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Formulation and Evaluation of Losartan Potassium Controlled Release Tablets Using Starch Based Polymers

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Abstract: The objective of the present investigation was to synthesize starch urea and cross linked starch urea, a new starch based polymers and to evaluate its application in the design of controlled release matrix tablets of losartan potassium. The release rate controlling efficiency of starch urea and cross linked starch urea was also compared with that of known polymers. Starch urea was synthesized by gelatinization of starch in the presence of urea where as cross linked starch urea polymer was synthesized by gelatinization of starch in the presence of urea and calcium chloride. Matrix tablets of losartan potassium (25 mg) were formulated by employing starch urea and cross linked starch urea polymers in different proportions and the tablets were evaluated. Losartan potassium release from the formulated matrix tablets was slow and spread over 24 h and depended on per cent polymer in the tablet. Release was diffusion controlled and followed first order kinetics. Non-Fickian diffusion was the drug release mechanism from the formulated tablets. Losartan potassium release from matrix tablets formulated with 40% starch urea and 40% cross linked starch urea are the best formulations. Starch urea and cross linked starch urea polymers was found to suitable for the design of oral controlled release tablets of losartan potassium. The order of increasing release rate controlling efficiency with various polymers was-- cross linked starch urea > starch urea > ethyl cellulose > HPMC. Cross linked starch urea and starch urea is a better release rate controlling polymers than HPMC, ethyl cellulose and methyl cellulose for obtaining controlled release over 24 h.

Keywords: Losartan Potassium, Modified Starches, Controlled Release, Polymers, Matrix tablets

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Introduction

Conventional dosage forms produce fluctuating drug concentration in blood and tissue which may lead to an insufficient therapeutic efficacy. To

control the rate of drug delivery into the systemic circulation, various oral dosage forms have been prepared and studied. Polymeric matrix is an

interesting option when formulating an oral controlled release of a drug (Vyas and Khar, 2002; Loyd *et al.*, 2006). The most popular among the oral drug delivery systems are the matrix tablet systems which contains uniformly dissolved or dispersed drug in the polymer core. In the matrix tablets, the drug is homogeneously dispersed in either a hydrophilic polymer (or) lipophilic polymer matrix (Chein, 1982). The drug release from the matrix tablets depends upon drug diffusion through the polymers and /or erosion of polymers. The use of water soluble (or) bio-erodable polymers in the fabrication of matrix tablets has been increased. This is because if the polymers are sufficiently polar they can interact with aqueous medium and generate sufficient energy to disperse the polymer chains from the glassy state.

Starch is a natural, biodegradable polymer and modified starches are reported as fillers, disintegrants and dry binders. Starch is one of the most widely used carbohydrate polymers and it is composed of two polysaccharides: linear amylose and branched amylopectin. Cross-linked high amylose starch has been introduced as matrix for controlled drug release. Modified starch, also called starch derivatives, are prepared by physically, enzymatically, or chemically treating native starch, thereby changing the properties of the starch. Modified starches are used in practically all starch applications, such as in food products as a thickening agent, stabilizer or emulsifier; in pharmaceuticals as a disintegrant; or in paper as a binder (Shang, 1988; Chowdary *et al.*, 2008; Panna *et al.*, 2008). Starches are modified to enhance their performance in different applications. Starches may be modified to increase their stability against excessive heat, acid, shear, time, cooling, or freezing; to change their texture; to decrease or increase their viscosity; to lengthen or shorten gelatinization time; or to increase their visco-stability (Mesnukul *et al.*, 2008; Ahmed and Souad, 2008; Josias *et al.*, 2009).

In the present work, an attempt has been made to prepare controlled release matrix tablets

of losartan potassium by wet granulation method using newly prepared polymers like modified starch urea and starch urea. The rate retarding capacity of the new polymers prepared is compared with the formulations prepared with standard polymer like hydroxyl propyl methyl cellulose (HPMC).

