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Development and *in vitro* evaluation of gastroretentive drug delivery system of Losartan Potassium

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ABSTRACT

In the present study, development of Gastroretentive Drug Delivery System (GRDDS) of Losartan potassium, an anti-hypertensive drug was designed to increase the gastric residence time. Formulations were prepared using wet granulation method, employing polymers like HPMC K4M, HPMC K15M, carbopol 934P and sodium alginate. Sodium bicarbonate and citric acid were used as gas generating agents. Tablets were evaluated for various parameters like hardness, friability, uniformity of weight, drug content uniformity, drug polymer interaction studies, swelling index, in vitro floating studies, In vitro drug release and short term stability studies. Drug release analysis on the basis of Higuchi-Korsmeyer model indicated that diffusion is the predominant mechanism controlling the drug release. The drug polymer interaction studies indicated no interaction. The short term stability study showed no significant change.

Keywords: Losartan potassium, Gastroretentive Drug Delivery System, HPMC, Carbopol 934P, Sodium alginate.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation [1]. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone leading to diminished efficacy of administered dose.

To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolonged gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release and improves the drug solubility that are less soluble in a high pH environment. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. In the present work gastroretentive drug delivery system of Losartan potassium tablets were prepared.

Losartan potassium is a class I anti-hypertensive agent called as angiotensin II (AG II) receptor antagonists used for the treatment of hypertension [2]. It is well absorbed, the systemic bioavailability of losartan potassium is approximately 33% and a half life of 1.5 to 2.5hours. Hence, enhanced gastric retention time of Losartan potassium controlled release dosage form will increase its absorption. Therefore losartan potassium is considered a suitable candidate for the design of gastroretentive drug delivery system with a view to improve its oral bioavailability.

MATERIALS AND METHODS

Losartan potassium was obtained as a gift sample from Alkem pharma Ltd., Taloja, HPMC K4M and K15M were kindly supplied as a gift sample from Colorcon, Goa. Carbopol 934P, lactose, microcrystalline cellulose, citric acid, talc was gifted by SD fine chemicals, Mumbai. Sodium alginate and polyvinyl pyrrolidone was obtained from Genuine Chemicals, Mumbai. Sodium bicarbonate was obtained from Qualigens pharma, Mumbai. Magnesium stearate was obtained from Central drug house limited.

Procedure for preparation of GRDDS of Losartan potassium

All the ingredients were accurately weighed, passed through sieve no. 60 and transferred to a clean porcelain mortar except magnesium stearate and talc [3]. PVP (3% w/v) binding solution is added to the mixture in the mortar in small quantities, thorough mixing of the mixture is done until a coherent mass is formed. Then it is passed through sieve no.12 and the wet granules were spread on a paper and dried in hot air oven at 30^0C-40^0C for 30 minutes.

Tablets were compressed on a rotary punching machine (Clit pilot press) using flat surfaced, round shaped punches of 8mm and 9mm diameter.

Evaluation of GRDDS of Losartan potassium

Hardness test: The crushing strength (Kg/cm²) of tablets was determined by using Monsanto hardness tester. In all the cases, mean of three replicate determinations were taken. The results are given in table-3.

Friability test: This was determined by weighing 10 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min [4]. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated according to

$$\text{Percent friability} = \frac{\text{Weight}_{\text{final}} - \text{Weight}_{\text{original}}}{\text{Weight}_{\text{original}}} \text{x}100$$

The results are given in table-3.

Uniformity of weight: The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weighed data from the tablets were analyzed for sample mean and percent deviation.The results are summarized in table-3.

Uniformity of drug content: 5 tablets were powdered in a glass mortar and 100 mg of powder was placed in a 100 ml stoppered conical flask. The drug was extracted with 0.1N HC1 with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 5 hour and filtered into 100 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more 0.1 N HCI through filter, further appropriate dilutions were made and the absorbance was measured at 250nm against blank. The results are given in table-3.

