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FORMULATION AND EVALUATION OF FILM COATED RANOLAZINE SUSTAINED RELEASE MATRIX TABLETS

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RESEARCH ARTICLE

ABSTRACT

The aim of the present work is to formulate and evaluate film coated sustained release matrix tablets. Ranolazine is a BCS-II drug having half life 5-6 hours and shows high pH dependent solubility. It is freely soluble in aqueous solutions having pH below 4.5 and as pH increases, solubility decreases dramatically. The present work is done by using one pH dependent polymer (Eudragit L 100-55), one pH independent polymer (HPC-LF). In vitro release studies were performed for all the formulations using USP type II apparatus (paddle method) in 900 ml of 0.1N hydrochloric acid at 50 rpm for 24 hours and analyzed by UV spectrophotometer at 272nm. Further, in-vitro release pattern of drug from the optimized formulation was compared with innovator formulation and it was found to be super imposable with the Innovator product Ranexa based on dissimilarity and similarity factors.

Keywords: Ranolazine, Eudragit L 100-55, HPC-LF, sustained release, matrix tablets, Ranexa.

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Deepika : Ranolazine sustained release matrix tablets

INTRODUCTION

Ranolazine[1,2,3] is indicated for the treatment of chronic angina, Ranolazine may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy and angiotensin receptor blockers. The recommended initial dose of Ranolazine is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient's response, further titrated to a recommended maximum dose of 750 mg twice a daily. Ranolazine plasma half-life is 5-6 hours. After oral administration of Ranolazine, peak plasma concentrations (Cmax) are typically observed between 2 and 6 hours. Steady state is generally achieved within 3 days of twice-daily dosing. The terminal half-life at steady state after

oral administration of ranolazine is about 7 hours, due to the absorption rate-limited elimination. From the preformulation studies, Ranolazine was found to be freely soluble drug in acidic medium below pH 4.5 and solubility decreases as pH increases. To provide sustained release action of Ranolazine, one or more pH dependent polymers were choosen to control the dissolution profile of developed formulation so that, the drug is released slowly and continuously while passing through stomach and Gastro intestinal tract. In this work,one pH dependent polymer (Eudragit L 100-55),one pH independent polymer(HPC-LF) and Meglumine as alkaliser.

MATERIALS AND METHODS

Ranolazine was received as a gift sample MSN Laboratories Pvt. Ltd, Hyderabad. Micro crystalline cellulose(Avicel pH 101) was purchased from Dow Chemical Company, Eudragit L 100-55 was purchased from Evonik Industries, HPC-LF was purchased from Dow Chemical Company, Meglumine is gift sample from MSN Laboratories Pvt. Ltd., Magnesium stearate was obtained from Emco industries, Opadry Yellow was obtained from Colorcon Asia Pvt Ltd.,

Analytical Method

Ranolazine in pure form and designed formulation was analyzed using UV spectrophotometric method. The stock solution (100µg/ml) was prepared in distilled water and diluted to obtain a concentration of 10µg/ml. Solution was kept in fused silica cuvette 10mm.The UV spectrum was recorded from range of 200-400nm using Schimadzu UV-Visible spectrophotometer at 1cm slit width. The same procedure was carried out using 0.1N HCl buffer which showed a λmax at 272nm which is shown in Fig:1.

Preparation of sustained release matrix Tablets:

Ranolazine sustained release Matrix Tablets were prepared by wet granulation method by the compositions given in Table:1. Required quantities of Ranolazine, Eudragit, Hydroxy Propyl Cellulose(HPC-LF), and Micro crystalline cellulose were weighed and mixed. This dry mix was sifted through #40 mesh and mixed in a poly bag for uniform distribution of API. To dry mix, Meglumine solution was added to make wet granules. Granules were dried for 30 minutes and the dry granules were sieved through #20 mesh. Magnesium stearate was sifted through #60 mesh and added to dry granules and mixed for 5 minutes. The granules obtained were compressed with 17×8 mm caplet shaped standard concave punches using 8 station compression machine. Film coating suspension was prepared by dispersing opadry 31F82585 yellow into purified water by stirring. This coating suspension was sprayed onto tablets in pan coating equipment. Finally film coated sustained release matrix tablets were obtained.

The Ranolazine sustained release matrix Tablets were evaluated for appearance, Friability, Weight variation, Hardness, Thickness, Diameter, Drug content uniformity, Coating thickness, and Invitro drug release studies[19].

Appearance

The general appearance of a tablet, its visual identity and over elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet to tablet and for monitoring trouble free manufacturing.

Friability

For each formulation, the friability of 20 tablets was determined using the Roche friabilator. This test subjects a number of tablets to combined effect of shock abrasion by utilizing a plastic chamber which revolve at a speed of 25 rpm, dropping the tablets to distance of 6 inches in each revolution. A sample of preweighed 20 tablets were placed in Roche friabilator, which were then operated for 100 revolutions for 4

minutes. The tablets are then de-dusted and reweighed. A loss of less than 1% in weight in generally considered acceptable. Percent friability (% F) was calculated.

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness, Thickness, and Diameter

Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users. Manufacturing processes such as coating, packaging and printing can involve considerable stress, which the tablet must be able to withstand. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured. Thickness, diameter and hardness was determined using Vernier calipers & Hardness tester.

