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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LOSARTAN POTASSIUM USING MELTGRANULATION TECHNIQUE

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ABSTRACT

The purpose of the present study was to develop a sustained release matrix tablet of Losartan Potassium, a highly water soluble drug by employing hydrophobic Meltable binders like bees wax, stearic acid and emulsifying wax. $HPMCK_4M$ was also added in some formulations to extend the release upto 12 hrs. The effect of wax ratio on release was studied. Tablets were prepared by melt granulation technique by incorporating 25% and 20% of wax, HPMC was added at a concentration of 5%. The granules were subjected to pre compression parameters like angle of repose, Carr's index, Hausner's ratio, bulk and tapped densities. Drug: wax interaction was determined by FTIR and DSC studies. Tablets were evaluated for various parameters like hardness, friability, weight variation and drug content. The values are within the acceptable limits for all the formulations. Drug release from the matrix tablet was studied by using paddle type of apparatus. Dissolution was carried out in 0.1N HCl for 2 hrs, and next 10 hrs in pH 6.8 phosphate buffer in order to mimic the in vivo conditions. Among all the formulations, F6 showed maximum release(99%) at end of 12 hrs. The release data was subjected to various kinetic models to know the mechanism of drug release. All the formulations followed zero order kinetics, and from n values obtained from Peppas plot, the release mechanism was anamolous transport.

Key words: Losartan potassium, Melt granulation, Meltable binders, Dissolution, FTIR, DSC.

INTRODUCTION

The oral route is a route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike [1]**.** In long term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [2]. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, and show better patient compliance, and increase safety margin for high potency drugs [3]. Controlled release oral products have attracted the attention of formulation scientists over the last three decades due to an array of advantages they offer [4-7].

Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Now a day by using melt granulation process in the pharmaceutical industry variety of dosage forms and formulations such as immediate release and sustained release pellets, granules, tablets are formulated. This technique is better than a conventional granulation due to no water or organic solvents are needed. The process is less time consuming and uses less energy than wet granulation. The drug to binder ratio was shown to impact the degradation behavior of the drug product. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. Extrusion is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under pressure [8-9]. The process of melt granulation involves wetting and nucleation, coalescence step, attrition and breakage.

Losartan Potassium is an orally active non-peptide Angiotensin-2 receptor antagonist used in treatment of hypertension. It is white to off- white, crystalline powder freely soluble in water, sparingly soluble in Isopropyl alcohol, slightly soluble in Acetonitrile. Losartan potassium has half life of 1.5 – 2 hrs and generally administered as immediate release tablet at a dose of 25 – 100mg three to four times a day. When

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administered such frequently, dose related side effects like nausea, dizziness are even more due to fluctuations in drug plasma concentration levels.

Hence present study was aimed towards formulation and invitro evaluation of sustained release matrix tablet of Losartan Potassium using melt granulation technique by employing bees wax, stearic acid and emulsifying wax as meltable binders and to study the effect of wax concentration on the release rate.

MATERIALS & METHODS

Losartan Potassium was produced as a gift sample from Aurobindo Pharma Ltd. HPMC was produced from Yarrow chemicals. Stearic acid was purchased from Sd fine chemicals & Emulsifying wax was purchased from Lobachemi. All other chemicals and reagents used were of analytical grade.

Estimation of Losartan Potassium

An UV-VIS spectrophotometric method was used for the estimation of Losartan Potassium. A stock solution of Losartan Potassium was prepared in distilled water and the absorbance of Losartan Potassium was measured at 241nm using Elico UV-VIS spectrophotometer SL 150.
As the dissolution studies were carried out in 0.1 N HCl and 6.8 pH buffer the calibration curves were constructed in these media. The standard solutions were prepared at a concentration of 2- 10µg/ml and absorbance was measured at 241 nm. The data was given in Table:2 and shown in Fig: 1 & 2

Formulation of tablets by melt granulation technique

Sustained release granules were prepared using wax as retarding material. For the preparation of sustained release formulation bees wax, emulsifying wax and stearic acid were used at two different concentrations & in combination of waxes by trial and error basis. Hydrophobic wax granules were prepared by exactly weighing waxes as per formulation design & melting them in a porcelain dish on a water bath at a temperature of its melting point. Drug and diluents were gradually added to the molten mass with continuous stirring .The molten mass was allowed to cool, dried and then sized with a 16 mesh sieve. Prior to compression 2.5 %(w/w) of magnesium stearate & talc were added & the resulting powder blend was compressed on a Elite mini press using 8 mm round punches to the hardness of 6-8 kg/cm^2.The formulations are shown in Table-2

Characterization of granules

The granules prepared by melt granulation technique were evaluated for various precompression parameters like bulk & true densities, carr's index, angle of repose, Hausner's ratio. Tapping method was used to measure the densities and carr's index

Compressibility index = $[\rho t-\rho b / \rho t] \times 100$

Hausner ratio= $\rho t/ \rho b$

Where ρt = tapped density

ρb = 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 [10]**.** The data was given Table-3

COMPATIBILITY TESTING OF DRUG WITH POLYMER

FTIR Studies

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. The IR spectra of pure drug and combination were shown in Figures- 3 & 4 respectively.

