/MCC in the outer shell. The lag time was from 0.5 to 18.5 h and could be modulated as it decreased as the amount of MCC in the outer layer increased. There was no modification or chemical interaction between the drug and the excipient.*

Conclusion: *Formulation LPP2, with HPMC/MCC of (30:70) in the outer shell and showing a predetermined lag time of 6 h prior to burst release of the drug from the press-coated tablet was taken as the optimized formulation.*

Keywords: *Losartan potassium, press-coated tablet, hydroxypropylmethylcellulose, microcrystalline cellulose, Fourier-transform infrared spectroscopy and powder X-ray diffraction.*

Received: 12 April 2011 *Revised accepted:* 22 September 2011

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INTRODUCTION

Hypertension is a chronic disorder present in over 90 % of all patients with cardiovascular (CV) disease and is a major risk factor for CV disease which sometimes leads to sudden death [1,2]. Treatment of this disease condition occurring in the early hours is not convenient by using conventional immediate release dosage form. Hence, chronotherapeutic drug delivery system (ChDDS) may be useful for such patients since the drug is released at a predetermined lag time. Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match the rhythms of disease, in order to optimize therapeutic outcomes and minimise side effects [3,4]. It is designed such that drug release is modulated in a manner that ensures that maximum concentration (C_{max}) of the drug is reached at the maximum intensity of the disease condition. C_{max} of the drug is normally reached within 1 - 2 h for many conventional dosage forms and this may not match with the maximum intensity of the disease state. Hence, for effective therapy, it is always advisable to provide maximum drug concentration at maximum intensity of disease condition.

Losartan potassium is a highly specific, non-peptide angiotensin II antagonist indicated for the treatment of hypertension [5]. It blocks the renin–angiotensin system by suppressing the effects of angiotensin II at its receptors [6], It is a weakly acidic yellowish white crystalline powder with a pK_a of 4.9. Chemically, it is 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[2_-(1H-tetrazol-5-yl)biphen ly l-4-yl)methyl]imidazole with a biological half life of 2-2.5 h [6,7]. The adult dose is 25 mg, 50 mg and 100 mg once daily (based on requirement) for prophylaxis, normal treatment and severe conditions.

Press-coated tablets (PCT) are formulations comprising of an inner core that contains the active pharmaceutical ingredient and surrounded by an outer layer of polymer and/or excipients that dissolves or disintegrates slowly to produce lag time. The advantages of this technique include low equipment cost, short processing time and reduced production steps. It does not require the use of a large amount of organic solvents compared with the spray coating which needs a high amount of solvent for dissolving the drug or polymer used for coating, besides the solvents are often expensive and hazardous to the environment [8].

The purpose of the present study was to modulate the predetermined time lag of PCT of losartan potassium using an admixture of hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC) as excipient in the outer layer.

EXPERIMENTAL

Materials

Losartan potassium was received as a gift from Ipca Laboratories Pvt. Ltd, Mumbai, India. Hydroxy propyl methyl cellulose HPMC 100 KM (Aurbindo Pharma Ltd, Hyderabad, India), MCC, Croscarmellose sodium (CCS), Polylvinylpyrrolidone (PVP K30) were received free of charge from Aurbindo Pharma Ltd, Hyderabad, India and were used as diluent, disintegrant and binding agent, 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 immediate release formulations of losartan potassium tablets (CT) P1 and P2 were purchased from the market. Their manufacturing and expiring dates, and batch numbers were recorded. The manufacturing dates of Alsartan (P1) and Covance (P2) are May 2007 and August 2008, respectively, while their corresponding expiring dates are April 2010 and July 2011.

Preparation of an optimised core tablet (OCT)

From preliminary studies in our laboratory, an optimized core tablet was formulated using various concentrations and different types of diluents, disintegrants and binders. The composition is shown in the footnote of Table 1. The ingredients were then passed through a sieve of 710 µm aperture size, transferred to a poly bag and blended for 5 min. Talc and magnesium stearate, passed through a sieve of 500 µm aperture size before weighing, were added to the blend and mixed for 2 min. The resulting blend was compressed with a rotary compression machine (Model Riddhi, Ahmedabad, India) to form a 6 mm biconvex tablet. The mean weights of the tablets were 106.5 ± 3.2 mg.