Drug content uniformity

100 mcg/ml of API standard solution is prepared by using methanol as solvent. Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 1000 mg of API into a 1000 ml volumetric flask. Dissolve with the aid of 1000 ml of methanol. Shake and sonicate for one hour and filter. Dilute to prepare equivalent 100 mcg/ml solution with methanol. The absorbance of the resulting solution was measured at the λmax 272 nm. The content of drug is calculated.

In Vitro Drug Release Studies:

In vitroDrug release study for prepared sustained release tablets of Ranolazine were conducted for 24hrs using (Electro lab USP XXIITDT-08L) with type USP-II apparatus(paddle) at 50rpm speed at 37° C ± 0.5° C in 900 ml of 0.1N HCl. After appropriate dilution, the sample solution was analyzed at 272nm for ranolazine by a UV-spectrophotometer. The amounts of drug present in the sample were calculated with the help of appropriate calibration curve. Also the *in vitro* drug release study for the marketed tablet was conducted.

Kinetics of In-vitro drug release[15,16,17,18]:

To analyze the mechanism of release and release kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix and Korsemeyer- Peppas. In this by comparing the r-values obtained, the best-fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation-

$$Qt = Q_0 + K_0 t$$

Where

Qt = amount of drug dissolved in time t,

Q_0 =initial amount of drug in the solution and

K_0= zero order release constant.

First order kinetics:

To study the first order release rate kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \text{log } Q_0 + K_1 t/ 2.303$$

Where

Q_t= amount of drug released in time t,

Q_0=initial amount of drug in the solution and

K_1= first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids or solid matrices. Mathematical expressions were obtained for drug particle dispersed in uniform matrix behaving as the diffusion media, and the equation is

$Qt = KH. T^{1/2}$

Where

Qt= amount of drug release in time t,

KH = Higuchi dissolution constant.

Korsmeyer and Peppas release model:

To study this model the release rate data are data fitted to the following

Equation

$M^{t}/ M^{\infty} = K.t^{n}$

Where

M t/ M∞ = the fraction of drug release,

K = release constant,

t = release time and

n = Diffusional exponent for the drug release that is dependent on the shape of matrix dosage form.

RESULTS AND DISCUSSION

Physical appearance, hardness, friability, weight variation and drug content uniformity of different tablet formulations were found to be satisfactory (Table: 2). The manufactured tablets showed low weight variation and high degree of drug content uniformity.

In the present study an attempt was made to develop sustained release matrix tablets of Ranolazine using film coating technique.

The compatibility between pure drug and excipients used in formulation were confirmed by FT-IR studies.

An analytical method was developed to estimate Ranolazine in 0.1N HCl at 272nm. This method was found to obey Beer`s Lambert Law in the concentration range of 2-10µg/ml was shown in the Table: 3 and Fig:2.

Preformulation studies were carried out in which we found out that the Ranolazine was freely soluble in the acid medium below pH 4.5 and the solubility was decreasing as the pH increases was shown in the Table: 4.

To provide sustained release of Ranolazine, one or more pH- dependent polymer were chosen to control the dissolution profile of the Ranolazine formulation so that the formulation developed would release Ranolazine slowly and continuously as the formulation passed through the stomach and gastrointestinal tract. Eudragit L100-55 was selected as pH-dependent polymer, Micro crystalline cellulose was used as filler and meglumine was used as alkalizer..

F1 formulation was prepared by dry granulation method and was found that the tablets were not having good pre-compression parameters and post compression parameters.

The formulations F2-F9 were prepared by wet granulation method, the tablets were then evaluated for their shapes, colour, thickness, friability, weight variation, drug content uniformity and *in vitro* dissolution studies. The tablets were caplet shaped and pale yellow in colour with uniform thickness. The hardness and friability values of all tablets were within limits. The drug content uniformity confirmed that the drug content was within limits and the results were tabulated in Table: 2.

In vitro dissolution was carried out in 0.1N HCL and drug releases were observed for the formulations F2-F9 and the results were tabulated in Table:5.

Initially low concentration of polymers Eudragit L100-55 (6-7%) and HPC-LF (3.0-3.5mg) were used in formulations as shown in Table:1 which showed the drug release of 99% in 8 hours, then it was planned to increase the concentration of these polymers in a specific range in order to control the release.

Then three trails were tried with increasing the concentration of the Eudragit L100-55 (8-9%) and HPC-LF (4-5mg). Here the release was observed to be 95% in 8 hours which indicated that the concentrations of the polymers to be increased further.

Two more trails were performed by increasing the concentration of the Eudragit L100-55 (9-10%) and HPC-LF (5-6mg). In the first trail F7 it was found that the drug release was extending upto 20 hours but the initial release and the release at the 8th hour were not with in the limits. In the second trail F8 it was observed that the release was extending for 24 hours but the initial control over the release was not achieved.

As 24 hours extension of the drug release was achieved in F8 formulation to get the initial control over the release keeping the concentration of the Eudragit L100-55 (10%) constant the concentration of the HPC-LF was increased to 7mg in formulation F9. The dissolution profile obtained by the F9 formulation was showing an extension of drug release upto 24 hours and the initial control over drug release was achieved. Based on drug release kinetic profiles, regression coefficient R^2values and n values were calculated which were tabulated in Table:6 .Drug release profiles were shown in Fig:3-10.