Characterization by DSC thermo grams

DSC was performed to characterize thermal changes in melting behaviour of Losartan Potassium with other excipients present in different formulations. Thermograms were obtained by using a differential scanning calorimeter at a heating rate 10^{o}C /min over a temperature range of 50-400^{o}C. The sample was hermetically sealed in an aluminium crucible. Nitrogen was purged at the rate of 10 ml/min for maintaining inert atmospheres. The thermograms of pure drug and combination were shown in Figures 5&6 respectively.

Evaluation of tablets

The prepared sustained release tablets were evaluated for Thickness using 6 tablets (Vernier calipers), uniformity of weight using 20 tablets (analytical balance), hardness using 6 tablets (Monsanto hardness tester) and friability using 20 tablets (Roche type friabilator) [11-12].

Drug Content Estimation

Five tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 20 mg of Losartan Potassium was transferred to a 100mL volumetric flask, and the Losartan Potassium was extracted into 75mL methanol. This solution was filtered and collected in to a 100mL volumetric flask and made up to the volume with methanol. The solution was suitably diluted with 0.1N HCl and the absorbance was measured at 241nm. Content uniformity was calculated using formula [13],

% Purity = 10 C (Au / As)

Where,

C - Concentration,

Au and As - Absorbance's obtained from standard preparation and assay preparation respectively. The data was given in Table-4.

In-Vitro dissolution studies

The tablet samples were subjected to *In-vitro* dissolution studies using USP Type II dissolution apparatus at 37±2°C and 50 rpm speed. To mimic the Gastrointestinal conditions, as per the official recommendation of USFDA, 900 ml of 0.1 N HCL was

used as dissolution medium for initial 2hr and 6.8pH buffer for next 10 hr. Aliquot equal to 5 mL was withdrawn at specific time intervals and replaced with fresh buffer. The aliquots were diluted and drug release was determined spectrophotometrically at a wavelength of 241 nm by comparing with the standard calibration curve.

Release Kinetics

Zero Order Equation

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation [14]:

$$X = X_0 - K_0 t$$

where,

X = Amount of drug released at time t

X_0 = Amount of drug released initially

K_0 = Zero order rate constant

Higuchi Square Root Law

The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion. A form of the Higuchi Square Root Law is given by equation [15]:

$$Q = K_s\sqrt{t}$$

Where, Q = Amount of drug dissolved at time t

K_s = Higuchi rate constant

Korsermeyer Peppas Equation

The Korsemeyer's equation, which derived from, the linear line of log cumulative percentage vs. log time curve, is $M_t / M_\infty = Kt^n$

Where Mt and M∞ are the absolute and the cumulative amount of drug released in time t and infinite time; k is a constant incorporating the structural and geometric characteristics of the device and 'n' is the release exponent which is indicative of the mechanism of release [16].

RESULTS AND DISCUSSION

The prepared granules were evaluated for various pre compression parameters and data was given in Table-. The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content. All the values are within the range and data was given in Table.

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 prominent and sharp endothermic peak at 274 ^{0}c in the pure Losartan Potassium (Fig 6.3) represents the melting point of Losartan Potassium .In all the DSC spectrums the characteristic drug melting point was observed with slight changes in terms of broadening or shifting towards lower temperature. This could be due to mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility. From these results there was no drug excipients interaction. This indicates the choice of excipients used in the formulation of matrix tablets were suitable which are shown in the figures 5& 6.

