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Formulation and Evaluation of Sustained Release Matrix Tablets of Losartan potassium

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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, formulations such as F1 to F9. Hydrophilic polymer like Hydroxypropyl methylcellulose (HPMC), hydrophobic polymer like Ethyl Cellulose(EC) and natural polymer like Xanthan Gum(XG) were used. Compatibility of the drug with various excipients was studied. The compressed tablets were evaluated and showed compliance with Pharmacopoeial limits. The optimized formulation(F3) on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and friability. All tablets but one exhibited gradual and near completion sustained release for Losartan potassium, and 96.45% released at the end of 10h. The results of dissolution studies indicated that formulation F3 (drug to polymer 1:1.5), 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 polymer ratio. Applying exponential equation, all the formulation tablets(except F3) showed diffusion-dominated drug release. The mechanism of drug release from F3 was diffusion coupled with erosion.
Keywords: Losartan potassium, hydroxypropyl methylcellulose, ethyl cellulose, xanthan gum, sustained release, matrix Tablets.

Introduction and Experimental

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. Sustained release matrix tablet 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[1,2].

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 Potassium in a sustained release dosage form with dual release characteristics i.e., burst release followed by an extended release over 8 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[3,4].

Materials

Losartan potassium was obtained from Fourrts India Pvt Ltd., Chennai. HPMC K100M was received

as gift samples from Griffon laboratories Pvt. Ltd., Mumbai. Micro-crystalline cellulose was received as gift samples from Griffon Pvt. Ltd., Mumbai, India. Other materials Xanthan Gum, Ethyl cellulose, Polyvinylpyrrolidone, Talc and Magnesium Stearate were purchased from Qualigens fine chemicals, Mumbai, India.

Preparation and characterization of granules

The granules were prepared by wet granulation method and were evaluated for their bulk density, tapped density, compressibility index, angle of repose and Hausner ratio. The tapping method was used to determine the bulk density, tapped density, percent compressibility index and Hausner ratio.

Compressibility index = $[\rho_t - \rho_b / \rho_t] \times 100$

Hausner ratio= ρ_t / ρ_b

Where ρ_t = tapped density

ρ_b = initial bulk density of tablet blend.

Angle of repose θ of the tablet blend measures the resistance to particle flow and was determined by fixed funnel method [5].

Formulation of sustained release Tablets

After evaluation of granules the sustained release matrix tablets were formulated by compressing the granules using (8mm diameter, round flat faced punches) multiple punch tablet compression machine (Cadmach Machinery Ltd., Ahmedabad, India). The tablets were formulated such that each tablet contains 50 mg of Losartan potassium and total weight of 250 mg, containing 20% (w/w) of the drug. The batch size for each formulation was 100 tablets.

Compatibility testing of drug with polymer

Fourier transforms 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[6].

Differential scanning calorimetry

Differential scanning calorimetry **(**Shimadzu, Japan) was used to examine the thermal behaviour of pure drug and drug additive mixtures. Compatibility studies were carried on samples of 1:1 physical mixtures of the drug (Losartan Potassium) with various excipients viz. hydroxypropyl methylcellulose, ethyl cellulose and xanthan gum. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.

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)[7,8].

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 100 ml 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 205.5 nm. Content uniformity was calculated using formula[9,]

% Purity = 10 C (Au / As) ---------- (9)

Where,

C - Concentration,

Au and As - Absorbance's obtained from standard preparation and assay preparation respectively.

***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 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 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 Whatman 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 8 hours and absorbance was measured at 205.5 nm using a Shimadzu-1700 UV spectrophotometer[10]. Drug concentrations in the sample were determined from standard calibration curve. The release data were calculated by using PCP disso V3 software.

Release kinetics

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as Zero order, First order, Higuchi and Korsmeyer-Peppas[11,12,13,14]. The kinetics of drug release was calculated by using PCP disso V3 software.

Stability study

Sustained release tablets of Losartan potassium formulated and accelerated stability studies were carried out as per ICH guidelines. Stability studies were carried out at 40^0 C / 75% RH for the optimized formulation (F3) for 3 months. The matrix tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, drug content and In vitro drug release[15].

Table 1: Composition of Losartan potassium SR matrix tablet

Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	50	50	50	50	50	50	50	50	50
HPMC K100M	50	75	100	-	-	-	-	-	-
Ethyl cellulose	-	-	-	50	75	100	-	-	-
Xanthan gum	-	-	-	-	-	-	50	75	100
MCC	125	100	75	125	100	75	125	100	75
PVP	20	20	20	20	20	20	20	20	20
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	250	250	250	250	250	250	250	250	250

*All the quantities are expressed as mg per Tablet.

