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Regular Article

Formulation and evaluation of controlled release matrix tablets of antihypertensive drug using natural and synthetic hydrophilic polymers

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The present study is to prepare and evaluate controlled release matrix tablets of Losartan potassium using natural and synthetic polymers. Tablets were prepared by direct compression method using different drug: polymer concentration. Fourier Transform Infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) study revealed no chemical interaction between drug and polymers used. Precompression and postcompression parameters complied with pharmacopoeial limit for the tablets. *In-vitro* release studies was performed and the results indicates that matrix tablet (F9) containing 50% w/w blend of natural and synthetic polymer has better controlled release for a period of 24 h.

Keywords: Losartan potassium, Natural gum, Synthetic polymer, Controlled release.

Controlled release dosage form covers a wide range of prolonged action formulations which provides continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance. Losartan potassium (Johnston 1995) is widely used in the treatment of hypertension, delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes (en.wikipedia.org/wiki/ losartan _potassium 2011), and microalbuminuria (>30 mg/24 h) or proteinuria (>900 mg/24 h). Developing oral controlled release matrix tablets for highly water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets (Sundaramoorthy 2008). As the fluid or media penetrates the matrix tablet, the polymer swells and drug diffuses from the system at a rate determined by nature and composition of polymer. A hydrophilic polymer from synthetic origin such as Hydroxy propyl methyl cellulose K4M (HPMC K4M) and from natural origin such as xanthan gum was used to develop controlled release matrix tablets of losartan potassium. Tablets were prepared by direct compression with alone and combination of polymers.

Materials and Methods

Losartan potassium was a gift sample from M/S Vijashree chemicals. Pvt. Ltd.

Hyderabad, Hydroxypropylmethylcellulose K4M (HPMC K4M) was a gift sample from Colorcon. Ltd. Goa, Xanthan gum (XG) was a gift sample from Krystal colloid Ltd. Mumbai, Microcrystalline cellulose (MCC) and Polyvinyl pyrolidone were gift samples from S.D. Fine. Pvt. Ltd. Mumbai and all the other chemicals used in the formulations were of analyltical grade.

Preparation of Losartan potassium matrix tablets

The controlled release matrix tablets of losartan potassium were prepared by the direct compression method. The drug, polymers and other excipients (batch size 50 tablets) were passed through sieve # 80. The controlled release tablets containing drug, matrix materials, diluents, binder and lubricants were mixed uniformly and compressed on 10 station tablet machine using 8 mm round and flat punches with hardness between 5-7 kg cm^{-2} (**Table 1**).

Preformulation studies of losartan potassium

FTIR study

The compatibility between drug and polymers was detected by IR spectra obtained on Shimadzu 8400, Japan. The pellets were prepared on KBr- press (startech lab, India). The spectra were recorded over the wave number range of 4000 to 500 cm^{-1} (**Fig 1**).

Table 1. Composition of Losartan potassium matrix tablets

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	80	80	80	80	80	80	80	80	80
XG	160	180	200	-	-	-	80	90	100
HPMC K4M	-	-	-	160	180	200	80	90	100
MCC	132	112	92	132	112	92	132	112	92
PVP	20	20	20	20	20	20	20	20	20
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total	400	400	400	400	400	400	400	400	400

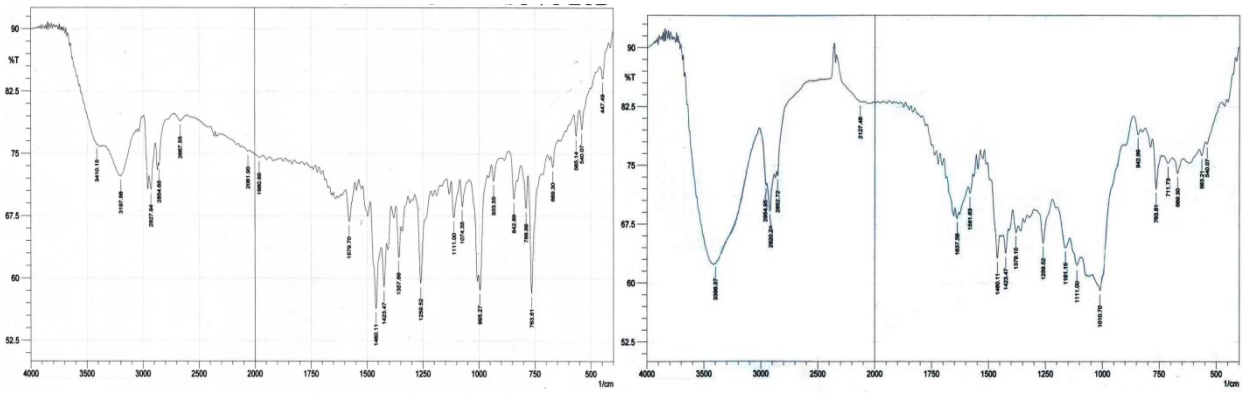

Fig 1. FT-IR spectra of Plane losartan potassium and F-9.

