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Formulation and In-Vitro Evaluation of Gastro-Retentive Drug Delivery System of Acyclovir

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ABSTRACT: Gastro-retentive tablets of Acyclovir were developed to increase its bioavailability by prolonging its gastric residence time. Present investigation was thought worthwhile to develop a gastro-retentive floating drug delivery system of Acyclovir to improve the efficacy of dosage form and dosing frequency. Acyclovir is a antiviral drug with low toxicity used in treatment of herpes simplex, vericella zoster, and acute herpetic keratitis viruses. It has maximum absorption in stomach and upper part of small intestine. Due to low gastric retention time, the bioavailability of drug is low as a large portion of drug misses absorption window. The gastro-retentive floating tablets (F1-F12) were prepared by direct compression method and formulated using different concentration of polymers. Combination of polymer, HPMC K4M, Ethyl cellulose and Cetosteryl alcohol along with gas generating agent like sodium bicarbonate with citric acid was used to increase the buoyancy time and to decrease the floating lag time. All tablets passed the compendial test and other pre & post compression parameters.The floating time was achived for more than 12 hrs. All the tablets showed the floating lag time less than 03 minute. The dissolution study was carried out in 0.1 N HCl using USP type II apparatus.

Keywords: Gastro-retentive, Acyclovir, Antiviral, Direct compression, Floating lag time.

I. INTRODUCTION

Oral solid dosage forms are most commonly used due to its ease of administration, self-medication, possibly versatility in formulation including an unpredictable rate of gastric emptying varying from person to person, a limited gastrointestinal transit period (8-12 hours)and the reality of the absorption window in the upper small intestine for several medicines. Such problems prompted researchers to develop a drug delivery device that can stay in the stomach for prolonged period of time. Attempts are made to develop a sustained drug delivery system that can provide a long-term therapeutically effective plasma drug concentration, thereby reducing dosing frequency and minimizing fluctuation in plasma drug concentration at a steady state by delivering the drug sustainably and reproducibly. To conquer the challenges, it is worth the drug distribution to reach a sustained gastric residence period. Gastro-retention leads to improved bioavailability, extending of drug release time, minimizing the drug loss and promotes drug solubility for which drugs are less soluble in a high pH environment.

The Sustained release floating drug delivery systems result in long-lasting intragastric buoyancy and can not only provide a continuous site of effective therapeutic activity but can also lead to decrease in side effects and improved patient compliance. Acyclovir is an antiviral drug with low toxicity. It is used in treatment of herpes simplex infection, varicella zoster infection, chicken pox and shingles. Recently, Acyclovir has been used in combination with AZT to treat AIDS patients. It is taken by mouth, applied as a cream, or injected. It has a relatively short plasma half-life (2-4hours). The plasma concentration reaches its therapeutic level in 1.5 to 2 hours. The total bioavailability of Acyclovir is estimated between 15% and 20% by mouth.

Acyclovir is absorbed only in stomach and initial part of small intestine and has 30% absolute bioavailability, the objective of present investigation was to developed floating tablets of Acyclovir by using gas generating agent. Prepared formulation retains in the stomach and subsequently provides sustained release of the drug over the period of time of gastro residence time.A controlled delivery system for drugs is usually designed to deliver drugs at a specific rate. Safe and effective blood levels shall be maintained for as long as the system continues to deliver the drug.

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Controlled drug delivery typically results in significantly constant blood levels of the active ingredient as compared to the uncontrolled variation seen when a patient uses several doses of rapidrelease traditional medication.

II. MATERIALS AND METHODS

Acyclovir was obtained as a gift sample from **Micro labs. Ltd,** and all other reagents used were of analytical grade. Floating tablets of Acyclovir were prepared by using different polymers like HPMC K4M, Ethyl cellulose and Cetosteryl alcohol either alone or in combination. Effervescent base of tablets were prepared by using Sodium bicarbonate and citric acid. The tablets were fabricated using direct compression technique. The micromeritic property of the drug and polymers were characterized with respect to the angle of repose, bulk density, tapped density and Carr's index. The formulated tablets were subjected for various evaluation parameters like hardness, thickness, density, weight variation, drug content, buoyancy lag time, total floating time andin-vitro drug release.