***In-Vitro* dissolution studies**

The dissolution studies were carried out initially for 2hrs in 0.1N HCl and for next 10hrs in 6.8pH phosphate buffer in order to mimic the in vivo conditions and the cumulative % drug release data was given in Table-5.The formulations F1, F2 were formulated by using Bees wax as meltable binder at a concentration of 25 and 20% (W/W) respectively. In FI the wax prolonged the drug release until 12hr, but with less percent of drug release, with about 70.71%, it may be due to poor penetration of dissolution medium in matrices due to increased lipophilicity at high concentration. So, F2 was formulated by decreasing the conc. of beeswax and maximum amount of drug was released at end of 10 hrs i.e 96.56%. In order to show better sustained action along with high percent drug release F3 was formulated with 20% (W/W) concentration of wax & 5% HPMC was included to sustain the release upto 12 hrs. The formulation F3 showed sustained action and also gave high percent drug release at the end of 12hr with about 92.25%. Among the F1, F2, F3 formulations F3 showed better sustained with high percent of release at end of 12hrs.The comparative dissolution profile was shown in figure-7.F4 & F5 are the formulations with stearic acid as the release retardant at the conc. of 25 and 20 % (W/W) respectively. Formulation F4 showed 81.93% at the end of 12 hr as the lipophilicity is less when compared to that of bees wax. Formulation F5 showed 98.98% at the end of 10hr. Decrease of polymer concentration could not sustain the drug release upto 12hrs hence, F6 was formulated by adding 5% HPMC. Among the F4, F5, F6 formulations F6 showed better sustained action with high percent drug release with about 99.96% at the end of 12 hr. The comparative dissolution profile was shown in figure-8.F7 & F8 are the formulations with stearic acid as the release retardant at the conc. of 25 and 20 % (W/W) respectively. Formulation F7 showed 81.93% at the end of 12 hr. Formulation F8 showed 98.98% at the end of 10hr.Decrease of polymer concentration could not sustain the drug release upto 12hrs hence, F9 was formulated by adding 5% HPMC. Among the F7, F8, F9 formulations F9 showed better sustained action with high percent drug release with about 94.89% at the end of 12 hr. The comparative dissolution profile was shown in figure-9.F10, F11 & F12 formulations are the combinations of meltable binders employed. Formulation F10 was formulated using 12.5% concentration of both beeswax & emulsifying wax and the release was 79.71% at end of 12 hr.F11 was formulated using 12.5% of each bees wax and

stearic acid; the release was 86.33% at end of 12 hrs. F12 was formulated by using both emulsifying wax & stearic acid at a concentration of 12.5% each. The release was 97% at end of 12 hrs. The comparative dissolution profile was shown in figure-10. Among three waxes employed bees wax showed more retardant effect followed by emulsifying wax and then stearic acid.

Release Kinetics

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations .The data were analyzed by the regression coefficient value (r2) of all batches were shown in Table-6 and zero order plots were shown in figures 11-14, peppas plots were shown in figures 15-18.

Table 1. Formulations prepared by melt granulation method

Ingredients mg/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan potassium(LP)	50	50	50	50	50	50	50	50	50	50	50	50
Bees Wax	50	40	40	-	-	-	-	-	-	25	25	-
Stearic Acid	-	-	-	50	40	40	-	-	-	-	25	25
Emulsifying Wax	-	-	-	-	-	-	50	40	40	25	-	25
$HPMCK_4M$	-	-	10	-	-	10	-	-	10	-	-	-
Lactose	92	102	92	92	102	92	92	102	92	92	92	92
Magnesium state	4	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Total weight(mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 2. Calibration curve data

Concentration(µg/ml)	Absorbance	
	0.1NHCl	pH 6.8
2	**0.079**	**0.091**
4	**0.132**	**0.158**
6	**0.201**	**0.216**
8	**0.253**	**0.283**
10	**0.317**	**0.345**

Table 3. Pre compression properties of all formulation

Powder Blend	Angle of Repose (θ)	Bulk density(ρb) (g/mL)	Tapped density(ρt)(g/mL)	Compressibility index (%)	Hausner's ratio
F1	28.1±0.01	0.57±0.01	0.71±0.04	19.0±0.01	1.24±0.01
F2	26.3±0.02	0.55±0.02	0.67±0.03	16.9±0.02	1.22±0.02
F3	27.6±0.03	0.55±0.01	0.70±0.01	19.9±0.02	1.27±0.03
F4	26.9±0.04	0.54±0.03	0.73±0.03	21.5±0.01	1.35±0.01
F5	26.9±0.05	0.57±0.01	0.67±0.03	20.8±0.02	1.26±0.02
F6	28.0±0.01	0.53±0.04	0.74±0.01	23.1±0.01	1.29±0.01
F7	32.6±0.04	0.56±0.01	0.74±0.02	23.7±0.01	1.30±0.04
F8	27.3±0.05	0.57±0.02	0.73±0.02	22.8±0.01	1.32±0.02
F9	27.9±0.01	0.58±0.03	0.72±0.02	18.7±0.02	1.24±0.01
F10	26.3±0.06	0.55±0.01	0.71±0.01	19.0±0.02	1.24±0.01
F11	27.6±0.03	0.54±0.03	0.73±0.03	20.8±0.02	1.35±0.01
F12	26.9±0.04	0.57±0.01	0.67±0.03	19.9±0.02	1.26±0.02