Table 2: Physico-chemical characterization of Losartan potassium SR matrix tablets

F Code	Dimension		Hardness (kg/cm^2)**	Friability (%)*	Weight variation (%)*	Drug content (%w/w)*
	Diameter (mm)**	Thickness (mm)**				
F1	8.0±0.0	4.18±0.11	5.66±0.408	0.284±0.00	251.0±1.40	100.86±1.2
F2	8.0±0.0	4.15±0.12	5.75±0.418	0.454±0.05	251.15±1.4	99.47±1.3
F3	8.0±0.0	4.15±0.13	5.50±0.447	0.402±0.05	250.85±1.3	100.72±1.5
F4	8.0±0.0	4.13±0.12	5.83±0.258	0.385±0.07	250.45±1.3	100.33±0.8
F5	8.0±0.0	4.18±0.11	5.91±0.376	0.360±0.02	250.7±1.42	100.5±0.95
F6	8.0±0.0	4.11±0.11	6.16±0.683	0.376±0.06	251.3±1.49	100.14±0.9
F7	8.0±0.0	4.13±0.12	5.58±0.376	0.403±0.04	252.4±1.40	100.5±1.68
F8	8.0±0.0	4.15±0.13	5.57±0.37	0.361±0.00	251.45±1.4	99.39±1.5
F9	8.0±0.0	4.10±0.12	5.66±0.408	0.349±0.09	250.9±1.48	98.54±1.7
Standards	-	-	4-8	<1	0.5	90-110

*All the values are expressed as mean± SD, n=3., ** n=6.

Table 3: Different kinetic models for Losartan potassium SR matrix tablets

Code	Zero order		First order		Higuchi		Peppas		Best fit model
	R^2	K_0 mg/h^{-1}	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	n	
F1	0.9474	10.063	0.8592	0.1938	0.8334	23.8548	0.9830	1.9166	Peppas
F2	0.9700	9.4137	0.9021	0.1766	0.8712	23.6698	0.9656	1.7465	Zero-order
F3	0.9820	8.2020	0.9157	0.1455	0.8820	21.6151	0.9781	1.5340	Zero-order
F4	0.8785	10.209	0.7772	0.1920	0.8285	24.6881	0.7632	1.2412	Zero-order
F5	0.9664	9.1268	0.9041	0.1668	0.8594	22.8722	0.9841	1.7415	Peppas
F6	0.9717	8.3925	0.9151	0.1530	0.8656	22.0509	0.9717	1.7309	Zero-order
F7	0.9699	8.3884	0.9632	0.1422	0.9049	22.3442	0.9419	1.4277	Zero-order
F8	0.9757	8.6500	0.9669	0.1507	0.9154	23.0754	0.9460	1.3418	Zero-order
F9	0.9641	8.1897	0.9469	0.1388	0.8782	21.6680	0.9519	1.6487	Zero-order

Table 4: Stability studies of optimized formulation (F3) of Losartan potassium SR tablet

Characteristic	Initials	1 Month	2 Month	3 Month
Hardness (kg/cm^2)*	5.50±0.447	5.16±0.288	5.00±00	5.3±0.29
Drug content (mg/Tablet)*	100.72±1.5	100.6±1.68	99.45±1.3	99.39±1.5
In vitro drug release at 10^{th} hour*(%)	96.45±0.97	95.73±0.77	95.45±0.77	95.00±0.62

*All the values are expressed as mean± SE, n=3.

Result and Discussion

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content, in vitro drug dissolution studies and stability studies. All the studies were performed in triplicate, and results are expressed as mean ±SD.

Characterization of granules blend

The granules prepared for compression of sustained release tablets were evaluated for their flow properties. Angle of repose was in the range of 20.07±0.473 to 22.11±0.207° which indicates excellent flow of the granules for all formulations. The bulk density of the granules was in the range of 0.774±0.005 to 0.786±0.05 g/ml; the tapped density was in the range of 0.867±0.005to 0.898±0.001 g/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 10.93±0.05 to 11.14±0.05%, the Hausner ratio was found to be in the range of 1.121±0.01 to 1.125±0.05, indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Compatibility testing of drug with polymer

Fourier transforms infra-red (FTIR) spectroscopy

Major functional groups present in Losartan potassium show characteristic peaks in IR spectrum. Figure 1 shows peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different polymer. The major peaks are identical to functional group of Losartan potassium. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

Differential scanning calorimetry

The Figure 2 shows different DSC thermogram for drug and drug with different polymers. DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