DSC study

Further the compatibility between drug and polymer was detected by DSC study. Thermograms were obtained by using a differential scanning calorimeter (NETZSCH, DSC 200PC, Japan) at a heating rate 10^{o} C/min over a temperature range of 35-250^{o} C. The sample was hermetically sealed in an aluminium crucible. Nitrogen

gas was purged at the rate of 10 ml/ min for maintaining inert atmospheres (**Fig 2**).

Identification

The drug was identified by the light absorption in the U.V. range of 200-400 nm. The absorbance's of drug solutions were 0.557 and 0.432 respectively for pH 1.2 and pH 6.8 at λmax 205.0 nm. This was in accordance with reported values (**Table 2**).

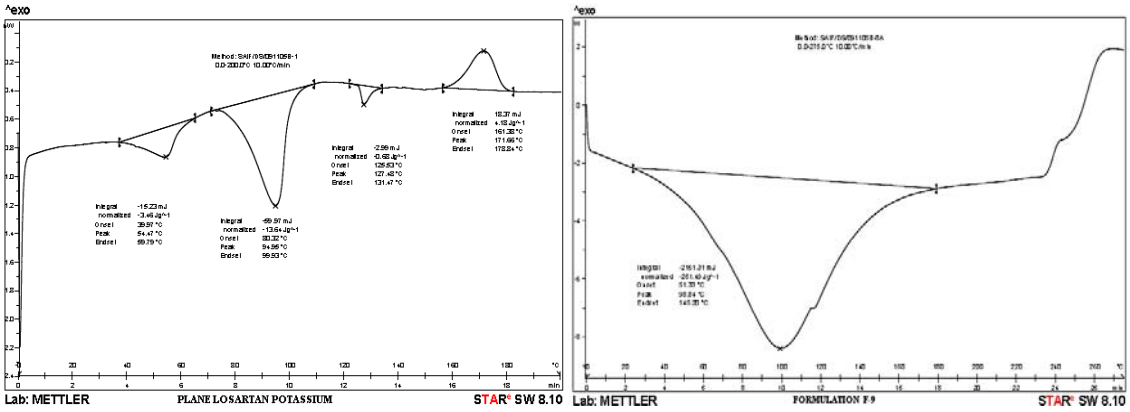

Fig 2. DSC thermo gram of Plane losartan potassium and F-9.

Solubility

The available literature on solubility profile of losartan potassium indicated that the drug is freely soluble in water and slightly soluble in acetonitrile. The results of losartan potassium solubility in various media are shown in the (**Table 3**).

Angle of repose

Angle of repose was determined using fixed funnel method. A glass funnel is held in place with a clamp on a ring support over a glass plate. Approximately 1 gm of powder is transferred into funnel keeping the orifice of the funnel blocked by the thumb. When the powder is emptied from funnel, the angle of the heap to the horizontal plane is measured.

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula.

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner ratio is an indirect index of ease of measuring the powder flow (Cooper 1986). It is calculated by the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25). Precompressional parameters are given in **Table 4.**

Table 2. Calibration curve for the estimation of losartan potassium in pH 1.2 and 6.8.

Concentration µg/ml	Absorbance*	
	pH 1.2	pH 6.8
0.0	0.0	0.0
3	0.132	0.096
6	0.234	0.178
9	0.331	0.275
12	0.443	0.341
15	0.557	0.432
18	0.644	0.529
21	0.747	0.620
24	0.871	0.714
27	0.972	0.810

*Average of three determinations

Table 3. Solubility study of losartan potassium

	Solubility (gm/ml)*		
Studies	**pH 1.2 (0.1 N HCl)**	**pH 6.8 (Phosphate buffer)**	**pH 7.0 (Water)**
Result	1.372	1.289	1.230

*Average of 3 determination.

Hardness

Monsanto hardness tester was used for the determination of the hardness. The tablet to be tested was held between a fixed and a moving jaw and reading of the indicator adjusted to zero. The force applied to the edge of the tablet is gradually increased by moving the screw knob forward until the tablet breaks. The reading is noted from the scale which indicates the pressure required in kg or lb to break tablets**.**

Weight variation

Weight variation study was carried out as per USP. Twenty tablets were randomly selected from each batch weighed individually (USP 2000). The average weight and standard deviation was calculated.