The F9 formulation dissolution profile was compared with the marketed product which was showing the similarity and dissimilarity factors in the acceptable range which is shown in Table: 7 and Fig:11.

The F9 formulation was considered as the optimized formulation as it was similar to the marketed product and this was scaled to pilot scale and the stability test for 2 months was carried out as shown in Table:8 and Fig:12.

Stability studies on formulation F9 showed no significant change in the physical appearance, hardness and drug content uniformity tests as conducted after 60 days.

CONCLUSION

This work is done by using one pH dependent polymer (Eudragit L 100-55),one pH independent polymer(HPC-LF) to sustain the release of drug. *In-vitro* release pattern of drug from the optimized formulation was compared with innovator formulation and it was found to be super imposable with the Innovator product Ranexa based on dissimilarity and similarity factors.

ABBREVIATIONS

BCS- Biopharmaceutical Classification

HPC-LF- Low Substituted Hydroxy Propyl Cellulose

API- Active pharmaceutical ingredient

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Table 1: Formulation of Ranolazine Sustained Release Matrix Tablets

Ingredients	F1 mg/tab	F2 mg/tab	F3 mg/tab	F4 mg/tab	F5 mg/tab	F6 mg/tab	F7 mg/tab	F8 mg/tab	F9* mg/tab
Ranolazine	500	500	500	500	500	500	500	500	500
Microcrystalline cellulose pH101	116.75	100.1	92.95	85.8	81.98	78.15	74.33	70.5	69.5
Eudragit L-100 55	33.25	39.9	46.55	53.2	56.52	59.85	63.17	66.5	66.5
HPC-LF	3	3	3.5	4	4.5	5	5.5	6	7
Meglumine	-	10	10	10	10	10	10	10	10
Purified Water	-	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	12	12	12	12	12	12	12	12	12
Total weight(mg)	665	665	665	665	665	665	665	665	665
Opadry yellow	20	20	20	20	20	20	20	20	20
Total weight(mg)	685	685	685	685	685	685	685	685	685

F= Formulation batches

F1 formulation batch was prepared by dry granulation method.

F9*=optimized formula

Table 2: Evaluation of Tablet Parameters

Formulation Code	Uniformity of Thickness (mm)	Hardness (kg/cm^2)	Friability%	Weight variation (mg)	Drug Content Uniformity (mg)
F1	5.44	3	0.07	683.28	499.32
F2	5.73	7	0.05	682.76	497.87
F3	5.79	9	0.09	684.12	503.76
F4	5.78	9.5	0.07	687.97	498.65
F5	5.85	10	0.06	688.63	502.43
F6	5.89	9.5	0.12	687.56	503.72
F7	5.83	11	0.08	686.87	501.59
F8	5.98	10.5	0.1	684.49	499.24
F9	5.90	11.5	0.1	685.95	500.86

Table 3: Standard Calibration Curve of Ranolazine at 272nm in 0.1N HCl Solution

S.No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.147
3	4	0.287
4	6	0.423
5	8	0.544
6	10	0.692

Table 4: Solubility Data at Different p^H Conditions

Solution in pH	Solubility(mg/ml)	USP solubility class
4.5	161	Freely soluble
5.5	5.84	Slightly soluble
6.5	1.63	Slightly soluble
6.8	0.83	Very slightly soluble
7.5	0.24	Very slightly soluble

Table 5: In Vitro release Profile of Ranolazine Tablets, Formulations F2 - F9

	Cumulative Percentage drug release								
Time (hrs)	F2	F3	F4	F5	F6	F7	F8	F9	Marketed Product
0	0	0	0	0	0	0	0	0	0
0.5	53.5	52.3	49.3	47.4	45.2	43.6	21.3	18.2	17.2
2	63.4	76.5	68.5	66.7	64.6	59.2	39.6	36.4	33.7
4	87.8	85.4	87.4	82.5	80.3	75.5	50.3	47.3	45.2
8	99.7	99.6	97.6	96.2	94.6	84.4	70.8	67.8	64.6
12	--	--	99.6	99.4	99.5	92.4	85.3	82.7	80.3
20	--	--	--	--	--	99.3	98.2	97.4	96.7
24	--	--	--	--	--	--	99.4	99.8	99.9

Table 6: Drug Release Kinetic Parameters of Formulations F2-F9

Formulation	Zero Order	First Order	Higuchi Matrix Model	KorsemeyerPeppas Plot	'n' value
	Regression coefficient R^2 values				
F2	0.6955	0.9614	0.9037	0.9302	0.234
F3	0.6445	0.9593	0.8826	0.9896	0.231
F4	0.6278	0.9948	0.8635	0.9749	0.233
F5	0.6609	0.9922	0.8857	0.9894	0.242
F6	0.6874	0.9779	0.9031	0.9934	0.256
F7	0.6257	0.9736	0.9624	0.9880	0.230
F8	0.8355	0.9805	0.9767	0.9938	0.408

F9	0.8628	0.9561	0.9864	0.9949	0.448
Marketed	0.8848	0.9753	0.9925	0.9974	0.464

Table 7: Similarity (F2) And Dissimilarity (F1) Factors Calculation for F9 Formulation

S.No	Time (hrs)	Rt value (Innovator)	Tt value (F9 formulation)	Rt-Tt	$(Rt-Tt)^2$
1	0.5	17.2	18.2	1	1
2	2	33.7	36.4	2.7	7.29
3	4	45.2	47.3	2.1	4.41
4	8	64.6	67.8	3.2	10.24
5	12	80.3	82.7	2.4	5.76
6	20	96.7	97.4	0.7	0.49
7	24	99.9	99.8	0.1	0.01

Similarity factor f_2= 82

Dissimilarity factor f_1= 3

Table 8: Cumulative % Drug Release from Tablets of the Formulation F9 During Stability Studies.