Table 4. Post compression properties of all formulation

Parameters / Formulations	Hardness (kg/cm2) ± SD	Percent friability	Weight Variation ± SD	Drug content (mg/tab)±SD
F1	5.5±0.2	0.25±0.01	200±0.02	96.5±0.02
F2	6.0±0.1	0.30±0.06	199±0.04	98.0±0.01
F3	5.5±0.12	0.45±0.04	202±0.02	99.0±0.01
F4	6.0±0.16	0.55±0.02	200±0.06	99.5±0.05
F5	5.5±0.09	0.21±0.03	198±0.07	98.0±0.01
F6	6.0±0.08	0.35±0.03	201±0.03	99.0±0.01
F7	5.5±0.07	0.40±0.02	202±0.04	98.5±0.02
F8	6.0±0.12	0.25±0.03	200±0.02	99.5±0.02
F9	5.5±0.14	0.55±0.01	201±0.04	99.4±0.02
F10	6.0±0.09	0.65±0.01	202±0.06	97.0±0.02
F11	5.5±0.12	0.55±0.02	198±0.07	98.0±0.01
F12	6.0±0.1	0.21±0.03	200±0.06	99.0±0.01

Table 5. Cumulative percent drug releases with standard deviation

Time (hrs)	Cumulative % drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	8.23 ± 0.12	17.37 ± 0.08	15.95± 0.05	11.37± 0.09	19.47± 0.07	15.61± 0.22	9.37± 0.09	19.87± 0.06	14.48± 0.02	10.26± 0.09	12.2± 0.25	14.46± 0.19
1	11.65 ± 0.09	23.31 ± 0.12	21.31± 0.2	20.64± 0.17	27.83± 0.13	23.05± 0.08	12.64± 0.17	23.95± 0.22	19.78± 0.27	14.02± 0.12	16.84± 0.1	23.2± 0.09
2	16.11 ± 0.06	31.63 ± 0.09	29.31± 0.11	31.88± 0.02	39.28± 0.07	37.09± 0.18	17.88± 0.02	31.47± 0.17	26.18± 0.08	15.91± 0.2	20.17± 0.15	31.64± 0.13
3	24.56± 0.2	48.36 ± 0.22	44.96± 0.32	38.77± 0.23	51.96± 0.2	46.11± 0.25	26.77± 0.23	48.17± 0.24	36.64± 0.16	31.46± 0.14	36.5± 0.28	45.71± 0.21
4	33.53 ± 0.11	56.07 ± 0.16	52.45± 0.26	44.21± 0.11	68.12± 0.12	55.09± 0.31	39.21± 0.11	60.55± 0.11	49.02± 0.22	41.73± 0.18	44.09± 0.09	56.23± 0.16
6	45.03 ± 0.24	70.57 ± 0.28	66.01± 0.09	56.98± 0.19	79.72± 0.24	64.43± 0.17	45.98± 0.19	78.1± 0.04	63.91± 0.07	51.36± 0.26	56.96± 0.03	68.29± 0.05
8	57.16 ± 0.15	82.72 ± 0.14	78.82± 0.12	69.24± 0.26	88.69± 0.11	75.27± 0.24	62.24± 0.26	89.34± 0.21	74.59± 0.03	62.88± 0.35	65.99± 0.16	78.27± 0.24
10	63.46 ± 0.06	96.56 ± 0.24	86.75± 0.33	77.47± 0.14	98.98± 0.01	89.09± 0.19	72.47± 0.14	96.02± 0.01	86.47± 0.15	71.28± 0.11	74.22± 0.22	85.11± 0.18
12	70.71 ± 0.13	-	92.25± 0.17	88.93± 0.06	-	99.96± 0.04	81.93± 0.06	-	94.89± 0.06	79.71± 0.31	86.33± 0.18	97.9± 0.07