Preparation of press-coated tablets (PCT).

The HPMC 100KM and MCC were accurately weighed as required for a batch of 100 tablets as per formulae given in Table 1. A solution of 7.5 % PVP in hydro alcoholic mixture of iso propyl alcohol and water in the ratio of 70:30 was used to wet mass the HPMC 100KM and MCC. The wet mass was pressed through a sieve of 710µm aperture size and dried for 2 hrs at 45^0C in a hot air oven (Tempo Instruments and equipments Pvt Ltd). The dried mass was again screened through a sieve of 500 µm aperture size. Talc and magnesium stearate were added to the dried granules and passed through a sieve of 500 µm aperture size and blended for 2 minutes. Half the amount of polymer granules was placed inside the die to make a powder bed. 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 at a constant compression force with a rotary compression machine (Model Riddhi, Ahmedabad) to form a bi convex tablet with a diameter of 9mm and weight 208±0.61mg.

Friability test

Five tablets were placed in the drum of a friabilator (Electro labs, Model EF2, Mumbai, India) rotating at 25 rpm for 4 min. The percentage dust formed due to the impact was determined and taken as index of friability. The test was carried out in triplicate.

Disintegration test (DT)

The method described in the British Pharmacopoeia [9] was followed using water maintained at 37±2 ℃ as the disintegration fluid. Six tablets were placed in the disintegration apparatus (Electrolab, 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 [10] as in Eq 1.

$T = 2P/\pi Dt$ …… (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 a Monsanto hardness tester (Tab Machines, Mumbai, India), using the procedure of Brook

Table 1: Composition of the press-coated tablets (PCT)

Ingredient (mg)	LPP 1	LPP2	LPP 3	LPP4	LPP5
HPMC 100 KM	0	30	50	70	100
MCC	100	70	50	30	0

Note: *Each tablet core contained losartan potassium (50 mg), Avicel (50 mg), CCS (2.5 mg), PVP K 30 (2.5 mg), magnesium stearate (0.5 mg), Talc (1mg) HPMC 100KM:MCC ratio in the outer coat layer LPP1 (0:100), LPP2 (30:70), LPP3 (70:30), LPP4 (100:0).*

and Marshal [11]. The mean values of the fracture loads were used to calculate T values for the various tablets.

In vitro drug release studies

OCT and two different CT formulations were subjected to *in vitro* drug release in 900 ml of 6.8 pH phosphate buffer for 90 min. while the PCT formulations were also subjected to *in vitro* drug release sequentially in two different suitable dissolution media to assess their ability to provide the desired lag time before drug release. USP Type I dissolution apparatus (Electrolab, Model TDT-08l, Mumbai, India) was used. The dissolution medium for the first 2 h was 900 ml of 0.1M HCl (pH 1.2) and continued in phosphate buffer (pH 6.8) for the next 22 h. The temperature of dissolution medium was maintained at 37 ± 0.2 ℃ and the basket was rotated at 50 rpm. An aliquot of 5 ml was withdrawn at predetermined time intervals and replaced with an equal volume of the fresh dissolution medium to maintain sink conditions. The samples were filtered through a 0.45 μm cellulose acetate filter and analyzed at λ_{max} of 230 nm, for the percentage drug release using an Elico SL 210 UV-Visible double beam spectrophotometer. One tablet was used for each determination and the experiment was performed in triplicates.

Drug content determination

In order to determine the content of losartan potassium, 5 tablets were weighed and crushed to fine powder. The powder equivalent to 50 mg of drug was weighed out, transferred to a 100 ml volumetric flask and made up the volume with phosphate buffer (pH 6.8).The resulting solution was filtered and 1ml of it diluted to 10 ml with phosphate buffer. The absorbance of the resulting solution was measured at 230 nm using a spectrophotometer and the drug content was computed.