Materials and Methods

Losartan potassium, a gift sample was obtained from Madras Pharmaceutical Ltd., Chennai, India. Starch was commercially procured from S. D. Fine-Chem. Ltd., Mumbai, India. Hydroxy propyl methyl cellulose (HPMC K70) was procured commercially from Hi-Media Laboratories Pvt. Ltd. The remaining chemicals were of analytical grade and were used as received.

Preparation of starch urea polymer (Te Wierik et al., 1996; Herman and Remon, 1989; Chowdary and Krishna, 2010):

Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part) was dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. While mixing heating was continued for 20 min to form starch urea polymer. The mass formed was spread onto a stainless steel plate and dried at 85°C for 6-8h. The dried polymer was powdered and passed through mesh No. 120.

Preparation of cross linked starch urea polymer:

Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part) and calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. While mixing heating was continued for 20 min to form cross linked starch urea polymer. The mass formed was spread onto a stainless steel plate and dried at 85°C for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Characterization of starch urea and cross linked starch urea polymers:

The prepared polymers was characterized by microscopical examination, melting point, solubility, swelling index, and various micromeritic properties namely bulk density, tap density, compressibility index and angle of repose and also by DSC and FTIR spectra.

Preparation of Controlled Release Tablets:

Matrix tablets of losartan potassium (25 mg) were prepared by employing starch urea and modified starch urea polymers in different proportions (10%, 20%, 30%, 40% and 50%). The required quantities of medicament and matrix material were mixed thoroughly in a motor by following geometric dilution technique. The binder solution (mixture of alcohol and purified water at 1:1 ratio) was added and mixed thoroughly to form dough like mass. The mass was passed through mesh no. 12 to obtain wet granules. The wet granules were dried at 60°C for 4 h. The dried granules were passed through mesh no. 16 to break the aggregates. The lubricants, talc (2% w/w) and magnesium stearate (2% w/w) were passed through mesh no. 100 onto dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multistation tablet punching machine (REMI Pvt. Ltd., Mumbai) to a hardness of 5-6 kg/sq.cm using round and flat punches. Matrix tablets were also prepared by employing known polymers like ethyl cellulose methyl cellulose and HPMC at 1:1 ratio of drug: polymer in each case for a comparative evaluation of their release retarding efficiency (Mine and Ferhan, 2003).

Evaluation of Tablets:

The prepared controlled release matrix tablets were evaluated for weight variation, hardness, drug content, thickness and for friability as per standard procedures. The tablet hardness (n=6) was evaluated by using Monsanto tablet hardness tester. Friability test (n=20) was conducted using Roche friabilator, Tablet thickness (n=20) was measured by digital Vernier caliper. Drug content of Venlafaxine HCl was analyzed Spectrophotometrically by measuring the absorbance of

standard and samples at 225 nm using double beam UV/Visible spectrophotometer (Elico, model SL -159).

Dissolution Testing and Data Analysis:

In vitro drug release studies for the controlled release tablets of losartan potassium was studied by using dissolution test apparatus employing a paddle stirrer at 50 rpm and temperature at 37±1°C. Phosphate buffer of pH 6.8 (900 ml) was used as dissolution fluid. Samples of 5 ml of each were withdrawn at 1,2,3,4,5,6,7,8,9,10,11,12 and 24 h time interval. Each sample withdraw was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and absorbances were determined at 206 nm for losartan potassium using UV-spectrophotometer.

Results and Discussion

The prepared polymers were characterized by microscopical examination, physical and chemical tests and their melting point, solubility, swelling index, pH, viscosity and various micromeritic properties namely bulk density, tap density, compressibility index and angle of repose were determined.

Both the polymers were found to be insoluble in water, aqueous fluids of acidic and alkaline pH. When tested for the melting point, starch urea was charred at 210 °C and modified starch urea at 165-170 °C. The angle of repose for both the polymers was found to be in the range of 25-30° for which the flow was excellent. The compressibility index for both the polymers was found to be in the range of 1-10% for which the flow was excellent.