Preparation of Acyclovir floating tablets

Gastro-retentive Acyclovir floating tablets were prepared by direct compression method. Acyclovir with various concentration of polymers such as HPMC K4M, Ethyl cellulose, Cetosteryl alcohol were used as release retardant polymers. Sodium bicarbonate and citric acid were used as gas generating agent. The other excipient used was MCC for its diluent's property. All the excipients were first sieved and then blended in mortar with pestle to obtain uniform mixing finally talc and magnesium stearate was mixed and then compressed on cadmach single punch machine using 10 mm flat punch. The weight of the tablet is adjusted to 450 mg and each tablet contained 200 mg Acyclovir. The compressed tablets of each formulation were then evaluated for tablet characteristic such as thickness, weight variation and friability.

Evaluation Tests

The flow properties of blend before compression were characterized in terms of Angle of repose, Tapped density, Bulk density, Carr's index and Hausner ratio.

Physical evaluation of Acyclovir gastro-retentive tablets

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of 10 tablets weremeasured using Vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, Hardness (Monsanto), Friability using 10 tablets (Roche friabilator).

Ingredients (mg/tablet)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
Acyclovir	200	200	200	200	200	200	200	200	200	200	200	200
HPMC K4M	160	140	120	-	-	-	100	80	60	140	130	120
Ethyl Cellulose	-	-	-	160	140	120	60	80	100	-	-	-
Cetosteryl Alcohol	-	-	-	-	-	-	-	-	-	20	30	40
Sodium Bicarbonate	50	50	50	50	50	50	50	50	50	50	50	50
Citric Acid	25	25	25	25	25	25	25	25	25	25	25	25
Micro Crystalline Cellulose	09	29	49	09	29	49	09	09	09	09	09	09

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Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Total	450	450	450	450	450	450	450	450	450	450	450	450

Table 1. Formulation chart of Gastro-retentive drug delivery system for Acyclovir

Determination of swelling index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of tablet was determined at predefined time intervals over a period of 12 hour. the swelling index (SI), expressed as percentage, was calculated from the following equation

$$SI = \frac{\text{weight of tablet at time(t)} - \text{initial weight of tablet}}{\text{initial weight of tablet}} \times 100$$

In-vitro buoyancy studies

In-vitro buoyancy studies were performed for all the 12 formulations as per the following method: The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Drug Content

Twenty tablets were powdered and equivalent to its average weight was added in 100ml of 0.1N HCl, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 254nm using 1.0N HCl as blank.

In-Vitro Dissolution Studies

The release rate of Acyclovir from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37± 0.5°C and 50 rpm. Samples (10ml) were withdrawn from the dissolution apparatus hourly and the medium was replaced by adding fresh dissolution medium. Filtered though a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at 254nm using a UV spectrophotometer. The % drug release was plotted against time to determine the release profile.

In-Vitro Drug Release Kinetic Studies

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to analyze the exact mechanism for the drug release and the release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi's, and Korsmeyer-Peppas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

Stability Studies

Selected formulation was tested for its stability. Short-term stability studies were performed at temperature 40±2°C over a period of 3 months. 5 tablets were packed in amber colored screw capped bottle and kept in stability chamber maintained at 40±2°C. Samples were taken at 1 month interval for their drug content estimation including physical parameters. At the end of 3 months period, dissolution test was performed to determine the drug release profile.

III. RESULTS AND DISCUSSION

Precompression parameters of Acyclovir granules

The formulation showed good flow property and compressibility index (Table no. 2). Angle of repose ranged from 24.61 to 29.84, Hausner's ratio ranged from 1.039 to 1.15 and the compressibility index ranged from 3.811 to 13.33. The LBD and TBD of the prepared granules ranged from 0.390 to 0.468 and 0.424 to 0.528 respectively. The results of angle of repose indicated good flow property of the blend and the

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value of Carr's index further showed support for the flow property.

