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Development and evaluation of sustained release matrix tablets of losartan potassium

U. Chandrasekhar[1], V. Viswanath[1, 2]*, B. Narasimha Rao[1], K. Gnana Prakash[1]

1. Dept. of Pharmaceutics, P. Rami Reddy Memorial College of Pharmacy, Prakruthi Nagar, Utukur, Kadapa, A.p.
2. Associate Professor, Dept. of Pharmaceutics, P. Rami Reddy Memorial College of Pharmacy, Prakruthi Nagar, Utukur, Kadapa, A.p.

Corresponding author: V. Viswanath
Email address: viswanathprrm@gmail.com
Address: Dept. of Pharmaceutics, P.Rami Reddy Memorial College of Pharmacy, Prakruthi Nagar, Utukur, Kadapa-516003, Andhra Pradesh, India.

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ABSTRACT:

The objective of the present study was to develop a sustained release matrix tablets of Losartan potassium, an anti hypertensive drug. The sustained release tablets were prepared by wet granulation and formulated using different drug and polymer ratios. Hydrophilic natural polymers like xanthan Gum (XG), guar gum and cellulose were used. Compatibility of the drug with various excipients was studied. The compressed tablets were evaluated and showed compliance with Pharmacopoeial limits. Formulation was optimized (F2) on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced matrix tablets with optimum hardness, consistent weight uniformity and friability. All tablets but one exhibited gradual and near completion sustained release for losartan potassium and 90.88% released at the end of 12h. The results of dissolution studies indicated that formulation F2 (drug to polymer 1:2) is the most successful of the study and exhibited drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio. Applying exponential equation, all the formulation tablets (except F2) showed diffusion-dominated drug release. The mechanism of drug release from F2 was diffusion coupled with erosion.

1. Introduction

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient's convenience, it is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials. The most commonly used method of modulating the drug release is to include it in a matrix system (Sankula et al., 2014; Raghavendra et al., 2013; Shailesh et al., 2013).

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 a plasma elimination half-life ranging from 1.5 to 2.5 hours. Administration of Losartan potassiumin a sustained release dosage form with dual release characteristics i.e., burst release followed by an extended release over 12 h, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration (Mohanty et al., 2012; Azharuddin et al., 2011).

2. Materials and method:

Losartan potassium as gift samples was recieved from Chandra lab, HYD India Pvt Ltd. Xanthan gum, guar gum was received as gift samples from Chandra lab,

HYD India Pvt Ltd. Micro Crystalline Cellulose, Poly Vinyl Pyrolidine as gift sample was received from Central drug lab, Bangalore. Isopropyl alcohol, Magnesium stearate, Talc as gift samples taken from Chandra lab, HYD India Pvt Ltd.

2.1 preparation of losartan potassiumby wet granulation

Step 1: Weighing and Blending - the active ingredient and disintegration agents were weighed and mixed.
Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. The liquid solution can be either aqueous based or solvent based. In this formulation the binding solution is pvp.
Step 3: Screening the damp mass into granules.
Step 4: Drying the granules (in hot air oven at 60^0C for one hour).
Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size which will allow even fill in the die cavity.
Step 6: Lubrication - A dry lubricant, gliding agent is added to the granules either by dusting over the spread-out granules or by blending with the granules. It reduces the friction between the tablet and the walls of the die cavity.
Step 7: Tableting: Last step in which the tablet is fed into the die cavity and then compressed between a lower and an upper punch. 7.5mm size punches were used for punching tablets.

Table 1: Formulation of Losartan potassium matrix tablet by using different types of natural polymers (%w/w)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Xanthan gum	50mg	100mg	150mg	-	-	-	-	-	-
Guar gum	-	-	-	50mg	100mg	150mg	-	-	-
Cellulose	-	-	-	-	-	-	50mg	100mg	150mg
MCC	225mg	175mg	125mg	225mg	175mg	125mg	225mg	175mg	125mg
PVP	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Magnesium stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Total weight	350mg	350mg	350mg	350mg	350mg	350mg	350mg	350mg	350mg

3. Results and discussion:

3.1 Compatibility testing of drug with polymer Fourier transform infra-red (FTIR) spectroscopy

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Losartan potassium was determined on fourier transform infrared spectrophotometer using KBr dispersion method. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using Parkin elmer- Pharmaspec-1 FTIR spectrophotometer (Bharathi et al., 2015).