Table 6. The Rate Constant and Regression values for all the formulations

Formulations	Zero order		Higuchi	Peppas	
	K0(mg/hr)	R2	R2	N	R2
F1	5.85	0.977	0.968	0.785	0.986
F2	9.06	0.961	0.986	0.636	0.989
F3	7.33	0.939	0.990	0.634	0.988
F5	6.6	0.985	0.962	0.789	0.984
F6	9.30	0.972	0.960	0.645	0.971
F7	7.52	0.890	0.987	0.561	0.978
F8	7.74	0.944	0.990	0.616	0.979
F9	9.57	0.954	0.981	0.719	0.978
F10	7.60	0.967	0.982	0.674	0.986
F11	8.99	0.965	0.968	0.727	0.956
F12	11.08	0.987	0.970	0.774	0.949

Figure 1. Calibration curve in 0.1NHC

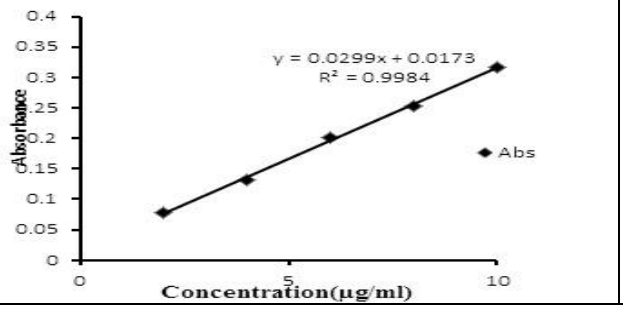


Figure 2. Calibration curve in 6.8pH

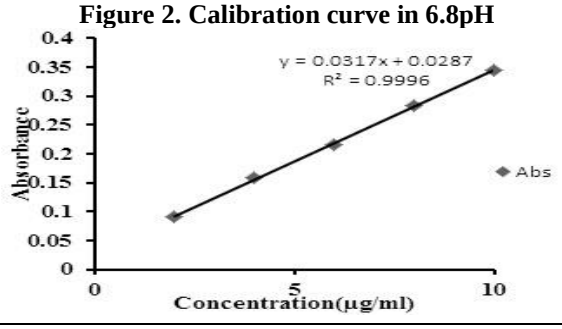


Figure 3. FTIR spectra of Losartan Potassium

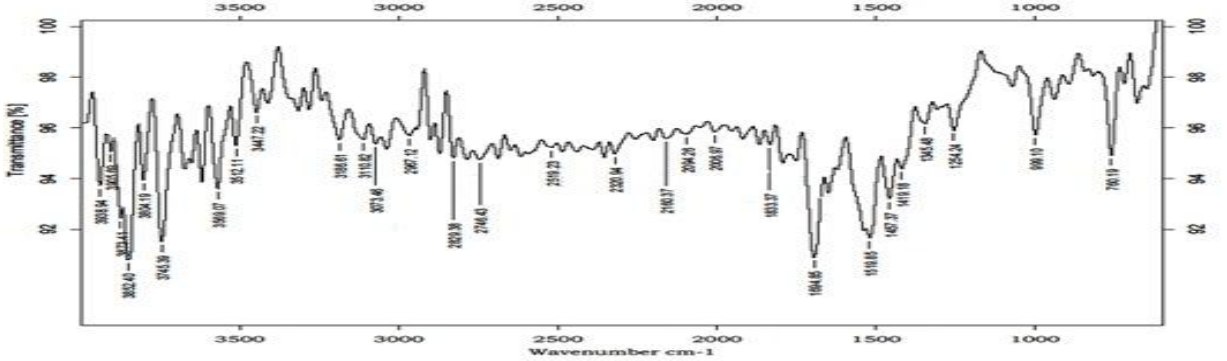


Figure 4. FTIR spectra of Drug and Stearic acid

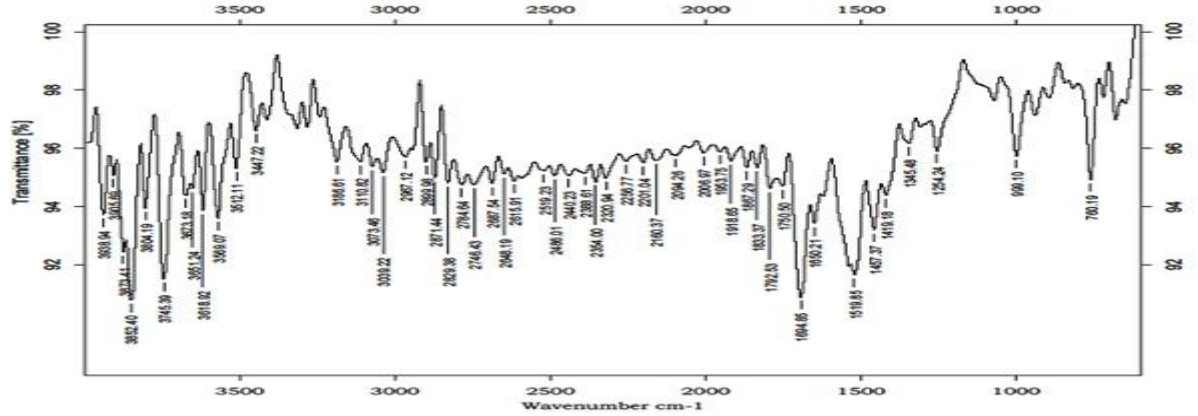
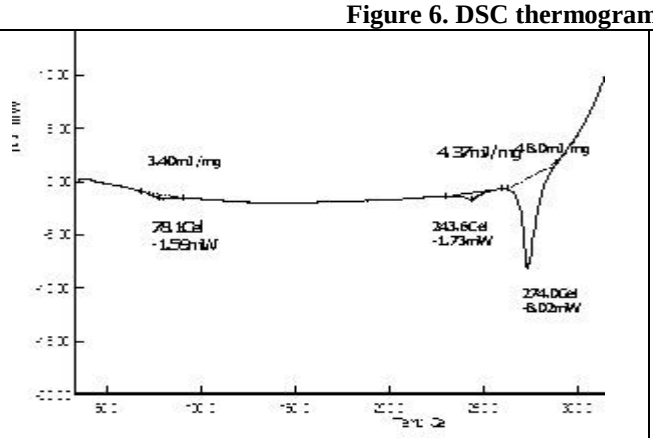