***In vitro* floating studies:** Floating time was determined by using USP XXIII dissolution apparatus-II using 900m1 of 0.1N HC1 and temperature was maintained at 37±0.5°C, throughout the study. The duration of floating (floating time) is the time the tablet floats in the dissolution medium (including floating lag time, which is the time required for the tablet to rise to the surface) is measured by visual observation. The results are summarized in table-3.

***In vitro* dissolution studies:** *In vitro* dissolution studies of GRDDS of Losartan potassium were carried out using USP XXIII tablet dissolution test apparatus-Il (Electrolab), using a paddle stirrer at 50 rpm using 900m1 of 0.1N HC1 at 37±0.5°C as dissolution medium. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 250 nm using UV-Visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicate. The results are given in table 4-5

Stability studies: Short-term stability studies were performed at a temperature of 40° ±1°C and relative humidity (RH) 75% over a period of three weeks (21 days) on the promising GRDDS tablet formulation FA. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in hot air-oven maintained at 40°±1°C and RH 75%. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and *In vitro* floating studies were performed to determine the drug release profiles, *In vitro* floating lag time and floating time. The data of dissolution and *In vitro* floating studies are shown in tables 7-9.

RESULTS AND DISCUSSION

In the present study, Gastroretentive drug delivery systems of Losartan potassium were prepared by using different viscosity grades of Hydroxy propyl methyl cellulose (HPMC),viz.,K4M and K15M (4,000 and 15,000cps respectively) and other polymers like Carbopol 934P and Sodium alginate at different drug to polymer ratios with or without gas generating agent like sodium bicarbonate and citric acid. Diluent used was lactose.

The weighed quantities of drug and polymers were mixed thoroughly in different ratios and GRDDS tablets were prepared by wet granulation method. The prepared GRDDS tablets were evaluated for its hardness, friability, uniformity of weight, uniformity of drug content, swelling index, drug-polymer interaction studies, *In vitro* floating studies, *In vitro* dissolution studies and short term stability studies.

Precompression parameters of Losartan potassium granules
The formulations showed good flow property and compressibility index (Table 2). Angle of repose ranged from 21 to 28, Hausner ratio ranged from 0.096 to0.168 and the Carr's index ranged from 17.45 to28.83. The LBD and TBD of the prepared granules ranged from 0.412 to 0.492 and 0.548 to 0.634 respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property. Given in table 3.

Hardness and friability: The hardness of the prepared GRDDS of Losartan potassium was found to be in the range of 4.2 to 4.8 kg/cm^2 and is given in table 3. The friability of all the tablets was found to be less than 1% i.e. in the range of 0.2% to 0.7% given in table 3.

Uniformity of weight: All the prepared GRDDS were evaluated for weight variation and the results are given in table 3. The percent deviation from the average weight was found to be within the prescribed official limits.

Uniformity of drug content: The low value of standard deviation indicates uniform drug content in the tablets prepared as observed from the data given in table 3.

***In vitro* floating studies**: *In vitro* floating studies were performed by placing tablet in USP XXIII dissolution apparatus-II containing 0.1N HCl, maintained at temperature of 37±0.5°C. The floating lag time and floating time was noted visually. The results are given in table 4-5.
In the initial GRDDS formulations of Losartan potassium, Formulations containing polymers like Carbopol 934P and Sodium alginate (CF1, CF2, CF3, SA1, SA2, SA3) the floating lag time was found to be in between 50 seconds to 100 seconds and remained under floating condition for less than 12hours.

Formulations containing optimum concentration of polymer (F1, F2, F3, F4, FA, FD) a gas generating agent sodium bicarbonate at varying concentrations has shown a floating lag time of 15 to 48 second remained under floating condition for 24hours.

The floating lag time was found to be more in the formulations which contains less gas generating agent (sodium bicarbonate) in the GRDDS formulations which may be due to delayed swelling of the polymer.