Post compression parameters of Acyclovir tablets

The tablets of all formulation remained smooth on its surface with no visible cracks. The thickness and diameter of tablets measured by Vernier calipers ranged between3.61 to 3.82mm, and 9.47 to 10.22mm respectively. The hardness of tablets between 4.3 to 5.1 kg/cm^2. The friability was found to be 0.15 to 0.96%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 96.70 to 101.70% which reflected good uniformity in drug content among different formulation. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The results are shown in table no. 3.

All the formulation showed values within the pharmacopoeial limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

In-vitro buoyancy studies

All batches of tablets were found to exhibit expected short floating lag time due to presence of sodium bicarbonate and citric acid. Decrease in the citric acid level increased the floating time and tablets were found to float for longer duration. Formulation F10 containing combination of Sodium bicarbonate and citric acid with Cetosteryl alcohol was found to achieve optimum in-vitro buoyancy and floatability for more than 12hrs. The results of in-vitro buoyancy studies are tabulated in table no. 4.

Swelling index studies

The swelling property was determined by placing the tablet in the dissolution test apparatus, in 900 ml 0.1N HCl at 37±0.5°C. The tablets were removed periodically from the dissolution medium and after removing free water, the weight gain was measured. Swelling index was calculated with respect to time, maximum swelling was seen with the formulations F4 and F8 containing Ethyl cellulose alone or in combination HPMC K4M respectively.

In-vitro dissolution studies

In-vitro drug release showed in table no. 5,three different polymers and their combination were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulation contain equal amount of gas generating agent. A significantly higher rate and extent of drug release was observed from the formulations based on HPMC K4M. Varying the amount of HPMC K4M affect the drug release. The result showed that the F3 formulation showed maximum drug release at the end of 12 hours compared to all the twelve formulations.

Drug Release Kinetics

The data obtained from in-vitro dissolution studies were fitted to mathematical model viz. Zero order, First Order and Higuchi Model and the co-efficient of regression value were compared. It was observed that most of the formulations followed zero order models as the co-efficient of regression value was more nearer to one. Among the twelve formulations,(Table no. 6), F3 was selected as the best formulation as its co-efficient of regression value was more near to unity. The data was subjected to Korsmeyer-Peppas equation for determination of release mechanism. The acceptable linearity was observed for all the developed formulation. The release co-efficient "n" varied from 0.953 to 0.998 that indicates both non-fickian and super case – II transport of a drug from polymer i.e. drug release follows both diffusion and relaxation of polymer chain.

Stability studies

Results of stability studies of formulation F3 indicated that it is stable at 40°C, 75±5% relative humidity. From the stability studies, it was clear that the formulations were physically and chemically stable for 90 days and there was no significant change in the physical parameters, drug content and in-vitro dissolution release profiles.

IV. CONCLUSION

For drugs with narrow absorption window a unique pharmaceutical dosage form with gastro-retentive properties would enable an extended absorption phase. And thusincrease in bioavailability after oral administration, such dosage form would be retained in the stomach and release the drug in a controlled and prolonged manner so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Floating tablets of Acyclovir were successfully prepared by direct compression method, using different concentration of polymers to control its release. Sodium bicarbonate and citric

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acid was used as gas forming agent which help floating of tablets in the stomach.It is concluded that Gastro-retentive tablets of Acyclovir was successfully formulated with an approach to increase the gastric residence time and thereby improving drug bioavailability.Gastro-retentive tablets of Acyclovir using HPMC as hydrophilic polymer and sodium bicarbonate as gas generating agent by direct compression method is achieved.The formulated tablets showed compliance with various physico-chemical parameters; tablet dimensions, hardness, friability, total floating time, tablet density and swelling index.Dissolution studies of F3 shown maximum drug release as compared to other formulations, i.e. 90.66% in 12 hours with polymer HPMC in drug polymer ratio of 1:0.6.