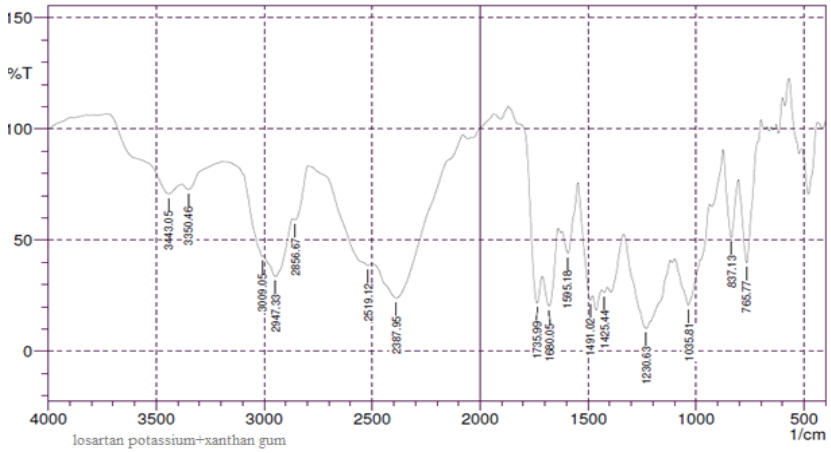

Fig. 1: FTIR for Losartan potassium+ Xanthan gum

3.2 Evaluation of sustained release tablets

The prepared sustained release tablets were evaluated for dimension (Diameter and Thickness) using 6 tablets (Vernier calipers), uniformity of weight using 20 tablets (Shimadzu BL-220H analytical balance), hardness using 6 tablets (Monsanto hardness tester) and friability using 20 tablets (Roche type friabilator) (Addanki Gopikrishna et al., 2016; S. Ullas et al., 2016).

Table 2: Physical properties of losartan potassium sustained release tablets

Formulations	Diameter* (mm)	Thickness* (mm)	Weight variation **(mg)**	Hardness* (kg /cm^2)	Friability (%)	Drug content* (%)
F_1	10.05±0.030	4.45±0.11	351±5	5.1 ± 0.12	0.191	97.00±0.24
F_2	10.06±0.040	4.50±0.04	350±5	5.5 ± 0.24	0.149	98.90±0.22
F_3	10.04±0.030	4.49±0.05	354±5	5.8 ± 0.21	0.146	97.86±0.34
F_4	10.02±0.030	4.45±0.12	345±5	5 .2± 0.23	0.149	98.75±0.32
F_5	10.02±0.054	4.46±0.03	347±5	5.9 ± 0.12	0.145	96.26±0.46
F_6	10.05±0.064	4.54±0.23	351±5	6.1 ± 0.14	0.191	98.45±0.26
F_7	10.07±0.022	4.52 ±0.2	352±5	5.2 ± 0.18	0.193	98.00±0.28
F_8	10.05±0.035	4.51±0.12	349±5	5.4 ± 0.22	0.146	99.72±0.30
F_9	10.04±0.059	4.53 ±0.3	348±5	6 .1± 0.21	0.191	98.82±0.34

3.3 Drug content of Losartan potassium

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar, an accurately weighed quantity of powder equivalent to 20 mg of drug was transferred to a 100ml volumetric flask. Few ml of water was added and shaken for 15 min. Volume was made up to 100 ml with distilled water. The solution was filtered through whatmann filter paper (No.41). 5 ml of the filtrate was diluted to 100 ml with 0.1N HCl. Then absorbance of the resulting 10 µg/ml solution was recorded at 234 nm (A. Rajendra et al., 2012).

3.4 *In-Vitro* dissolution studies

The *in vitro* dissolution was carried out using USP dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India). The tablets were placed in the 0.1N hydrochloric acid for first 2 hours and pH 6.8 phosphate buffers for next 8 hours respectively, then the apparatus was run at 37°C ± 0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution medium. The 5 ml aliquots were withdrawn at intervals of 1, 2, 4, 6, 8, 10, 12 hours and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through whatmann filter paper (No.41). 5 ml of sample was diluted to 10 ml 0.1N hydrochloric acid for first 2 hours and then with pH 6.8 phosphate buffers for next 10 hours and absorbance was measured at 205.5 nm using a Shimadzu-1700 UV spectrophotometer10. Drug concentrations in the sample were determined from standard calibration curve. The release data were calculated by using PCP disso V3 software (Wadher et al., 2011; Hareesh et al., 2015).