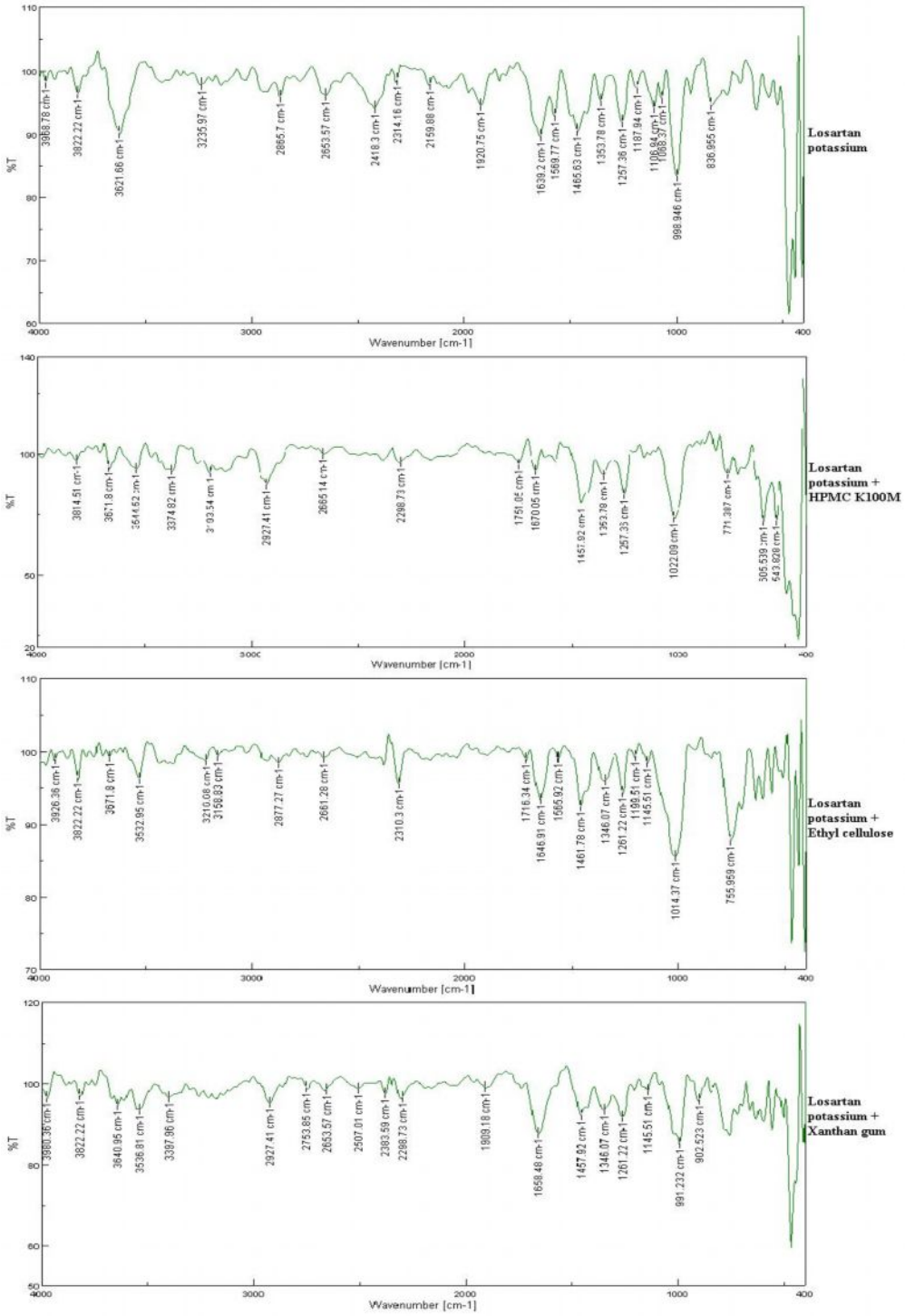

Figure 1: It shows the FTIR spectra of drug and drug with different polymers

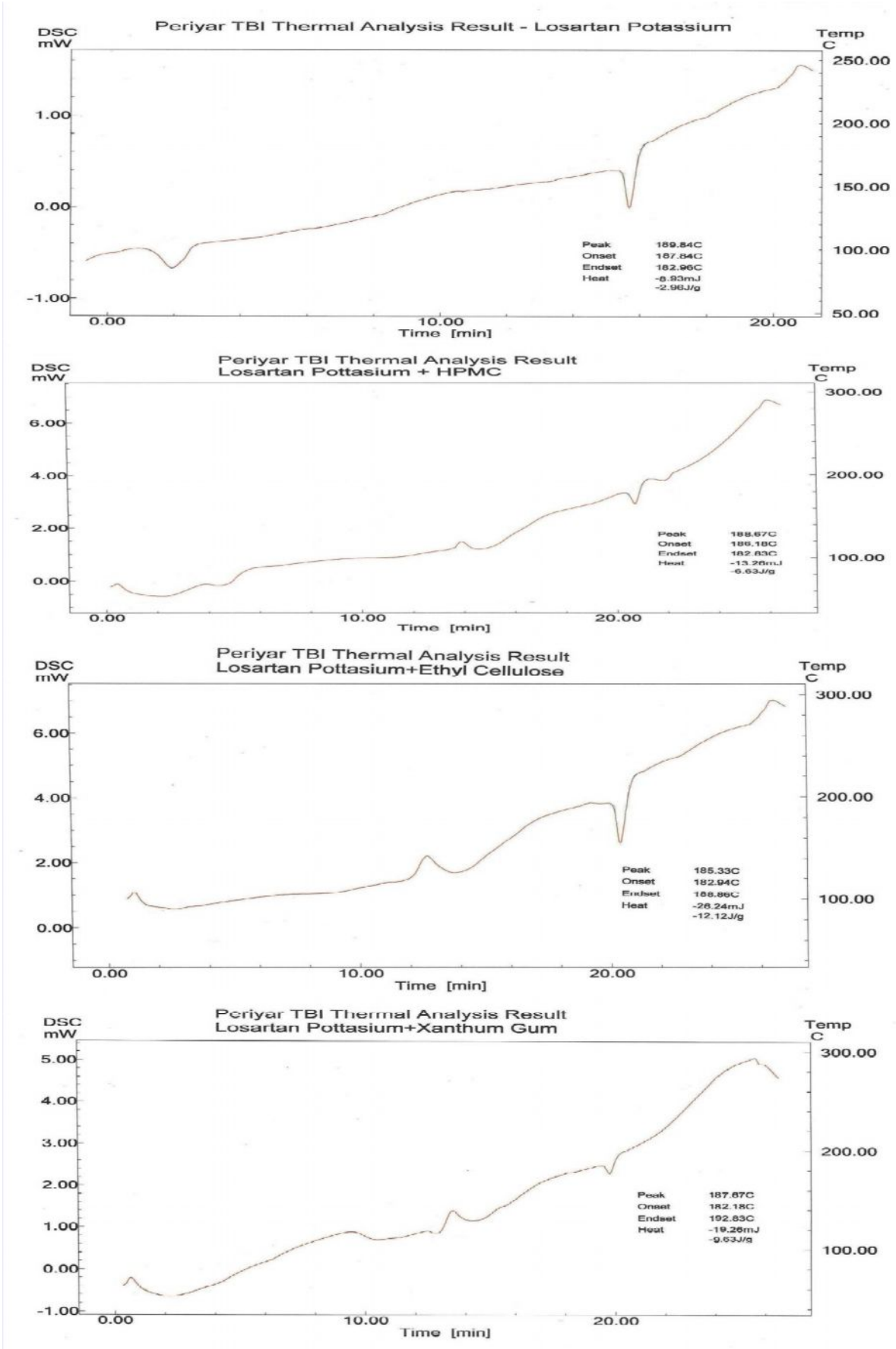

Figure 2: It shows the DSC thermogram of drug and drug with different pol ymers

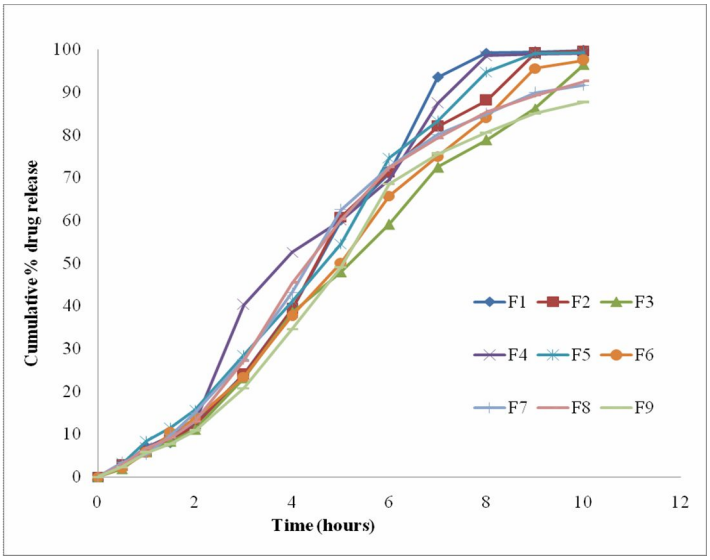

Figure 3: *In-Vitro* drug release profile of F1 to F9

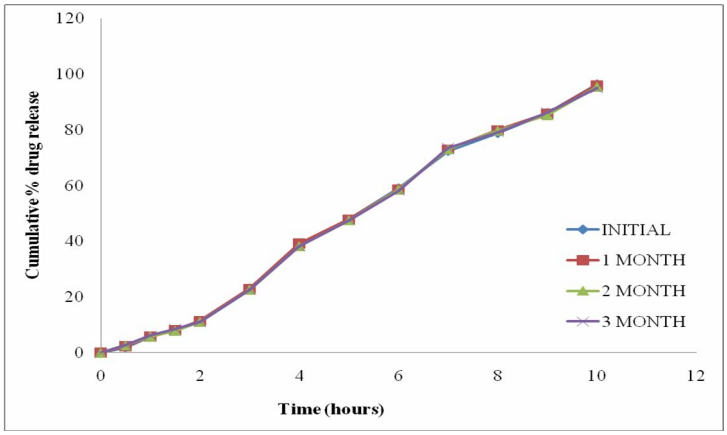

Figure 4: *In vitro* release profile of formulation F3 during stability study

Evaluation of Losartan potassium sustained release tablets

The Losartan potassium sustained release tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in Table 2. The thickness of sustained release tablets was measured by vernier caliper and was ranged between 4.10±0.12 and 4.18±0.11 mm. The weight variation for different formulations (F1 to F9) was found to be 250.45±1.3% to 251.3±1.49%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the sustained release tablets was measured by Monsanto hardness tester and was controlled between 5.50±0.447and 6.16±0.683 kg/cm^2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F9 was found to be in between 98.54±1.7to 100.86±1.2 of Losartan potassium, it complies with official specifications.

***In-Vitro* dissolution studies**

In vitro dissolution studies of all the formulations of sustained release tablets of Losartan potassium were carried out in 0.1N HCl for first 2 hours and pH 6.8 phosphate buffers for next 8 hours respectively. The study was performed for 10 hours, and percentage drug release was calculated at 1 hours time intervals. The results of *in vitro* dissolution studies of all formulations were shown in Figure 3.