Figure 6. DSC thermogram of drug and stearic acid



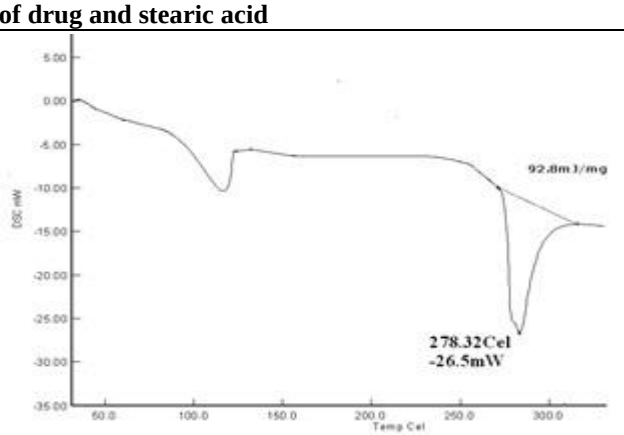


Figure 7. Comparitive dissolution profiles of formulations with Bees wax

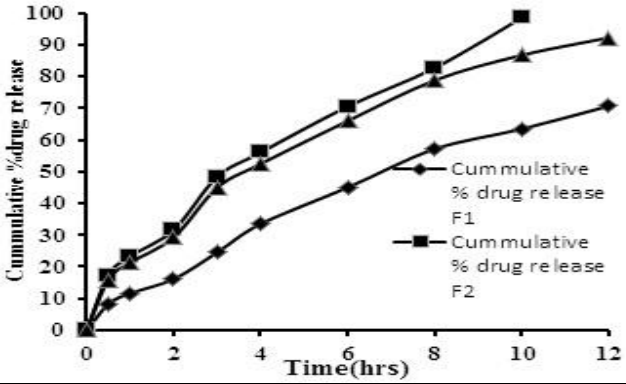


Figure 8. Comparitive dissolution profiles of formulations

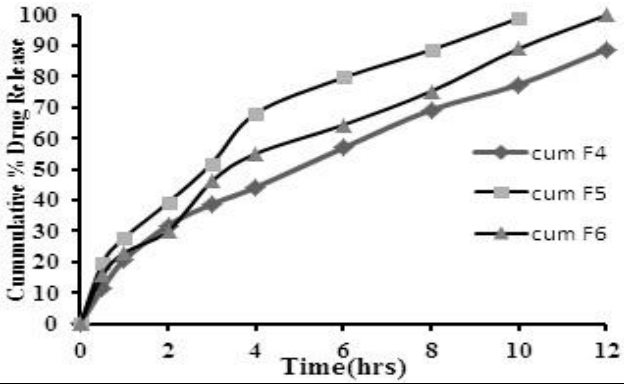


Figure 9. Comparitive dissolution profiles of formulations with Emulsifying wax

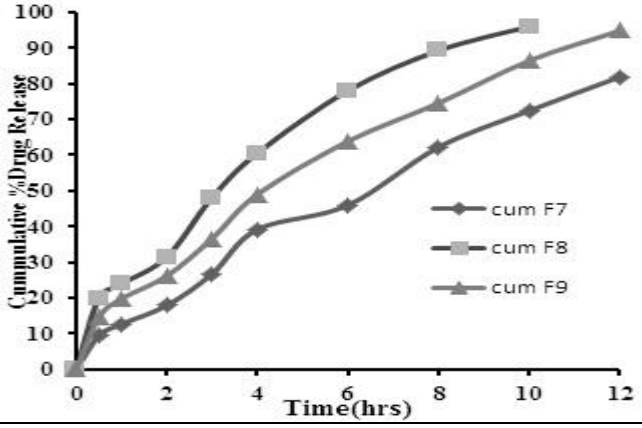


Figure 10. Comparative dissolution profiles of formulations with combination

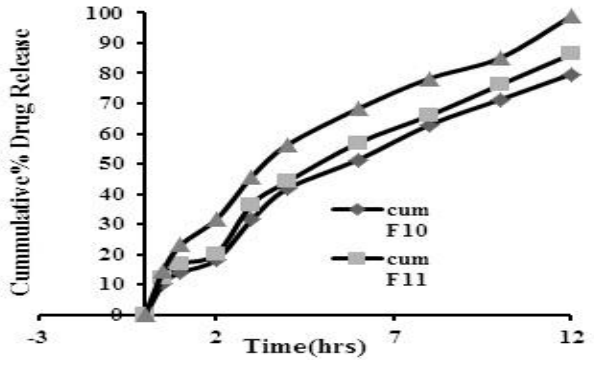