Fourier transform infra red (FTIR) studies

The FTIR spectrum of the different samples were recorded with 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^{-1}.

Powder X-ray diffraction (PXRD)

PXRD was performed using type XRD-7000 diffractometer (Shimadzu, Japan). The samples were exposed to Cu Ka radiation at 56 kV and 182 mA over the 2-theta range from 0˚ to 80˚ in increments of 0.5^0/min.

Statistical analysis

The data obtained were subjected to Student t-test to test for significance of difference between paired data and $p > 0.05$ was taken as significant. Origin 8 software package was used for the analysis.

RESULTS

Physicochemical parameters of the formulations

The friability values (%) for OCT and the two CT formulations, were 0.42 ± 0.05 (OCT), 0.51 ±0 .07 (P_1) and 0.53 ± 0.05 (P_2) respectively, while their corresponding tensile strength was 1.06 ± 1.2, 1.10 ± 1.36 and 1.10 ± 1.2 $MNm^{-2.}$. DT for OCT and the two CT were 2.0 ± 0.02, 9.0 ± 0.4, and 8.5 ± 1.0 min, respectively, and their drug content 99.1 ± 1.5, 99.3 ± 0.35 and 99.0 ± 0.13 %, respectively. On the other hand, the friability (%) of PCT, i.e., LPP1 to LPP5, was 0.33 ± 0.05, 0.30 ± 0.05, 0.35 ± 0.05, 0.36 ± 0.04 and 0.32 ± 0.04; tensile strength 1.12 ± 0.23, 1.23 ± 0.64, 1.23 ± 0.25, 1.12 ± 0.18 and 1.12 ± 0.36 MNm^{-2}; and drug content 99.9 ± 1.36, 99.58 ± 1.49, 99.86 ± 1.18, 99.78 ± 1.18 and 99.5 ± 1.25 %.

Drug release profile of standard losartan potassium formulations

The drug release profiles of the OCT and the two CT formulations are presented in Fig 1. The release parameters derived from the curves are shown in Table 2. It was observed that OCT showed comparable release profile with those of the two CT. For OCT and the two CT (P1 and P2) maximum release (m_∞) was 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 2.01, 1.87 and, 1.76 % min^{-1} for OCT, P1and P2, respectively. Overall, there was no significant difference between the release data of OCT and P1, OCT and P2 ($p > 0.05$).

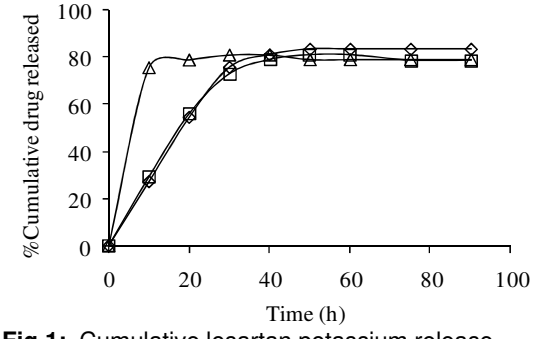

Fig 1: Cumulative losartan potassium release from OCT (Δ), P1 (◊), P2 (□) tablet formulations in phosphate buffer (pH 6.8).

Table 2: Dissolution parameters {m_∞ (%), t_∞ (min), m_∞/t_∞(%min^{-1})} for OCT and two CT (P1 and P2)

Formulation	OCT	P1	P2
m_∞ (%)	93	84	79
t_∞(min)	45	45	45
m_∞ / t_∞ (%min^{-1})	2.01	1.87	1.76

Drug release profile of test PCT losartan potassium formulations

The drug release profiles of the test PCT (LPP1 – LPP5) formulations of losartan potassium are shown in Fig 2. They indicate that losartan potassium release from the press-coated tablet exhibited a unique lag time before burst release. Generally, lag time increased as the amount of HPMC100KM in the outer layer increased. For instance, lag time of the formulations (with ratios of HPMC100KM: MCC as the outer coat) was 5.5, 9.5, 14.0 and 18.5 h for LPP2 (30:70), LPP3 (50:50) LPP4 (70:30) and LPP5 (100:0), respectively. The longest time lag (18.5 h) was for losartan potassium when only HPMC100KM was used.