It was observed that when an optimum concentration of sodium bicarbonate was used, there was a reduction in the floating lag time, when the dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of CO_2 gas within the swollen gel, thus causing floating as the matrix volume expanded and its density decreased.

Results show that as the amount of HPMC increased, total floating time also increased. This may be accounted to increased gel strength of the matrices. With subsequent hydration and swelling of the polymers a floating mass is produced. Continuous erosion of the surface allows penetration of water to the inner layers, maintaining surface hydration and buoyancy.

Tablets formulated with Carbopol 934P exhibited total floating time of less than 12 hours. This is due to high affinity of Carbopol towards water that promotes water penetration in tablet matrices leading to increased density [5]. In case of tablets formulated with sodium alginate, on hydration

failed to produce matrix of required strength, hence floating abilities were found to be poor i.e; less than 12hrs.

When equal proportion of sodium bicarbonate and citric acid (1:1) was used in formulation FA and FD the lag time was found to be less i.e; 15seconds and 23seconds which may be due to the immediate formation of CO_2 gas that provides buoyancy.

Hence it can be concluded that optimum concentration of sodium bicarbonate was found to achieve optimum *In vitro* floating of GRDDS of Losartan potassium.

***In vitro* dissolution studies**: *In vitro* dissolution studies were performed for all the batches of GRDDS of Losartan potassium using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. The *In vitro* drug release data was given in tables 4-5 and drug release profiles are shown in figure- 8, 12, 16, 20 and 24.

Formulations F1 and F2 containing drug : polymer ratio 1:0.6 and 1:0.8 prepared with HPMC K4M exhibited 84.55 and 82.81% of drug release in 12 hours respectively and the data is given in table 4 and drug release profiles are shown in figure 8.

Formulations F3 and F4 containing drug: polymer ratio 1:0.6 and 1.08 prepared with HPMC K15M exhibited 74.07 and 69.92% of drug release in 12 hours respectively and the data is given in table 4 and drug release profiles are shown in figure-12.

In vitro drug release data for formulations CF1, CF2 and CF3 are given in table 4 and drug release profiles are shown in figure 12. These formulations were prepared using Carbopol 934P in drug polymer ratios 1:0.3, 1:0.4 and 1:0.5 exhibited 75.21, 73.55 and 69.98% drug release rates in 12 hours respectively.

In vitro drug release data for formulations SA1, SA2 and SA3 are given in table 5 and drug release profiles are shown in figure-16. These formulations were prepared using Sodium alginate in drug polymer ratios 1:0.3, 1:0.4 and 1:0.5 exhibited 82.67, 77.56 and 76.03% drug release rates in 12 hours respectively.

In vitro drug release data for formulations FA, FB and FC are given in table 5 and drug release profiles are shown in figure-20 and 24. These formulations were prepared using HPMC K4M in drug polymer ratio of 1:0.8 by varying the concentration of the gas generating agent sodium bicarbonate.

In vitro drug release data for formulation FD is given in table 5 and the drug release profile is shown in figure-24. This formulation was prepared using HPMC K4M and Carbopol 934P in drug polymer ratio of 1: 0.8: 0.2, this exhibited 79.38% drug release rate in 12 hours.

In the above results, it was observed that as the concentration of the polymers increased, there is a decrease in the drug release rates. An increase in polymer concentration causes increase in viscosity of the gel as well as the gel layer with longer diffusional path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate.

Formulations containing higher HPMC viscosity grade have slower drug release rates when compared to formulations with lower HPMC viscosity grades i.e. formulations F1, F2, FA, FB,

FC containing HPMC K4M have showed a faster and formulations F3 and F4 containing HPMC K15M showed slower drug release rates comparatively.