Modified starch urea and starch urea prepared by reacting potato starch with urea at elevated temperatures was found to be a white, crystalline, non-hygroscopic powder and exhibited excellent flow characteristics. Modified starch urea and starch urea was insoluble in water and aqueous fluids of acidic and alkaline pHs. It also exhibited good swelling in water and no pasting and gelling property when heated at 100 °C.

Table 1: Formula for Losartan Potassium Tablets

S. No.	FFORMULATIONTION	LF1	LF2	LF3	LF4		
1	Drug(mg)	25	25	25	25		
2	Starch acetate (mg)	25	50	75	100		
3	Lactose (mg)	190	165	140	115		
4	Magnesium stearate (mg)	5	5	5	5		
5	Talc (mg)	5	5	5	5		
6	Total (mg)	250	250	250	250		
S. No.	FFORMULATIONTION	LF5	LF6	LF7	LF8	LF9	LF10
1	Drug (mg)	25	25	25	25	25	25
2	Starch urea (mg)	25	50	75	100	--	--
	Ethylcellulose	--	--	--	--	50	--
	HPMC K4M	--	--	--	--	--	50
3	Lactose(mg)	190	165	140	115	165	165
4	Magnesium stearate (mg)	5	5	5	5	5	5
5	Talc(mg)	5	5	5	5	5	5
6	Total (mg)	250	250	250	250	250	250

Table 2: Evaluation Values of the Prepared Tablets

Formulation	Thickness (mm)(n=5)	Weight variation (mg) (n=20)	Hardness (kg/cm ²) (n=5)	Friability (%) (n=5)	Drug content (%) (n=5)
LF1	3.04±0.010	Passed	5.5±0.05	0.5±0.01	98.15± 0.017
LF2	3.36±0.010	Passed	6.1±0.1	0.4±0.027	99.52± 0.015
LF3	3.45±0.013	Passed	5.6±0.056	0.41±0.017	98.56± 0.018
LF4	3.43±0.014	Passed	6.0±0.1	0.37±0.015	97.42± 0.021
LF5	3.05±0.012	Passed	6.3±0.05	0.5±0.010	96.96± 0.026
LF6	3.25±0.013	Passed	5.5±0.11	0.53±0.013	98.01± 0.019
LF7	3.02±0.07	Passed	5.6±0.05	0.45±0.013	97.21± 0.032
LF8	3.13±0.011	Passed	6.2±0.09	0.4±0.015	97.42± 0.038
LF9	3.01±0.05	Passed	5.0±0.01	0.52±0.010	98.96± 0.016
LF10	3.07±0.09	Passed	5.8±0.11	0.51±0.013	98.01± 0.021

Matrix tablets of losartan potassium were prepared (Table 1) by employing different proportions of new polymers as well as standard polymers by conventional wet granulation method. Hardness of the tablet was in the range of 5-6.5 kg/sq.cm. Weight loss in the friability test was less than 0.56% in all the cases. All the tablets prepared contained the drug within 100±3% of the labeled claim. All the matrix tablets were found to be non-disintegrating in water and aqueous, acidic and alkaline fluids. As such the prepared tablets were of good quality with regard to drug content, hardness and friability. The

results of physical parameters evaluation are shown in Table 2.