When cumulative % drug release plotted versus time it was observed that, for three of the polymers used, an increase in polymer concentration induce a decrease in the release rate. The drug release rate from xanthan gum matrix was found to be less as compared to HPMC K100M. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. Whereas formulation containing ethyl cellulose(F4 to F6) gave higher drug release as compared to formulation containing HPMC K100M (F1 to F3) and xanthan gum (F7 to F9), which may be

due to quick hydration of polymer matrix within 1 to 3 hours, after which matrix might get started to erode.

It is expected that the developed formulation should have the following theoretical drug release profile, *i.e.*, 96.45% for 10hrs. Formulations F1 to F2 and F4 to F9 failed to meet the needed theoretical drug release profile. Formulation F3 met the needed theoretical drug release profile and has the sustain action i.e.,retarding the drug release so the release is for a long time and thus more bioavailability; for these reasons, it was considered the best formulation among all the nine formulations of this series.

Release kinetics

The data obtained from in vitro dissolution studies were fitted in different models viz. zero order, first order, Higuchi and Korsemeyer- Peppas equation, the results were shown in Table 3. It was also observed that highest correlation was found for Zero order profile ($R^2 > 0.99$), which indicates the drug release via diffusion mechanism from hydrophilic matrices. To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsemeyer- Peppas equation. A value of n for all matrices studied here was ranged between 1.2412 to 1.9166, indicating an anomalous behaviour corresponding to swelling, diffusion and erosion mechanism.

Stability study

The stability study results obtained were shown in Table 4. The Losartan potassium sustained release tablets did not show any significant change in physicochemical parameters and other tests. Thus, it was found that the sustained release tablets of Losartan potassium formulation (F3) were stable under these storage conditions for at least 3 months.

Conclusion

The aim of the study was to study the effect of various hydrophilic and hydrophobic polymers on in vitro release rate from sustained release tablets of Losartan potassium. Different types of matrix forming polymers like HPMC K100M, Ethyl cellulose and Xanthan gum were studied. The use of gel-forming polymer methocel K100M was successful to achieve the sustained drug release for 10 hours from Losartan potassium sustained release tablets. Formulation F3 showed sustained drug release for 10 hours so it was selected as the best formulation amoung all the nine formulations. The kinetics of drug release was best explained by zero order equation. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed. The Losartan potassium sustained release tablets were stable at 40°C/75% RH up to 3 months.

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