In formulations CF1, CF2, CF3 containing Carbopol 934P, with an increase in concentration of Carbopol there was decrease in drug release rate. This is due to higher affinity of Carbopol to produce water layer over tablet which prevents dissolution of drug [6]. Dissolution profile of batch containing Sodium alginate was not good because of high amount of drug release [7]. As the concentration of sodium alginate was increased drug release rate was decreased.

When a combination of HPMC K4M and Carbopol 934P was used in formulation FD, due to carbopol 934P the release rate was decreased. Carbopol 934P is a cross- linked polymer with a high molecular weight and viscosity; when it comes in contact with water, it swells and holds water inside its microgel network. This particular property is accounted for its release retardant effect [8]. The amount of drug released for a particular drug polymer ratio was found to be in the order of

Sodium alginate > K4M > K15M > Carbopol 934P.

Formulation FA containing sodium bicarbonate and citric acid (1:1) exhibited 84.24% of drug release in 12 hours whereas formulation FD exhibited 79.38% of drug release in 12 hours.

Swelling index: The swelling index of the tablets increases with an increase in the polymer content and the content of gas generating agent sodium bicarbonate. The swelling index was found to be ranging in between 144.49 to 437.93%. Among the various polymers used HPMC K4M showed highest water uptake, showed maximum swelling property.

IR Interpretation: The IR spectrum of Losartan potassium exhibits a characteristic peaks at 760 cm^{-1}, 1000 cm^{-1}, 1462 cm^{-1}, 1575 cm^{-1} and 2995 cm^{-1} due to chloride moiety, secondary hydroxyl group, aromatic ring, nitrogen moiety and an aliphatic chain respectively.

In case of HPMC a broad peak observed at 3491 cm^{-1} indicating the presence of primary alcoholic group present in the molecule, another prominent peak appear at 2925 cm^{-1} suggesting that it is a aliphatic molecule. The IR spectrum of formulation FA shows a broad peak at 3480 cm^{-1} indicating the presence of primary alcoholic OH group. A peak is shown at 1577 cm^{-1} and 760 cm^{-1} depicting nitrogen and chloride moiety. Another characteristic peak at 1000 cm^{-1} along with 1463 cm^{-1} corresponds to secondary hydroxyl group and aromatic moiety.

In comparison with pure drug, the absorption peak of the spectra for Losartan potassium in GRDDS form (formulation FA) showed no shift and no disappearance of characteristic peaks suggesting that there is no interaction between drug and excipients as shown in fig 1-3.

Drug release kinetics: The *In vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi and Korsmeyer models to ascertain the mechanism of drug release. The results of linear regression analysis of data including regression coefficient are summarized in table 6.

The regression coefficient ‘r’ value of zero order was observed that the ‘r’ values of zero order were in the range of 0.9634 to 0. 9989 indicating drug release from all the formulations were found to follow zero order kinetics.

The good fit of the Higuchi model to the dissolution profiles of all the formulations suggested that diffusion is the predominant mechanism limiting drug release since the 'r' values of Higuchi's plots were nearer to unity.

The *In vitro* dissolution data as log cumulative percent drug release versus log time were fitted to Korsmeyer et al equation, values of the exponent 'n' was found to be in the range of 0.7104 to 0.9937 indicating that the drug release is by Non-Fickian diffusion mechanism. Few formulations like F1, SA2 and FD showed 'n' values exceeding unity.

Among the various formulations studies, GRDDS formulation FA was considered as an ideal formulation which exhibited 70.83% of drug release in 10.0 hours and floating lag time of 15 seconds with a floating time of 24 hours. Hence it is selected for further short term stability studies.