The release profiles of the losartan potassium are shown in Figures 1 and 2, respectively. With losartan potassium the release from the prepared tablets was slow and spread over for 24 h and depended on the concentration of the polymers. The losartan potassium (LF1) tablets prepared with 10% w/w modified starch urea by using drug (25 mg) and polymer (25mg) in 1:1 ratio (Table 1), showed 98.29% drug release at 24 h, respectively. The losartan potassium (LF2) tablets

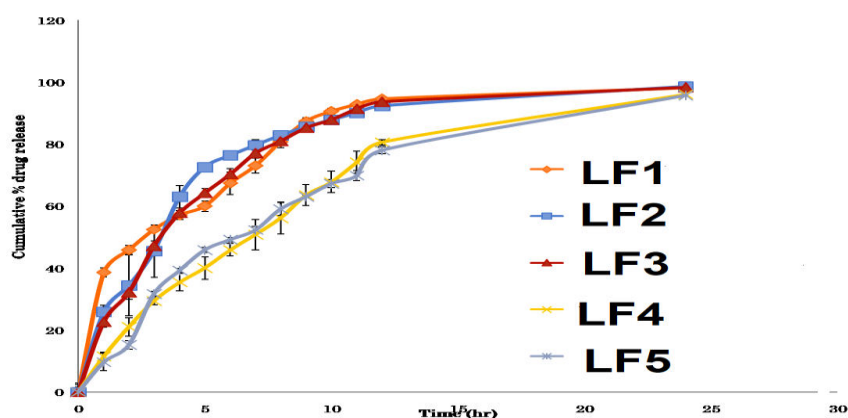


Fig. 1: Dissolution profile for losartan potassium tablets.

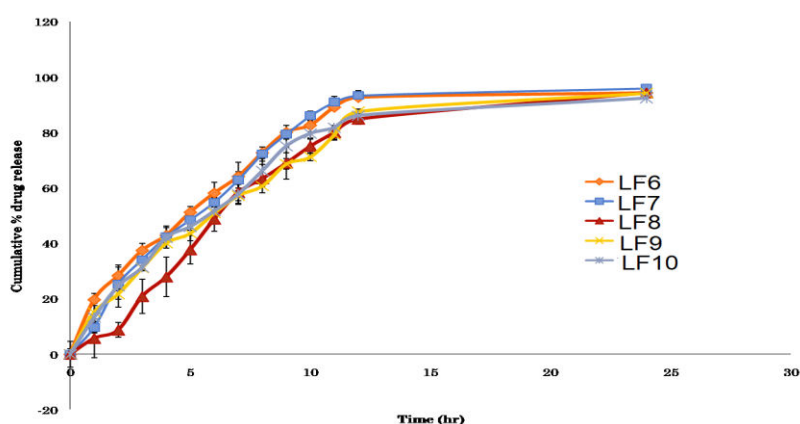


Fig. 2: Dissolution profile for losartan potassium tablets.

prepared with 20% w/w modified starch urea, by using drug (25 mg) and polymer (50 mg) in 1:2 ratio, showed 96.88% drug release at 24 h, respectively. The losartan potassium (LF3) tablets prepared with 30% w/w modified starch urea, by using drug (25 mg) and polymer (75 mg) in 1:3 ratio, showed 94.19% drug release at 24 h, respectively. The losartan potassium (LF4) tablet prepared with 40% w/w modified starch urea, by using drug (25 mg) and polymer (100 mg) in 1:4 ratio, showed 90.58% drug release at 24 h, respectively. The losartan potassium (LF5) tablet prepared with 10% w/w starch urea, by using drug (25 mg) and polymer (25 mg) in 1:1 ratio, showed 98.31% drug release at 24 h, respectively. The losartan potassium (LF6) tablets prepared with 20% w/w starch urea, by using drug (25 mg) and polymer (50 mg) in 1:2 ratio, showed 94.25% drug release at 24 h, respectively. The losartan

potassium (LF7) tablet prepared with 30% w/w starch urea, by using drug (25 mg) and polymer (75 mg) in 1:3 ratio, showed 92.42% drug release at 24 h, respectively. The losartan potassium (LF8) tablet prepared with 30% w/w starch urea, by using drug (25 mg) and polymer (100 mg) in 1:4 ratio, showed 92.42% drug release at 24 h, respectively. The losartan potassium (LF9) tablets prepared with 10% w/w ethyl cellulose by using drug (25 mg) and polymer (50 mg) in 1:1 ratio, showed 98.65% drug release at 24 h, respectively. The losartan potassium (LF10) tablets prepared with 10% w/w HPMC by using drug (25 mg) and polymer (50 mg) in 1:1 ratio, showed 98.17% drug release at 24 h, respectively.