3.5 Drug Release Kinetic Study:

The release data analysis was carried out using the different kinetic models. The Regression coefficient (R^2) values of different kinetic models are tabulated in table. This indicated that the release data of best foumulation [F2] showed best fitting to Korsmeyer model kinetics. The mechanism of Losartan potassium release is non-fickian diffusion for F2 formulations (S.Ullas et al., 2016).

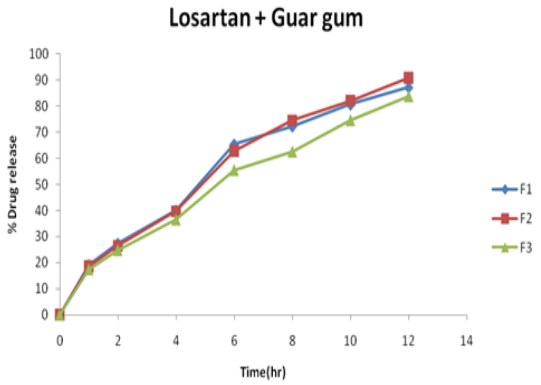

Fig.2: Dissolution for losartan potassium with guar gum

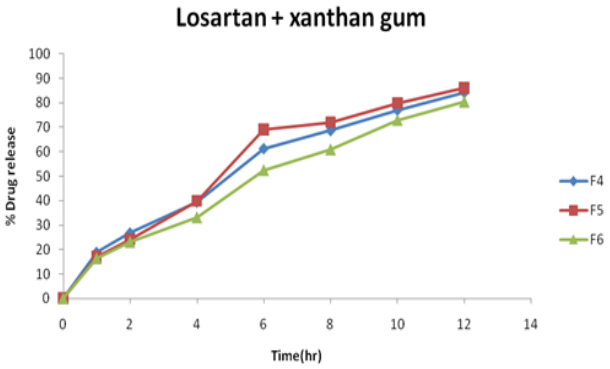

Fig. 3: Dissolution for losartan potassium with xanthan gum

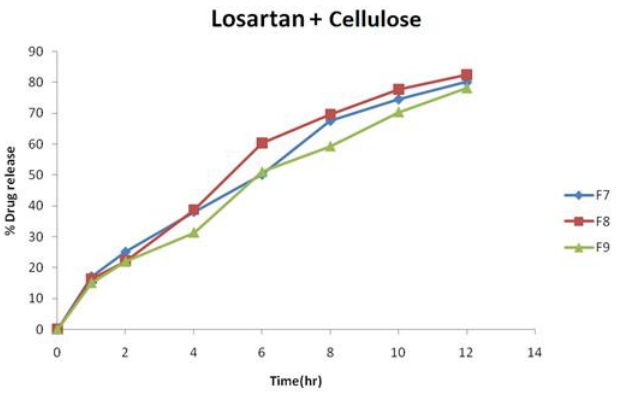

Fig. 4: Dissolution for losartan potassium with cellulose

Table 3: **Release kinetics of formulation F2**

Formulation	Zero order R^2 value	First order R^2 value	Higuchi R^2 value	Korsmeyer peppas	
				R^2 value	"n"value
F-2	0.964	0.981	0.976	0.987	0.670

Table 4: **Release rate kinetics to dissolution data for optimised formulation**

Time(hrs)	Cumulative % drug release	Log % drug unreleased	Log t	SQRT	Log Cum % release
0	0	0	0	0	0
1	18.64	1.910411	0	1	1.270446
2	26.46	1.866524	0.30103	1.414214	1.42259
4	39.73	1.780101	0.60206	2	1.599119
6	62.84	1.570076	0.778151	2.44949	1.798236
8	74.42	1.407901	0.90309	2.828427	1.87169
10	82.92	1.232488	1	3.162278	1.918659
12	90.42	0.981366	1.079181	3.464102	1.956265

4. Conclusion:

From the above results we can conclude that Losartan potassium was formulated with different types of natural polymers like guar gum, xantham gum and cellulose. The results of dissolution studies indicated that formulation F2 (drug to polymer 1:2) is the most successful of the study, exhibited drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing the polymer ratio.

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Conflict of Interest:

Authors have no conflict of interest from any point of view.

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