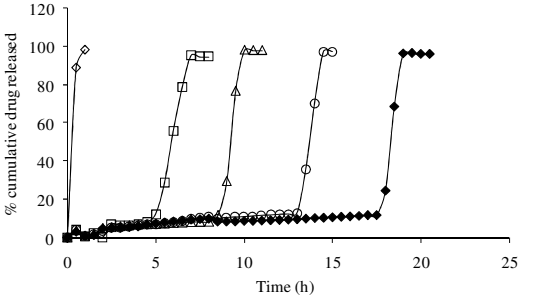

Fig 2: Cumulative losartan potassium release from LPP1 (◊), LPP2 (□), LPP3 (Δ), LPP4 (O), LPP5 (♦) tablet formulations in phosphate buffer (pH 6.8)

FTIR spectra

The spectra obtained are shown in Fig 3. All the characteristic peaks observed separately for both the drug and excipient (Fig 3a and b, respectively) remained unchanged in the optimised PCT formulation (Fig 3c).

Powder x-ray diffraction

The powder x-ray diffraction patterns of the drug and polymer (HPMC 100KM) as well as the optimized PCT are presented in Fig 4. Losartan potassium showed distinct characteristic crystalline peaks at 2θ angles of 11.5, 14.5, 19.5 and 24.2^0 (Fig 4a). On the other hand, HPMC 100KM showed no characteristic peaks which indicates that it is amorphous (Fig 4b). These peaks remained unchanged in the optimized PCT formulation (Fig 4c).

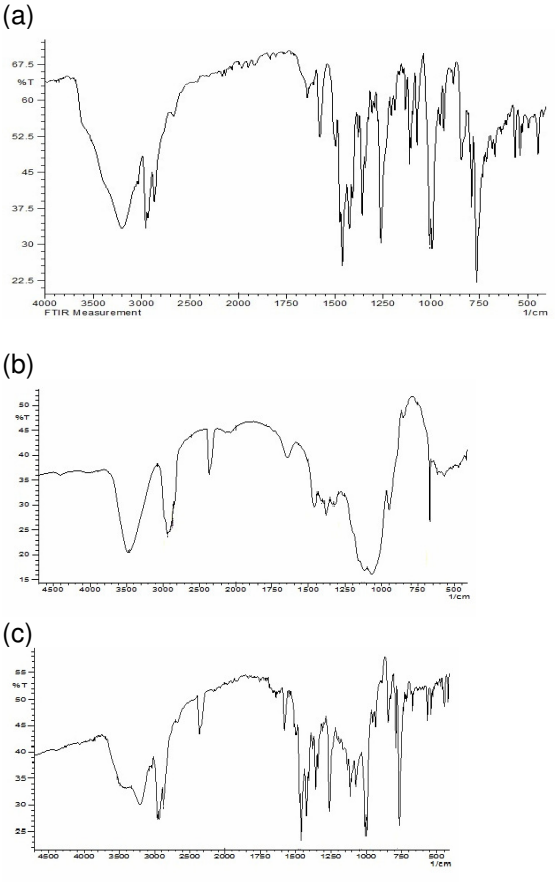

Fig 3: FTIR spectra of (a) losartan potassium, (b) HPMC 100KM and (c) press-coated tablet (PCT).

DISCUSSION

Physical properties of tablet

Friability is a measure of the ability of the tablet to withstand abrasion during packaging, handling and transportation. The friability values for all the formulations (OCT, two CT and optimised PCT) met the British Pharmacopeia (BP) requirements [9].