The release data of matrix tablets were fitted into various mathematical models to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is

Table 3: Kinetic equation and corresponding regression values for losartan potassium tablets

Polymers	Zero order (R ²)	First order (R ²)	Higuchi (R ²)	Hixson (R ²)	Korsmeyer Peppas	
					'n'	R ²
LF1	0.6957	0.9719	0.9248	0.901	0.4775	0.8731
LF2	0.7647	0.9711	0.9345	0.9217	0.6414	0.8839
LF3	0.7987	0.9508	0.948	0.9197	0.5821	0.9153
LF4	0.8435	0.9632	0.9281	0.9342	0.8568	0.8969
LF5	0.7791	0.9639	0.944	0.9071	0.6987	0.8483
LF6	0.6547	0.9665	0.9041	0.8743	0.4587	0.8603
LF7	0.7164	0.811	0.9159	0.8249	0.509	0.8897
LF8	0.7526	0.9216	0.9279	0.899	0.5956	0.8897
LF9	0.8393	0.9897	0.9674	0.9486	1.142	0.9143
LF10	0.7237	0.9647	0.9375	0.8994	0.4466	0.9065

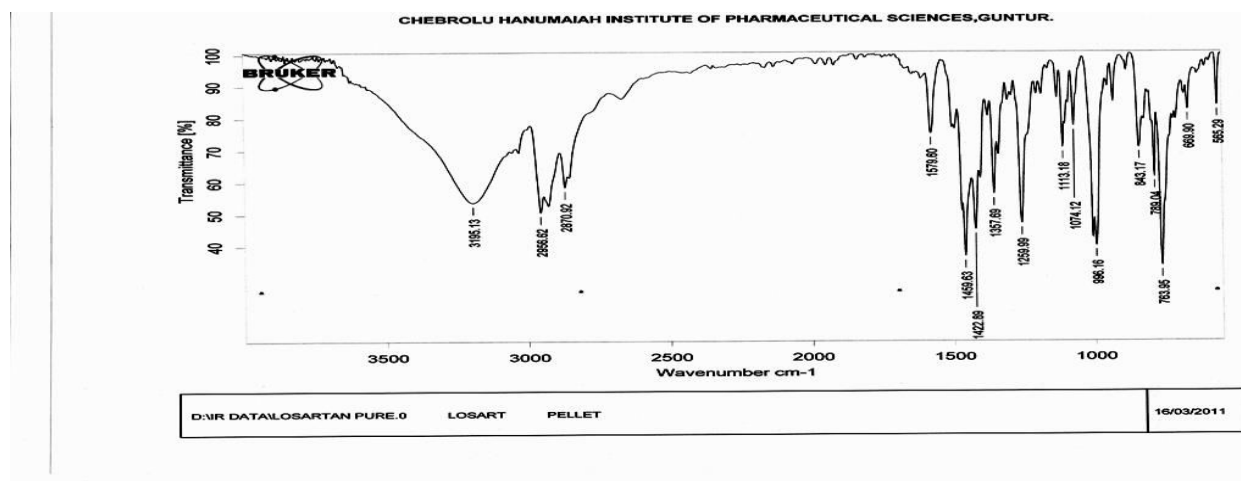


Fig. 3: FTIR spectra of pure losartan potassium.