Table 4. Micromeritic properties of precompressional powder blend.

Formulation code	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
LP	41.22 ± 0.16	31.19 ± 0.14	1.45 ± 0.07
F1	17.66 ± 0.32	18.25 ± 0.09	1.22 ± 0.02
F2	18.41 ± 0.15	19.37 ± 0.02	1.24 ± 0.01
F3	19.33 ± 0.87	18.05 ± 0.14	1.22 ± 0.02
F4	21.32 ± 0.41	17.90 ± 0.11	1.21 ± 0.03
F5	23.31 ± 1.27	19.12 ± 0.30	1.23 ± 0.01
F6	24.56 ± 3.01	17.46 ± 0.21	1.21 ± 0.03
F7	26.10 ± 0.94	19.72 ± 0.18	1.24 ± 0.01
F8	27.14 ± 1.44	16.95 ± 0.21	1.20 ± 0.03
F9	29.31 ± 2.41	19.09 ± 0.13	1.23 ± 0.01

All values are expressed as mean ± SD, n=3.

Table 5. Evaluation of different matrix tablets of losartan potassium

Formulation code	Hardness+ (kg/cm²)	Friability† (%)	Thickness† (mm)	Drug content+ (%)	Weight variation* (%)
F1	5.46 ± 0.18	0.31 ± 0.09	4.07 ± 0.08	98.21 ± 0.33	2.33 ± 0.01
F2	5.48 ± 0.06	0.28 ± 0.08	4.02 ± 0.04	98.01 ± 0.26	1.72 ± 0.32
F3	5.71 ± 0.48	0.22 ± 0.05	3.97 ± 0.05	98.45 ± 0.14	1.38 ± 0.16
F4	5.64 ± 0.38	0.34 ± 0.07	3.94 ± 0.08	98.32 ± 0.17	1.22 ± 0.11
F5	5.71 ± 0.32	0.32 ± 0.06	4.05 ± 0.04	98.41 ± 0.11	1.71 ± 0.37
F6	5.63 ± 0.44	0.29 ± 0.03	4.08 ± 0.06	98.11 ± 0.24	2.37 ± 0.12
F7	6.06 ± 0.32	0.35 ± 0.08	3.93 ± 0.05	99.32 ± 0.14	1.62 ± 0.43
F8	6.42 ± 0.34	0.33 ± 0.05	4.05 ± 0.05	98.52 ± 0.22	1.41 ± 0.33
F9	6.56 ± 0.53	0.29 ± 0.04	3.99 ± 0.04	99.93 ± 0.13	1.73 ± 0.69

All values are expressed as mean **±** SD, n = 5+, 10†, 20*.

Post compressional studies of the prepared matrix tablet

Uniformity of thickness

The crown-to-crown thickness of ten tablets from each batch was determined using micrometer calipers. The thickness variation limits allowed are ± 5% of the size of the tablet.

Friability

Friability of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution (USP 2000). Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were degusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test

Drug content

For determination of drug content at least five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer of pH 6.8 (USP 2000). Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 205 nm against blank. Drug content was calculated using standard curve. All parameters of post compressional studies of the prepared matrix tablet presented in **Table 5**.

Dissolution studies

The prepared matrix tablets were subjected to *in-vitro* dissolution studies using an 8 station USP dissolution apparatus (Electro Lab, TDT-08L, Mumbai). The dissolution studies were carried out in pH 1.2 for 2 hrs & in pH 6.8 for next 22 hrs at 37 ± 0.5^0 c and 100 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium (Deshmukh 2009). After filtration and appropriate dilution, the samples were analyzed at 205 nm for losartan potassium against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve (**Fig 3, 4 and 5**)

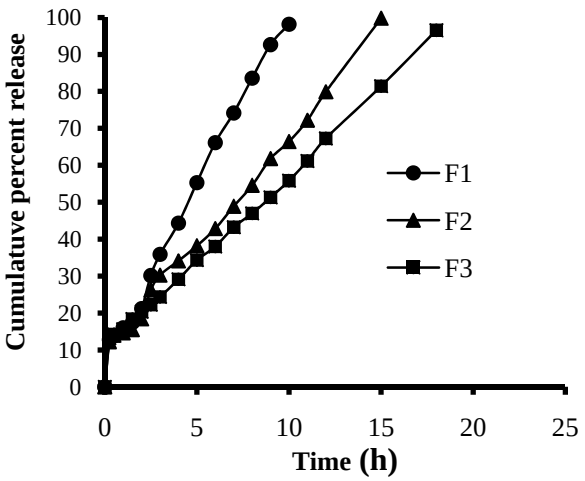

Fig 3. Effect of polymer level on *in-vitro* release of losartan potassium from XG matrix tablets.