Table 2: Results of precompression flow properties of Granules of Acyclovir

Sl. No.	Formulation Code	Loose Bulk Density(g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index	Hausner's Ratio
01.	F1	0.450±0.003	0.468±0.014	3.84±0.232	1.04±0.012
02.	F2	0.390±0.007	0.450±0.009	13.33±0.435	1.15±0.008
03.	F3	0.468±0.006	0.508±0.018	7.87±0.280	1.08±0.018
04.	F4	0.39±0.011	0.433±0.022	9.93±0.369	1.11±0.006
05.	F5	0.391±0.009	0.439±0.017	11.16±0.203	1.12±0.014
06.	F6	0.392±0.014	0.424±0.024	7.54±0.363	1.08±0.021
07.	F7	0.399±0.008	0.425±0.011	6.11±0.455	1.06±0.009
08.	F8	0.400±0.013	0.433±0.020	7.62±0.242	1.08±0.021
09.	F9	0.404±0.019	0.428±0.016	5.60±0.187	1.05±0.013
10.	F10	0.400±0.002	0.434±0.021	7.83±0.321	1.08±0.008
11.	F11	0.436±0.011	0.454±0.019	3.96±0.116	1.04±0.019
12.	F12	0.429±0.012	0.446±0.021	3.811±0.229	1.039±0.010

Table 3: Results of Post compression Properties of Acyclovir Floating tablets

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%w/w)	Weight Variation (mg)	Drug Content (%)
F1	3.77 ±0.05	4.6 ±0.42	0.17	449.54 ±1.28	97.25 ±0.75
F2	3.61 ±0.09	4.8 ±0.37	0.18	448.05 ±1.12	99.45 ±1.2
F3	3.69 ±0.08	4.3 ±0.65	0.96	449.87 ±1.10	101.07 ±0.31
F4	3.64 ±0.03	4.9 ±0.34	0.24	449.59 ±1.29	99.01 ±0.42
F5	3.82 ±0.10	5.1 ±0.33	0.22	449.98 ±1.47	98.94 ±0.82
F6	3.74 ± 0.09	4.4 ±0.54	0.19	450.35 ±1.05	101.47 ±1.0
F7	3.81 ±0.08	5 ±0.51	0.17	449.75 ±1.37	100.81 ±0.7
F8	3.81 ±0.03	4.9 ±0.62	0.73	450.15 ±1.30	96.70 ±0.51
F9	3.74 ± 0.02	5.1 ±0.39	0.22	450.02 ±1.03	99.53 ±0.5
F10	3.77 ±0.04	4.7 ±0.43	0.20	451.91 ±0.92	101.03 ±0.9
F11	3.69 ±0.07	4.6 ±0.49	0.15	449.51 ±0.97	98.20 ±0.25
F12	3.82 ±0.07	5 ±0.36	0.25	449.68 ±1.33	99.86 ±0.47

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Table 4: Results of In-vitro Buoyancy study and swelling index of Acyclovir Floating tablets

Formulation Code	Swelling Index	Floating Lag Time (sec)	Total Floating Time (hrs)
F1	28.04	32	>12
F2	35.84	49	>12
F3	42.27	41	>12
F4	53.51	126	>12
F5	33.81	119	>12
F6	47.66	110	>12
F7	42.19	70	>12
F8	54.31	84	>12
F9	28.80	78	>12
F10	56.71	12	>12
F11	48.73	20	>12
F12	43.41	23	>12

Table 5: Dissolution data of all Formulation

Sr. No.	Time in (HRS)	Cumulative% Drug Release											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	1	8.1	7.43	10.39	9.58	6.07	7.42	15.57	9.22	4.27	8.01	5.52	6.21
2	2	16.47	14.04	15.26	15.48	14.88	14.12	17.72	14.04	10.37	14.62	11.50	11.28
3	3	22.23	20.95	22.55	20.43	20.63	23.42	23.67	20.73	14.61	20.09	16.42	19.42
4	4	26.26	27.73	30.77	30.53	23.22	29.89	29.29	26.16	20.61	24.43	21.69	23.18
5	5	33.07	37.55	38.95	45.10	31.18	39.69	46.01	33.28	26.64	32.33	27.79	29.7
6	6	37.26	42.80	45.87	52.32	38.46	47.02	54.50	39.40	37.15	36.78	34.47	31.54
7	7	42.32	49.47	53.01	61.61	45.51	51.78	59.26	45.69	45.81	43.91	47.44	38.96
8	8	48.18	55.32	56.81	69.73	54.80	58.45	67.0	52.24	52.72	55.4	54.0	44.98
9	9	54.65	64.89	66.07	76.95	63.16	71.28	71.73	57.84	62.19	66.5	62.84	55.17
10	10	63.90	71.77	71.29	79.17	70.07	80.08	79.73	70.03	71.76	72.62	68.58	66.33
11	11	70.99	76.88	82.25	82.97	78.64	84.57	83.94	76.75	76.33	77.6	77.98	76.0
12	12	86.82	84.23	90.66	85.85	87.71	88.31	89.34	84.59	79.35	84.76	83.63	84.88