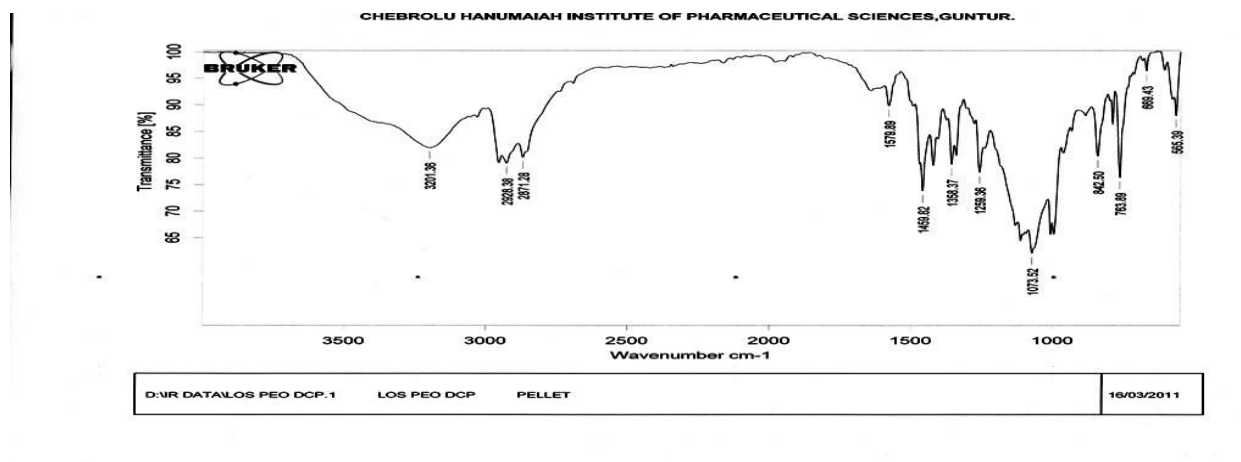


Fig. 4: FTIR spectra of losartan potassium tablets prepared with starch urea polymer.

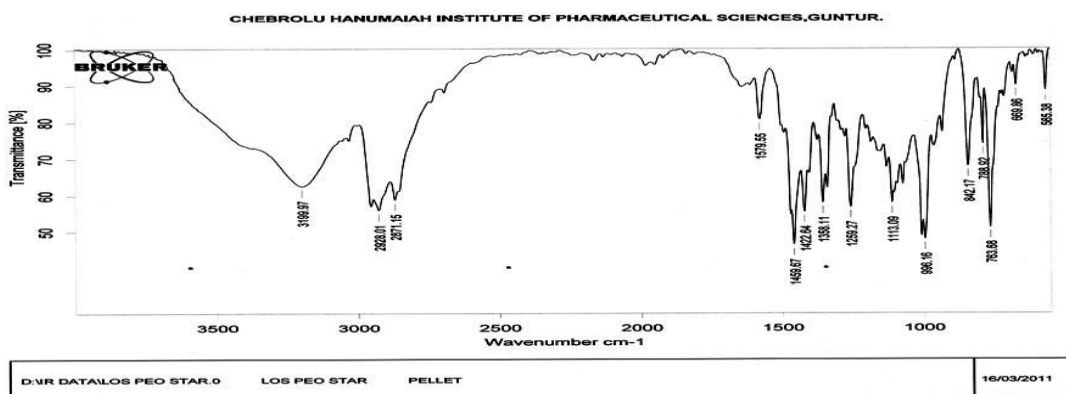


Fig. 5: FTIR spectra of losartan potassium tablets prepared with modified starch urea polymer.