Figure 11. Zero order plot for F1, F2, F3

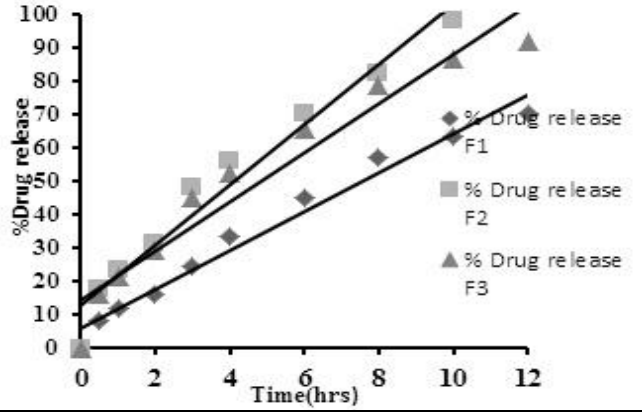


Figure 12. Zero order plot for F4, F5, F6

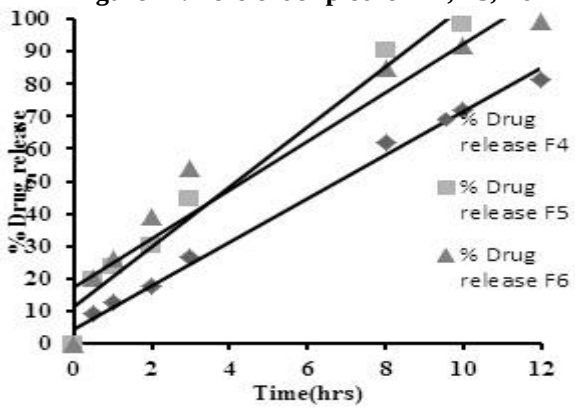


Figure 13. Zero order plot for F7, F8, F9

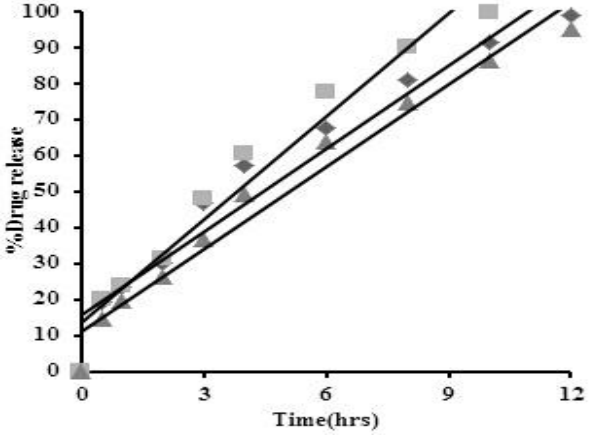


Figure 14. Zero order plot for F10, F11

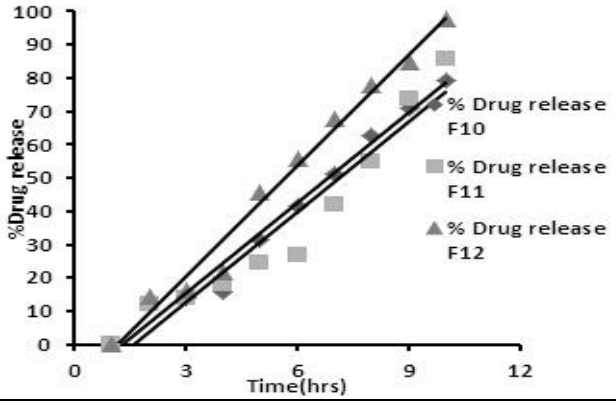


Figure 15. Peppas plot for F4, F5,F6

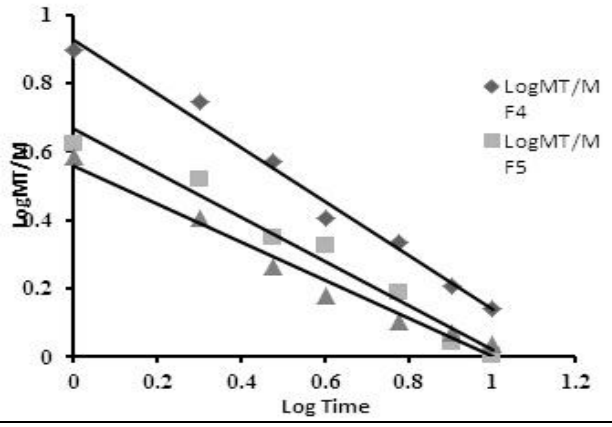


Figure 16. Peppas plot for F1, F2, F3

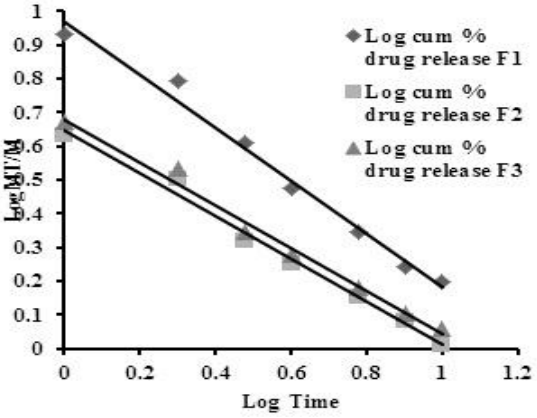


Figure 17. Peppas plot for F10, F11, F12