Drug release and lag time

It is well known that tablet tensile strength can affect the release rate of drug [12]. Previously, Katikaneni et al had reported that increase in tensile strength is accompanied by a decrease in release rate, due to a decrease in tablet porosity [13]. However, since there is no significant difference ($p > 0.05$) in tablet tensile strength among all the PCT formulations, it seems therefore that the lag time of losartan potassium release before burst release may be due to the varying ratio of HPMC:MCC blend used as the outer layer.

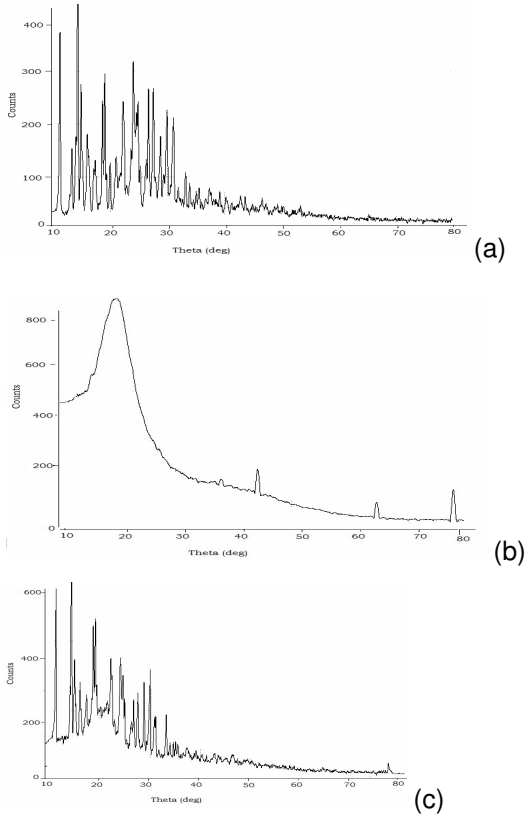

Fig 4: Powder x-ray diffraction pattern of (a) losartan potassium, (b) HPMC 100KM and (c) PCT formulation

Oral controlled-release formulations are designed to modify drug release in order to optimize drug therapy and hence improve patient's compliance. Of recent, researchers have focused on designing oral timed-release drug delivery systems for the treatment and/or management of diseases which follow circadian rhythm [14]. Hence, medications needed for the treatment and/or management of such disease conditions should be

administered at the necessary time to maintain a therapeutic blood level in the body system.

MCC was admixed with HPMC100KM to modulate the lag time and hence control the disintegration of the PCT. Drug release from OCT which did not have the outer layer was complete within 45 min, since there was no barrier to delay dissolution. Hydroxypropyl methylcellulose (HPMC) forms a firm gel but does not hydrate quickly while MCC is a good disintegrant and acts by a wicking mechanism. Hence, the drug was immediately released from the tablet core after the rupture of the surrounding outer layer containing MCC alone and admixture of HPMC100KM and MCC. This could be due to the pressure build-up within the PCT. This pressure built up might be attributed to the influx of dissolution medium by wicking effect due to the presence of MCC in the outer layer. This suggests that MCC might possibly be acting as a pore-forming agent in the outer layer rather than as a disintegrant, thus enhancing the penetration of water before rupturing the surrounding outer layer. The reason for the prolonged lag time (18.5 h) for the PCT prepared with HPMC100KM alone as the outer shell might be attributed to the high gelling effect of HPMC100KM which prevented the rapid influx of fluid into the outer layer that could have caused the rupture of the PCT to bring about burst release.

FTIR results ruled out the possibility of chemical interaction and complex formation between the losartan potassium and HPMC during the production process. Similarly, x-ray diffractograms also showed that the crystalline nature of the drug was maintained even after formulating it with HPMC. .

CONCLUSION

The findings of this work indicate that the time lag of press-coated losartan potassium tablets can be modulated from 5.5 to 14 h when MCC was blended with HPMC 100KM in the outer layer of the tablet. Formulation LPP2 with a lag time of 6 h before burst release of the drug from the press-coated tablet was taken as the optimized formulation. Losartan potassium showed no observable physical and/or chemical interactions with HPMC.

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