Table 6: Kinetic Release data of different Model for Best Formulation F3

Model	Slope	R^2
Zero order	7.217	0.996
First order	-0.076	0.880
Higuchi	32.84	0.967
Korsmeyer-Peppas	0.900	0.991

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Table 7: Stability study (40°C/75%RH) of Formulation F3

S. No.	Parameters	Observation						
		Initial	1 month		2 month		3 month	
			RT	40°C	RT	40°C	RT	40°C
1	Nature	Compact solid	Compact solid	Compact solid	Compact solid	Compact solid	Compact solid	Compact solid
2	Colour	White	White	White	White	White	White	White
3	Hardness (kg/cm^2)	4.3	4.3	4.2	4.2	4.2	4.0	4.0
4	Friability (%)	0.96	0.94	0.91	0.88	0.88	0.88	0.87
5	Content uniformity (%)	101.07	101.4	101.1	100.4	100.1	100.1	100.1

Figure 1: Zero order release kinetics formulation F3

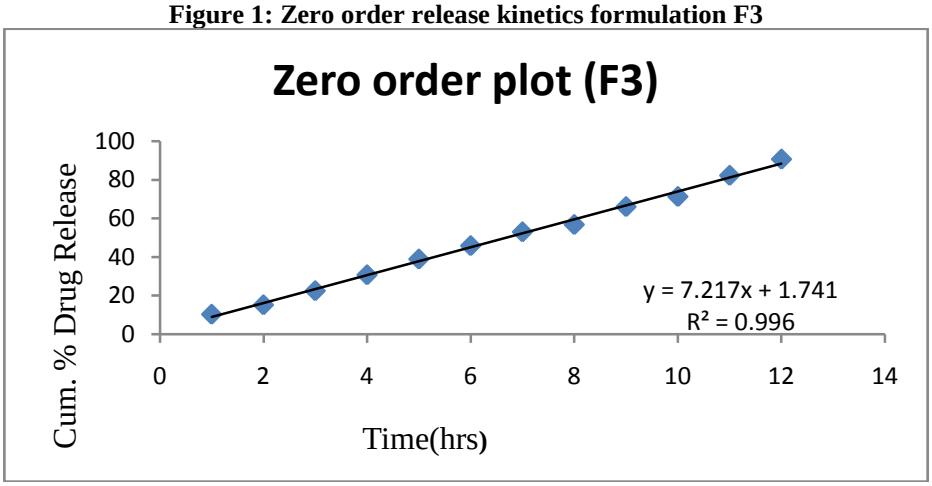

Figure 2: First order release kinetics of formulation (F3)