Time (hr)	Cumulative % drug release				
	Initial	One month		Two months	
		25^0C/ 60% RH	40^0C/ 75% RH	25^0C/ 60% RH	40^0C/ 75% RH
0.5	18.2	18.20	18.1	18.10	18.02
2	36.4	36.37	36.2	36.21	36.10
4	47.3	47.26	47.2	47.15	47.02
8	67.8	67.80	67.6	67.70	67.50
12	82.7	82.68	82.6	82.53	82.42
20	97.4	97.40	97.3	97.34	97.23
24	99.8	99.78	99.7	99.71	99.60

Fig 1: UV Scanning Report of Ranolazine in 0.1 N Hcl Solution

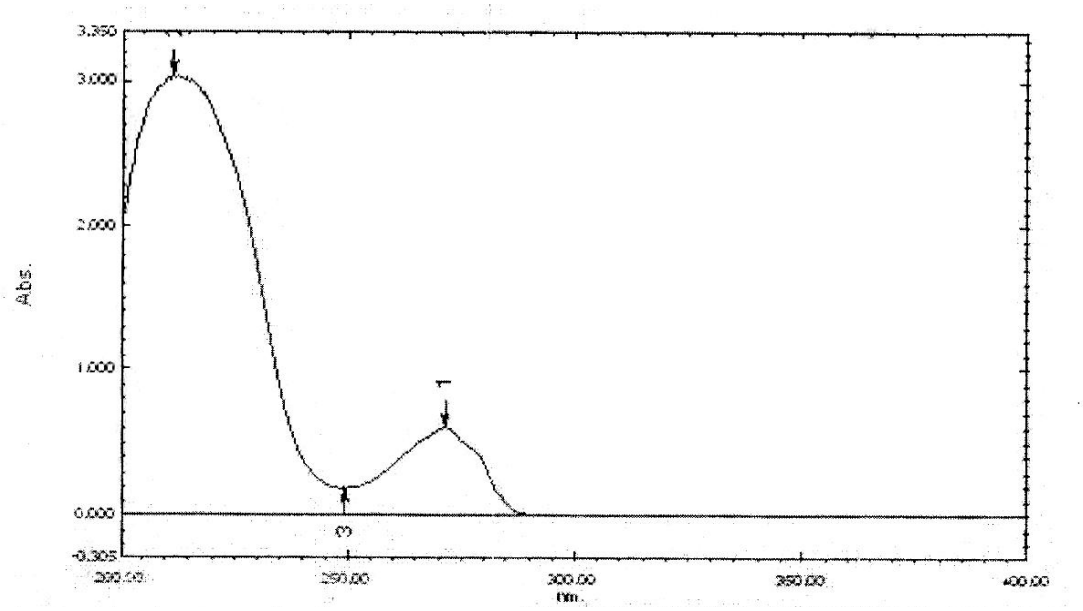


Fig 2: Standard Calibration Curve of Ranolazine at 272nm in 0.1N HCl

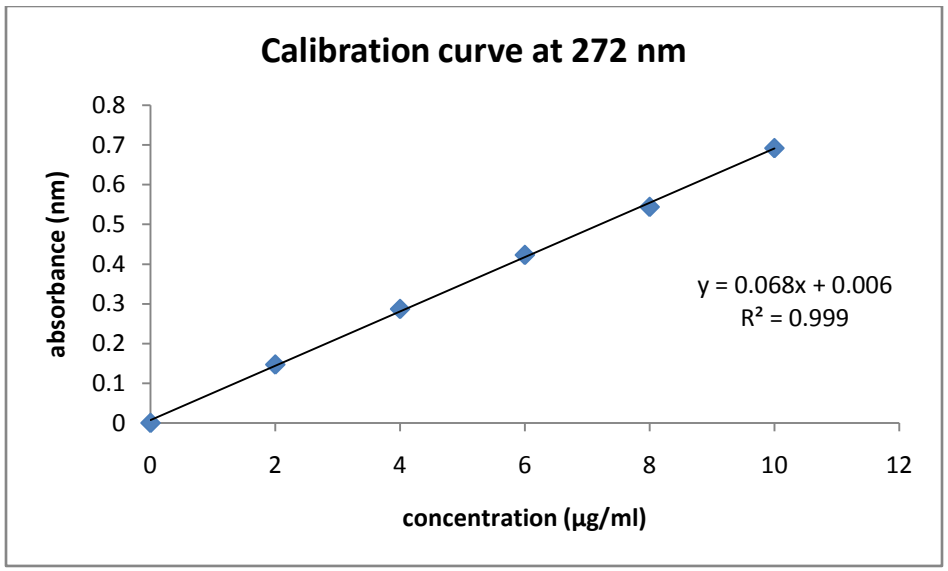


Fig 3: Zero Order Drug Release Plots for Formulations F2-F5