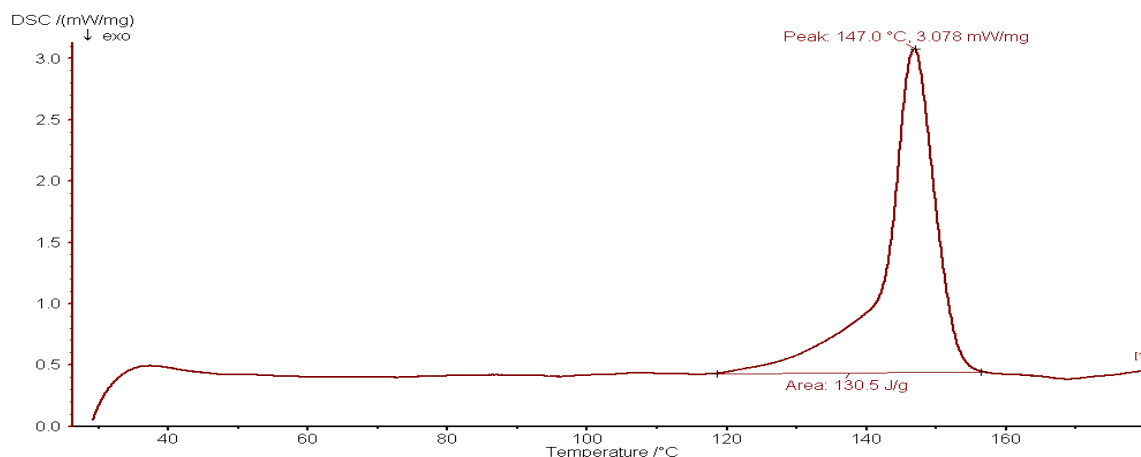


Fig. 6: DSC thermogram of pure losartan potassium.

released based on the correlation coefficient (r) value in various models. The ' r ' values for zero order, first order, Higuchi, Hixson and Korsmeyer-Peppas plot are given in Table 3. When the release data was analyzed as per zero and first order kinetic models, the best fit with higher correlation ($r > 0.9946$) was observed with first order model indicating that the drug release from all the tablets followed first order kinetics. Good linear relationships were observed between per cent polymer and release rate in both the cases. Thus drug release from the matrix tablets could be controlled by varying the proportion of polymers in the matrix.

The correlation coefficient obtained for Higuchi plot was found to be superior on

comparison with Hixson Crowell plot indicating that the release was diffusion controlled for all formulations except losartan potassium prepared with 50% methyl cellulose (LF13). To confirm the diffusion mechanism, the data was fit into Korsmeyer Peppas equation.

Generally if ' n ' value is 0.45 or less indicates Fickian diffusion, if ' n ' value is 0.45-0.89 indicates anomalous/non-Fickian diffusion which refers to combination of both diffusion and erosion controlled rate release, if ' n ' is equal to 0.89 and above indicates case-II transport which refers to erosion of the polymeric chain. The drug release obtained for losartan potassium are in between 0.45-0.89 which indicates non-Fickian diffusion controlled release except losartan potassium

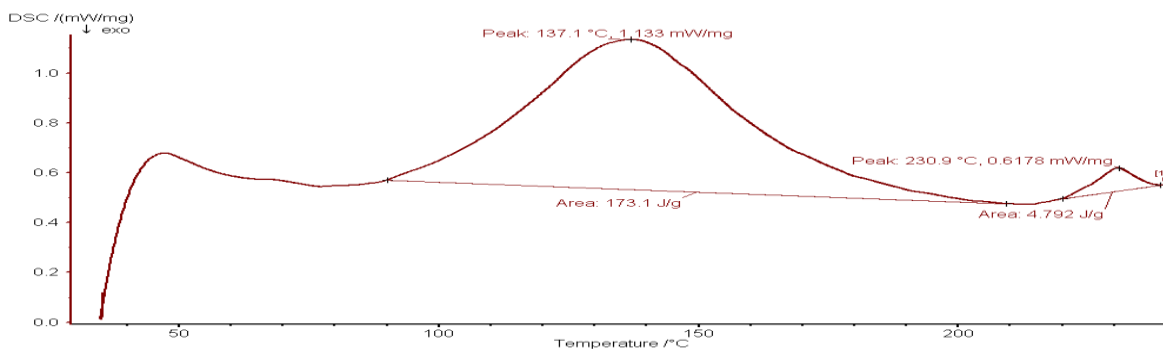


Fig. 7: DSC thermogram of losartan potassium tablets prepared with starch urea.