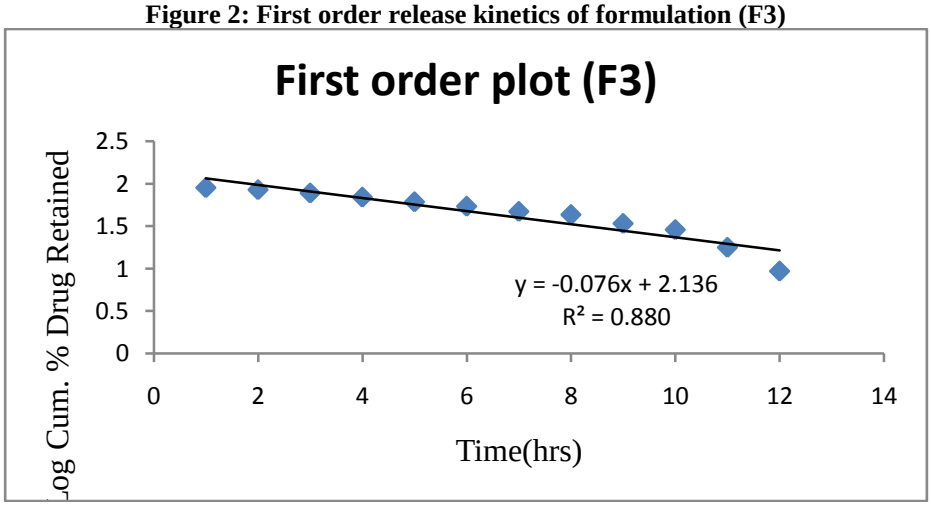

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Figure 3: Higuchi release kinetics of formulation (F3)

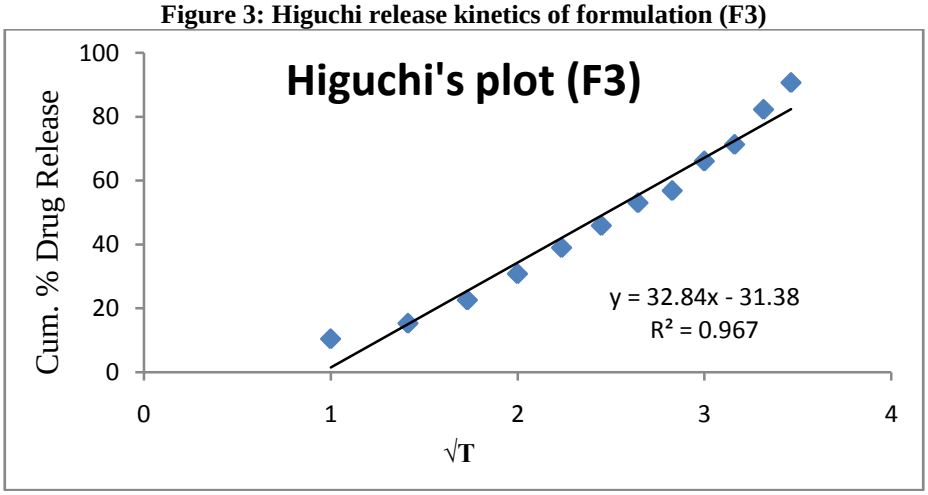
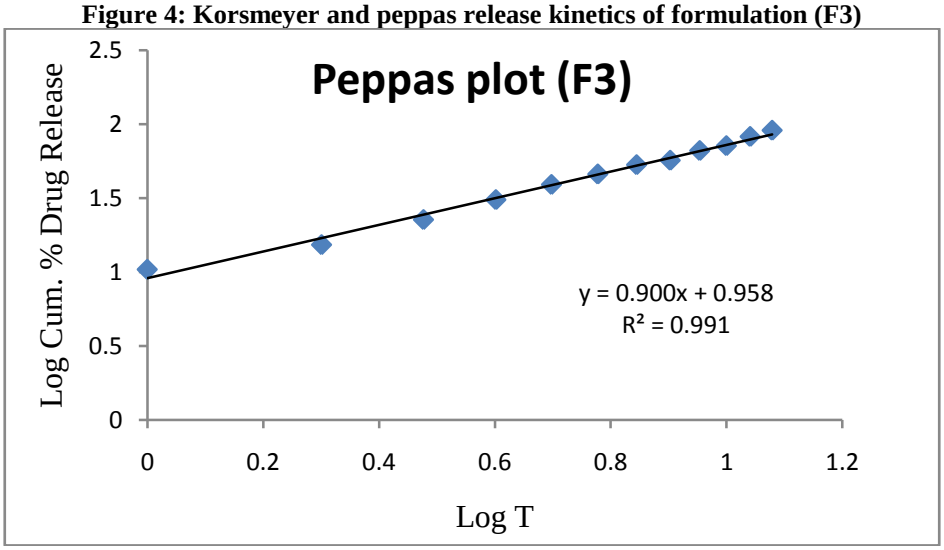


Figure 4: Korsmeyer and peppas release kinetics of formulation (F3)



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