Stability studies: Short term stability study was performed for formulation FA at 40 ± 1^0C and RH 75% for 3 weeks (21 days). The samples were analysed for percent drug content, *In vitro* floating ability and *In vitro* drug release studies. The results are given in table 42 to 44. No appreciable difference was observed for the above parameters

Drug – Polymer ratios for the preparation of GRDDS of Losartan potassium

Table-1: Formulation chart (for 1 tablet)

Ingredient (mg)	F1	F2	F3	F4	CF1	CF2	CF3	SA1	SA2	SA3	FA	FB	FC	FD
Losartan potassium	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M	60	80	-	-	-	-	-	-	-	-	80	80	80	80
HPMC K15M	-	-	60	80	-	-	-	-	-	-	-	-	-	-
Carbopol 934P	-	-	-	-	30	40	50	-	-	-	-	-	-	20
Sodium alginate	-	-	-	-	-	-	-	30	40	50	-	-	-	-
Sodium bicarbonate	40	60	40	60	20	30	40	20	30	40	20	30	40	20
Lactose	50	50	50	50	50	50	50	50	50	50	40	30	20	30
Citric acid	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	4	4	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	4	4
PVP (3%)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2. Precompression flow properties of granules of Losartan potassium

Powder Blend Batch no.	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (0)
F1	0.485	0.591	17.45	0.087	21
F2	0.438	0.548	19.00	0.096	22
F3	0.472	0.612	18.25	0.163	28
F4	0.486	0.598	22.67	0.141	25
CF1	0.491	0.586	24.71	0.085	24
CF2	0.422	0.634	19.45	0.099	22
CF3	0.492	0.628	24.67	0.107	21
SA1	0.482	0.610	25.90	0.124	21
SA2	0.429	0.587	26.73	0.115	23
SA3	0.413	0.576	28.83	0.168	25
FA	0.423	0.599	19.05	0.098	22
FB	0.414	0.613	19.76	0.156	21
FC	0.412	0.629	20.08	0.115	22
FD	0.465	0.622	21.67	0.125	26

Table–3: Physical properties of GRDDS formulations F1 to FD

Formulation Codes	Hardness (kg/cm^2)	Friability (%)	Floating lag time (Seconds)	Floating time (hrs)	Percent drug content* ± SD	Weight variation
F1	4.8±0.23	0.2%	30	24	98.40±0.55	276.60
F2	4.8±0.16	0.3%	28	24	98.13±1.51	316.85
F3	4.5±0.16	0.5%	48	24	98.60±0.62	276.55
F4	4.8±0.09	0.4%	39	24	98.50±0.60	316.45
CF1	4.7±0.12	0.2%	100	<12	95.33±1.05	222.55
CF2	4.8±0.28	0.3%	82	<12	97.3±1.25	242.60
CF3	4.6±0.04	0.4%	50	<12	96.00±0.62	262.75
SA1	4.6±0.08	0.3%	85	<12	98.40±0.30	222.10
SA2	4.2±0.04	0.4%	74	<12	98.50±0.87	242.20
SA3	4.5±0.12	0.6%	60	<12	97.13±0.35	262.10
FA	4.8±0.08	0.5%	15	24	98.73±0.98	266.75
FB	4.5±0.08	0.3%	28	24	96.13±1.19	266.85
FC	4.6±0.04	0.7%	26	<12	98.66±0.66	267.00
FD	4.6±0.2	0.6%	23	24	96.00±1.08	267.05