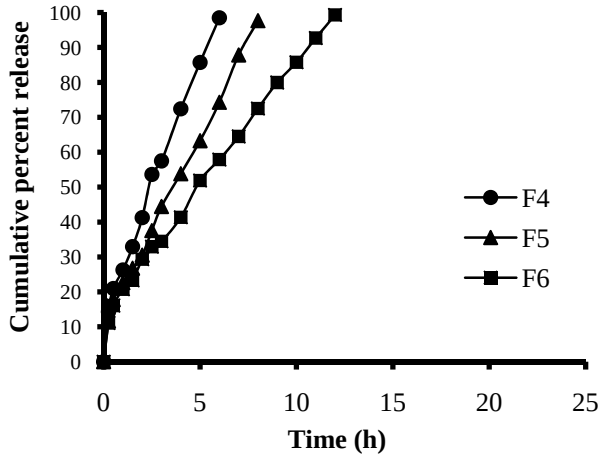

Fig 4. Effect of polymer level on *in-vitro* release of losartan potassium from HPMC K4M matrix tablets.

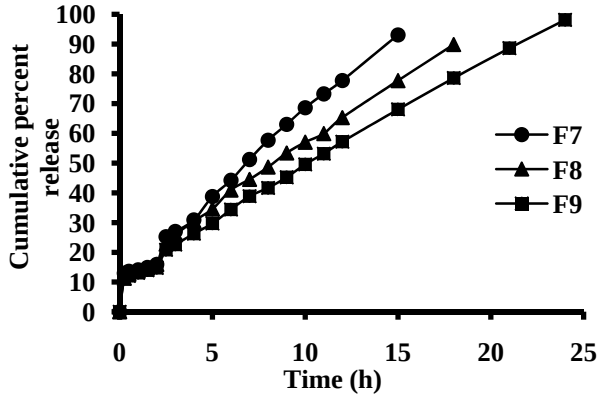

Fig 5. Effect of polymer level on *in-vitro* release of losartan potassium from XG - HPMC K4M matrix tablets.

Results and Discussion

In the present study FT-IR data of the formulation was compared with the standard spectrum of pure drug losartan potassium and the characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymeric carrier (formulation) were noted. The IR spectrum of the formulation F9 showed that there is no significant evidence for interaction between drug and the polymer. The DSC thermogram revealed that there is no any appreciable change in the nature of the melting endotherms suggesting that the drug has not lost its characteristic properties even in its formulation form as there is no interaction of the drug with the polymer and other excipients used for the study. Plain losartan potassium exhibited angle of repose value of 41.22 ± 0.16° indicating poor flow property. It was further supported by high Carr's index (31.19 ± 0.14) and Hausner's ratio (1.45 ± 0.07). Hence it was necessary to use directly compressible vehicles like MCC to improve the flow property of losartan potassium. Very good flow property was observed with MCC and lubricants. The tablets of different batches of xanthan gum and HPMC K4M alone and in combination were found uniform with respect to thickness (3.93 to 4.08 mm), hardness (5.46 to 6.56 kg/cm^2) and friability (0.22 to 0.35 %) indicating good handling property of the prepared matrix tablets. Weight variation (1.22 to 2.37%) and drug content (98.01 to 99.93%) were within prescribed pharmacopoeial limits. Dissolution study of all the formulations was carried out using 0.1 N HCl pH 1.2 for 2 h and in phosphate buffer pH 6.8 upto 24 h (Yeole 2006). Formulations F1 to F3 were prepared by using xanthan gum of 40%, 45% and 50%w/w and F4 to F6 were prepared by using HPMC K4M of 40%, 45% and 50%w/w of tables respectively. Formulation F7 to F9 was prepared with polymer blend of xanthan gum and HPMC K4M (1:1) using different concentrations like 40%, 45% and 50% w/w of tablet. Among all these formulation F9 has shown the controlled release of drug for 24 h. The controlled drug release is due to increased proportion of polymers.

Conclusion

Results of the present research study confirmed that the polymer concentration plays a major role in drug release. As the polymer concentration of the tablets increased the drug release was prolonged in a controlled manner.

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