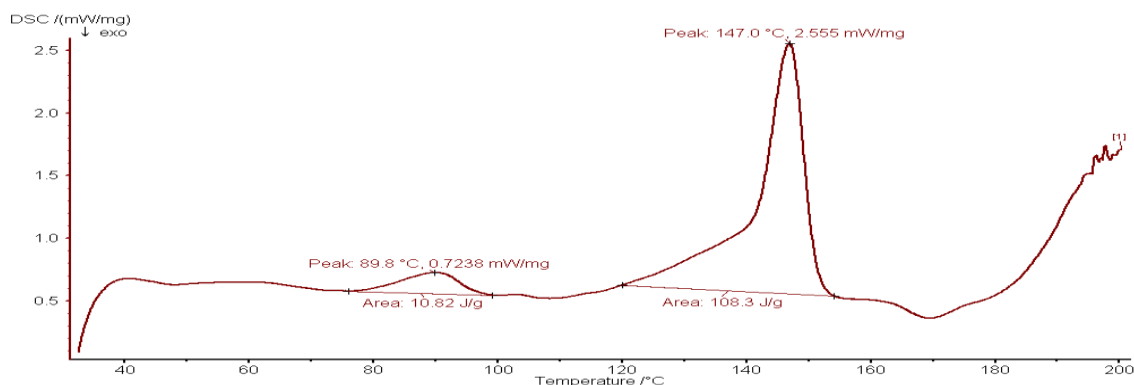


Fig. 8: DSC thermogram of losartan potassium tablets prepared with modified starch urea.

prepared with 40% starch urea (LF9) which indicates case-II transport (>0.89) mechanism controlled by swelling and relaxation of the polymer chains.

The order of increasing release rate controlling efficiency observed with various polymers was-- modified starch urea > ethyl cellulose > HPMC. Thus modified starch urea and starch urea polymer was found to be a better release rate controlling polymers than HPMC and ethyl cellulose with losartan potassium.

The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. IR spectra of pure losartan potassium showed characteristic peaks at $3400\text{--}3100\text{ cm}^{-1}$ due to the aromatic C-H stretching, $2970\text{--}2850\text{ cm}^{-1}$ are due to the alkane C-H stretching, $1470\text{--}1430\text{ cm}^{-1}$ are due to C-H deformation, $1600\text{--}1450\text{ cm}^{-1}$ are due to C=C stretching, $800\text{--}550\text{ cm}^{-1}$ are due to C-Cl, $1350\text{--}1260\text{ cm}^{-1}$ are due to O-H stretching, 3000--

2500 cm^{-1} are due to chelate compound O-H stretching, $3400\text{--}3200\text{ cm}^{-1}$ O-H bending, $1690\text{--}1640$ are due to C=N stretching, $1350\text{--}1000\text{ cm}^{-1}$ are due to aromatic C-N stretching, $1206\text{--}1025\text{ cm}^{-1}$ are due to tetrazole group and $1640\text{--}1560\text{ cm}^{-1}$ are due to N-H bending. FTIR spectra of the optimized formulations displayed all the characteristic bands of drug, without any significant spectral shift. This suggested that there was no potential chemical interaction between the components of the formulations. The FTIR spectra are given in Figure 3 (Pure losartan potassium), Figure 4 (losartan potassium tablets prepared with starch urea polymer) and Figure 5 (FTIR spectra of losartan potassium tablets prepared with modified starch urea polymer).

The DSC curve of pure losartan potassium (Fig. 6) showed two exothermic peaks at 56.4°C and 186.3°C corresponding to its melting point ($183.5\text{--}184.5^{\circ}\text{C}$). The DSC curve of starch urea polymer (Fig. 7) showed the exothermic peak at 112.2°C

whereas for modified starch urea (Fig. 8) the broad exothermic peaks were obtained at 137.1°C and 230.9°C. Thus, it was concluded that losartan potassium is compatible with all the excipients used in the formulation.

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