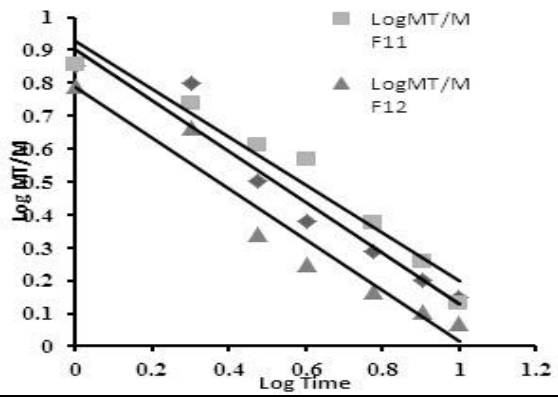
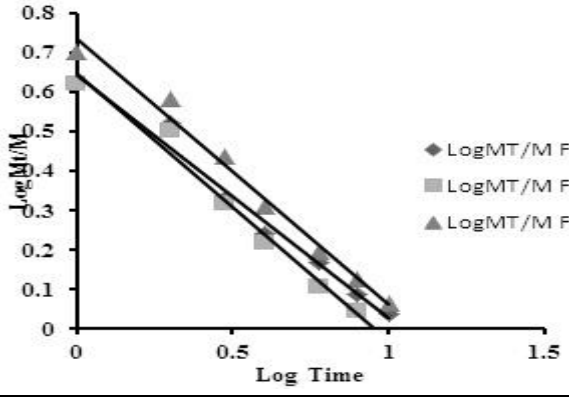


Figure 18. Peppas plot for F7, F8, F9



CONCLUSION

All the formulations followed zero order kinetics with high regression values. From the Higuchi plots, the release mechanism was found to be diffusion initially. On extending 60% of dissolution data to Peppas equation, the release mechanism was diffusion followed by erosion as the n values obtained are in the range of 0.5 to 0.9.

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