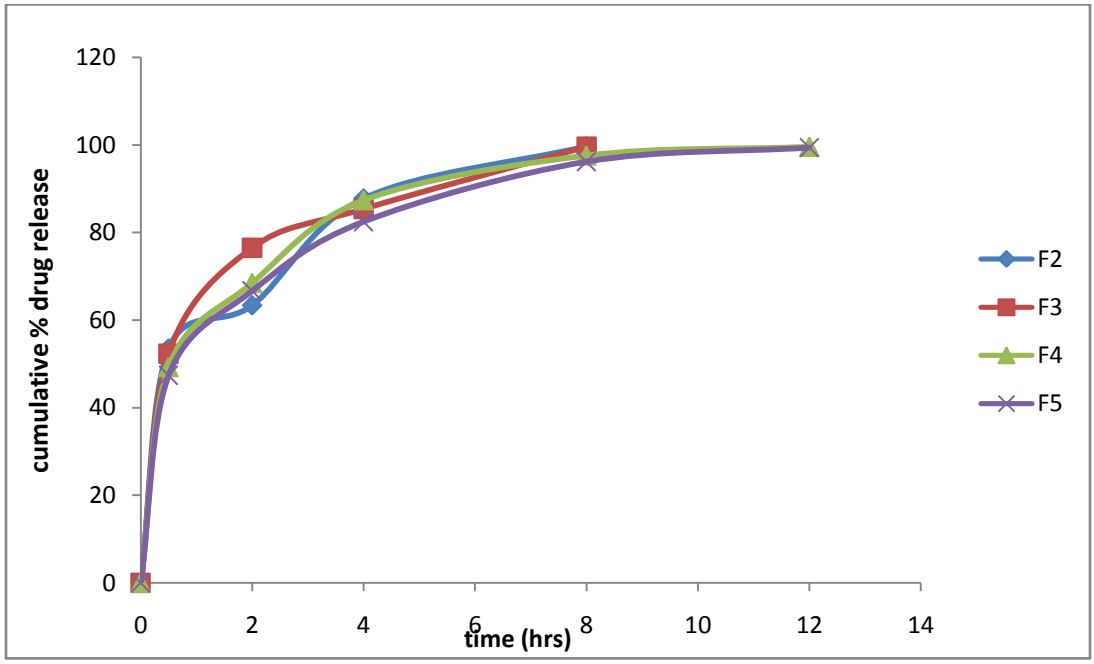


Fig 4: Zero Order Drug Release Plots for Formulations F6-F9

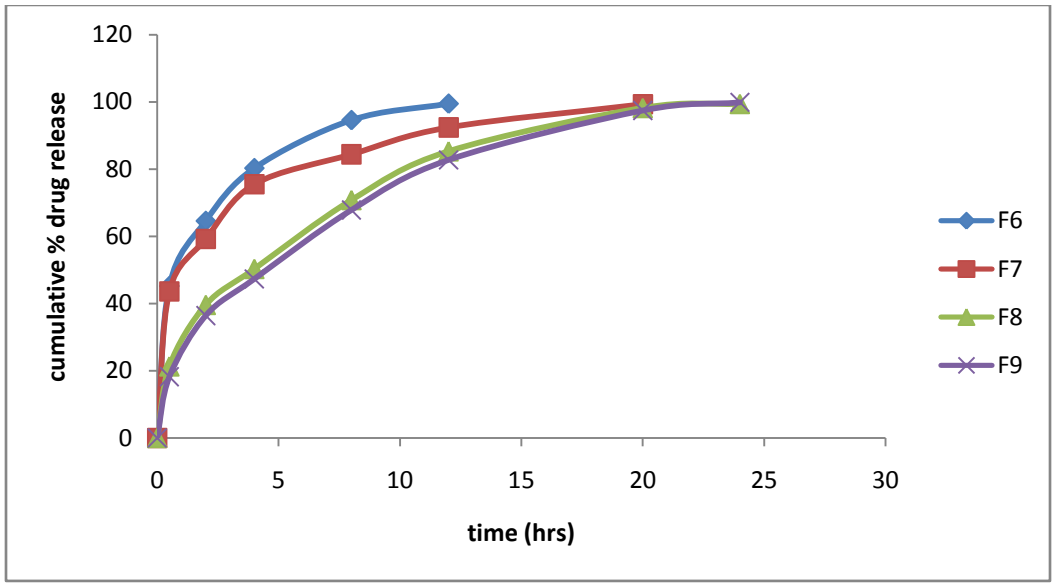


Fig 5: First Order Drug Release Plots for Formulations F2-F5

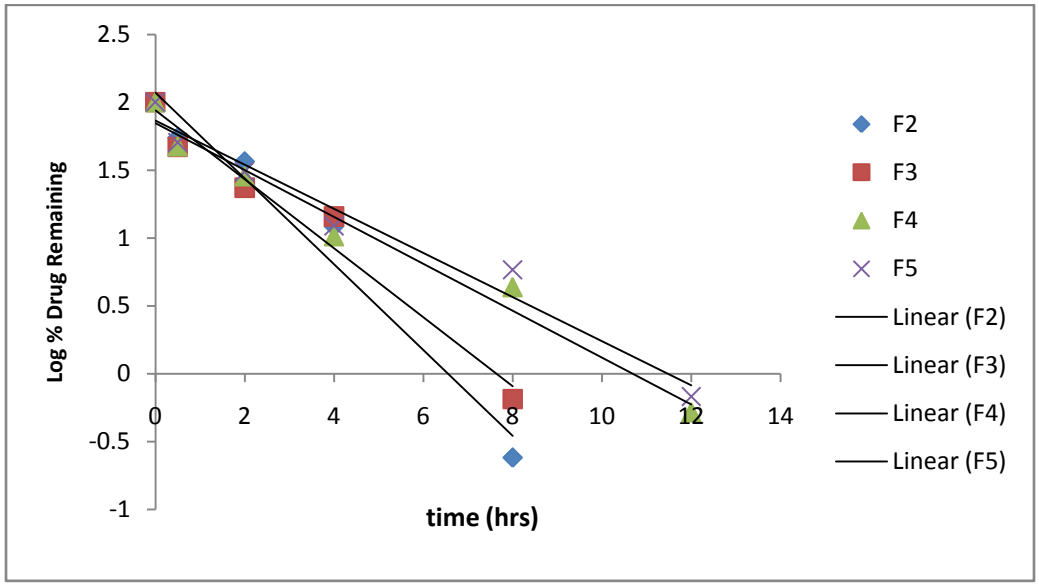


Fig 6: First Order Drug Release Plots for Formulations F6-F9

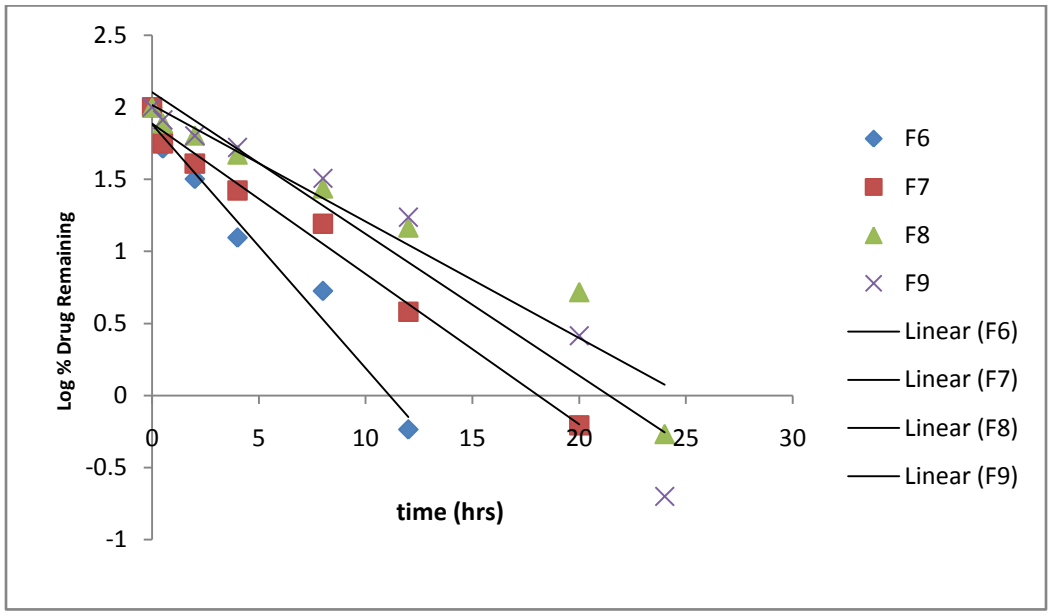


Fig 7: Higuchi Plots for Formulations F2-F5

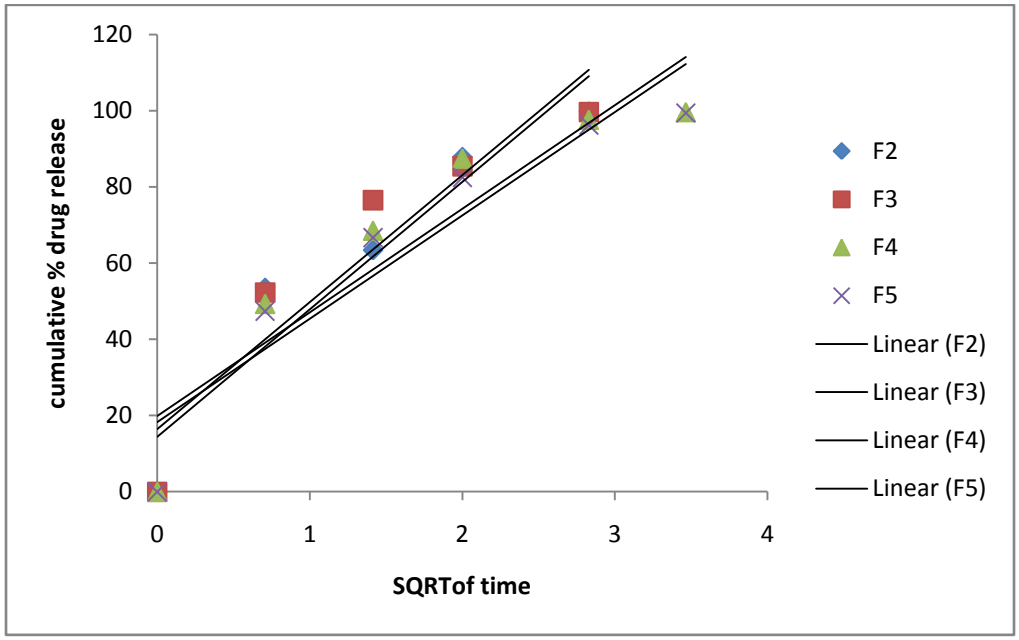


Fig 8: Higuchi Plots for Formulations F6-F9

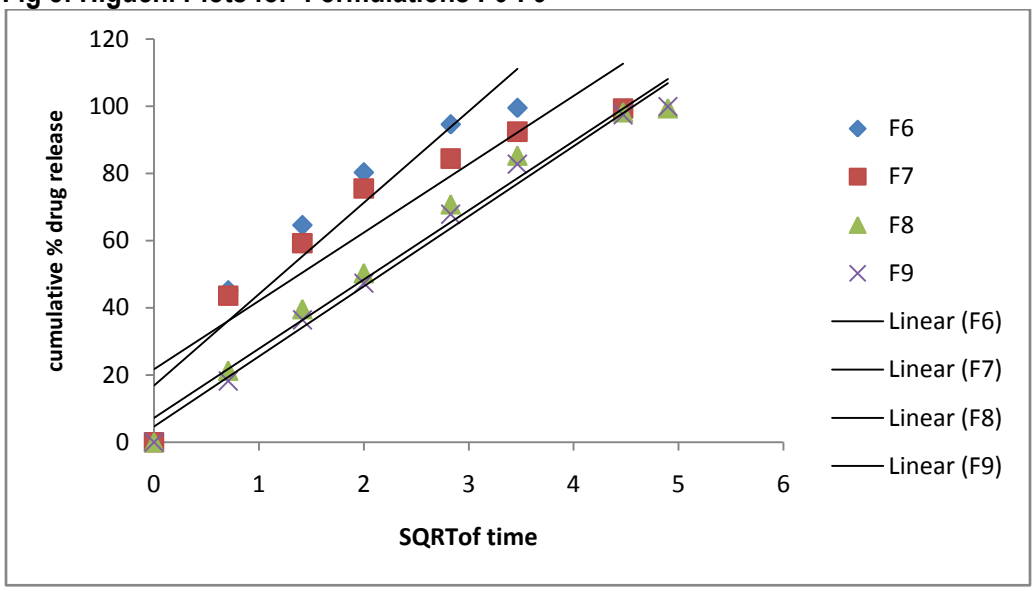


Fig 9: Peppas Plots for Formulations F2-F5

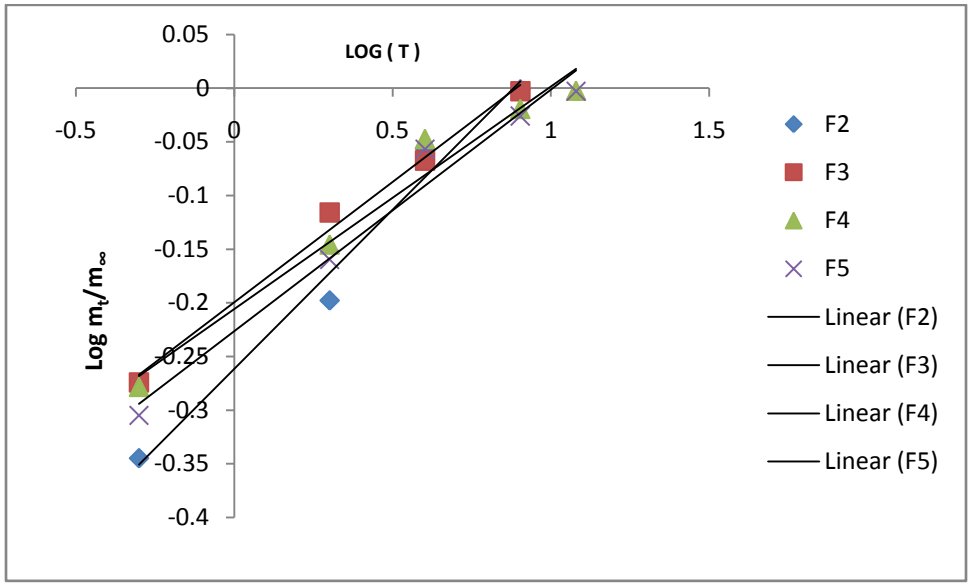


Fig 10: Peppas Plots for Formulations F6-F9

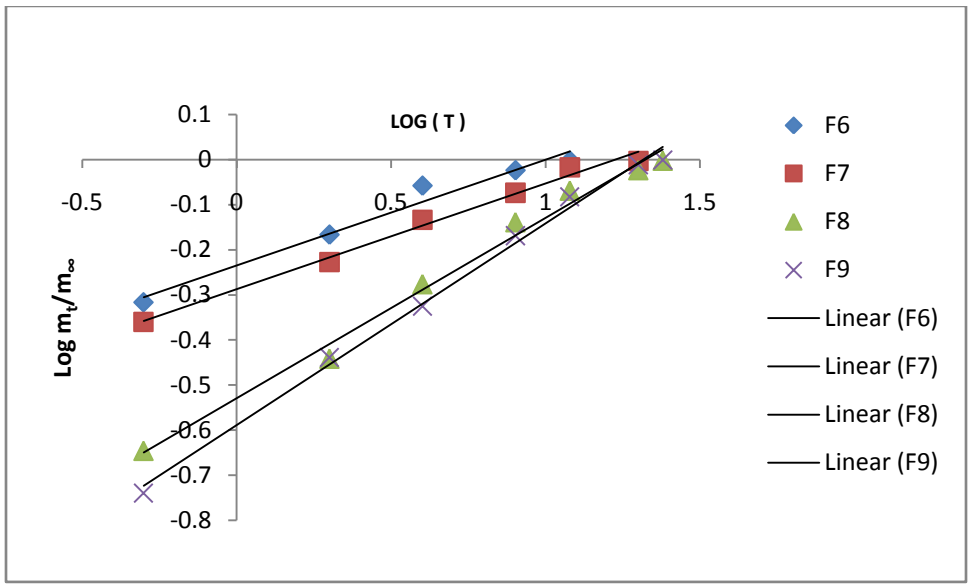


Fig 11: Comparison of Drug Release Profile of F9 and Marketed Product

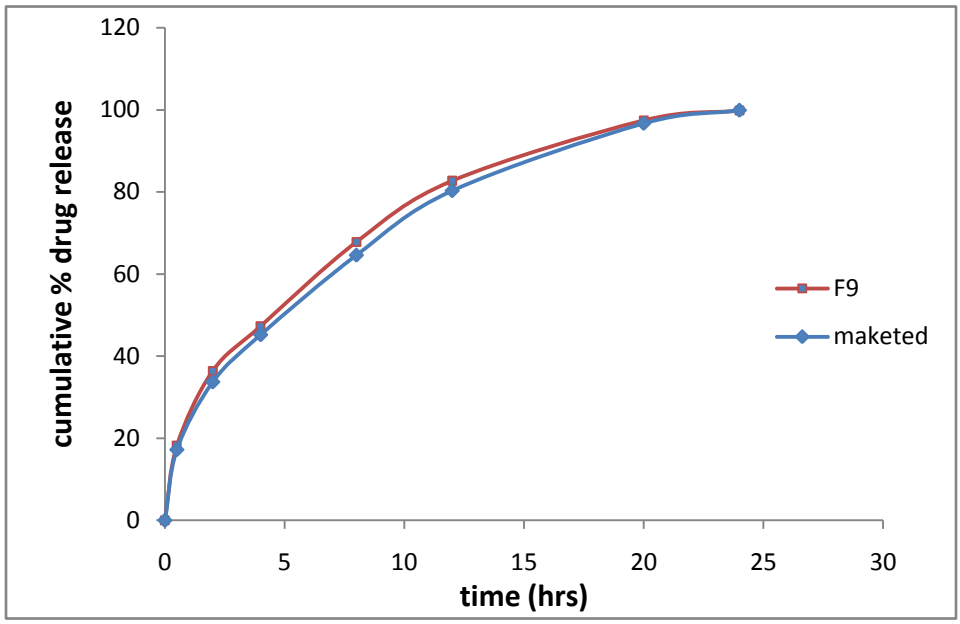
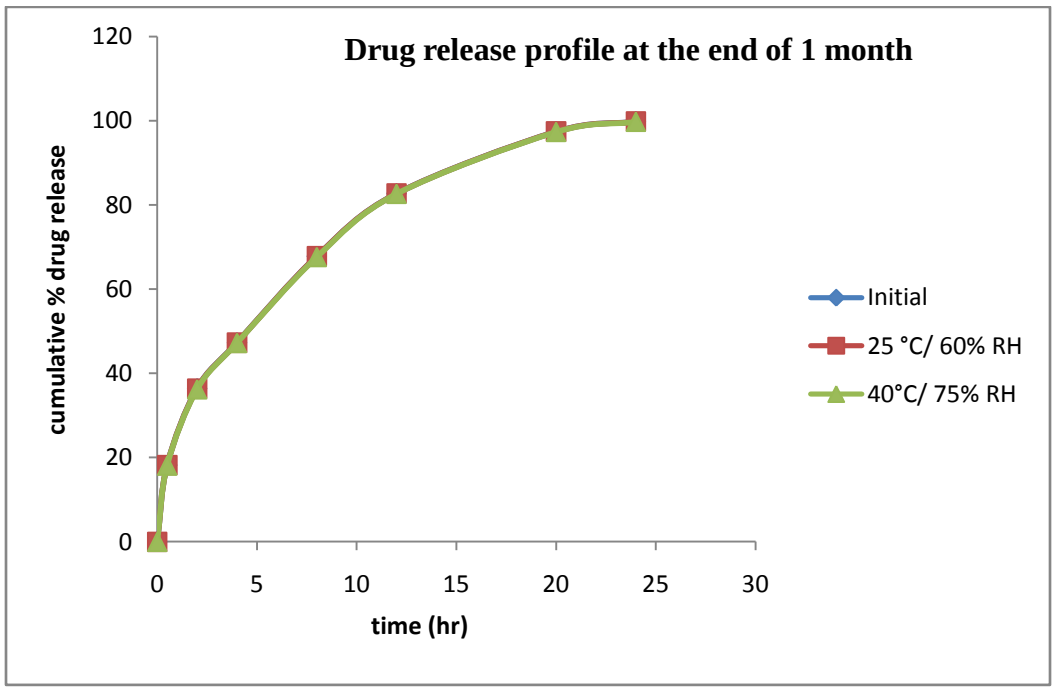


Fig 12: Drug Release Profile at The end of 1st Month



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