**Average of three determinations*

Table -4: *In vitro* release data of GRDDS of Losartan potassium F1 to CF3

Sl. No.	Time (Hrs)	F1	F2	F3	F4	CF1	CF2	CF3
		Cumulative * percent drug released ±SD	Cumulative * percent drug released ±SD	Cumulative * percent drug released ±SD	Cumulative * percent drug released ±SD	Cumulative * percent drug released ±SD	Cumulative * percent drug released ±SD	Cumulative * percent drug released ±SD
1.	01	10.79±1.95	4.59±1.21	8.59±0.89	5.29±2.02	11.43±1.98	8.66±0.45	6.87±0.76
2.	02	17.32±1.91	11.98±3.54	14.50±1.41	11.54±3.42	20.54±1.61	15.51±2.79	13.80±1.69
3.	03	22.98±1.88	19.03±4.18	20.75±2.12	18.05±4.09	33.17±4.47	23.84±3.23	23.46±3.07
4.	04	29.34±1.84	24.87±4.13	27.64±2.05	27.02±5.67	38.80±4.19	33.16±2.60	29.11±4.36
5.	05	36.04±1.80	33.19±3.47	32.12±1.36	33.06±3.95	47.91±0.20	42.22±1.53	37.90±4.82
6.	06	44.83±1.74	39.70±4.78	41.20±2.85	39.93±4.35	52.90±2.08	49.22±3.41	43.33±4.32
7.	07	50.90±1.69	46.49±3.36	45.82±3.44	48.44±3.09	57.03±2.62	53.98±2.36	48.97±3.45
8.	08	56.84±1.63	54.01±1.52	52.90±2.12	52.95±1.69	64.15±1.27	57.57±0.68	53.96±2.99
9.	09	63.95±1.55	61.28±1.96	58.61±1.98	59.56±2.20	67.38±3.00	59.71±2.67	55.88±3.41
10.	10	70.19±1.47	69.33±1.45	66.03±3.47	61.81±2.31	70.74±2.19	62.50±1.42	59.09±3.10
11	11	75.78±1.38	77.07±2.50	69.65±1.97	64.13±0.82	73.20±1.12	68.08±1.11	64.79±1.39
12	12	84.55±1.28	82.81±0.14	74.07±0.46	69.92±0.93	75.21±0.88	73.55±0.59	69.98±0.53

**Average of three determinations*

Table-5: *In vitro* release data of GRDDS of Losartan potassium SA1 to FD.

Sl. No.	Time (Hrs)	SA1	SA2	SA3	FA	FB	FC	FD
		Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD	Cumulative* percent drug released ±SD
1.	01	10.89±1.11	4.46±1.57	2.50±0.71	3.35±0.84	10.62±1.37	13.23±0.86	4.29±0.21
2.	02	17.23±2.81	8.19±3.44	7.30±0.71	9.91±2.52	17.54±1.76	19.51±2.06	13.65±0.19
3.	03	26.81±4.45	14.071±5.55	13.68±2.20	17.28±1.82	22.80±2.56	23.51±3.50	20.41±0.27
4.	04	34.49±5.61	21.60±3.73	20.95±2.40	25.68±1.50	28.83±3.37	28.90±3.13	26.89±0.57
5.	05	45.25±6.93	28.09±5.76	28.38±6.36	31.24±0.64	34.19±3.08	33.50±4.26	33.26±0.38
6.	06	53.71±8.83	35.93±6.52	35.77±4.74	39.90±2.04	41.60±3.94	40.04±2.95	41.04±0.43
7.	07	58.28±6.56	43.21±5.28	42.30±4.41	48.32±2.34	51.58±2.91	47.96±1.64	48.17±0.63
8.	08	64.87±6.63	50.95±2.25	46.70±3.81	55.15±1.70	61.01±3.91	54.36±0.33	52.76±0.13
9.	09	71.53±3.68	57.15±5.17	53.29±3.21	62.76±0.91	70.98±3.07	58.36±1.66	59.52±0.89
10.	10	75.91±1.47	63.38±1.59	59.72±1.11	70.83±0.96	74.86±0.49	62.45±3.93	67.18±0.73
11	11	80.41±0.90	70.13±0.89	68.42±0.31	79.06±0.81	75.38±0.37	66.31±1.71	73.04±0.85
12	12	82.67±0.38	77.56±0.32	76.03±0.57	84.24±1.46	76.21±0.10	72.69±1.12	79.38±0.47

**Average of three determination*

Table-6: Regression analysis data of formulations of Losartan potassium

Batches		Zero Order	First Order	Higuchi's Equation	Peppas Equation
F1	r	0.9981	0.9412	0.9735	0.9937
	a	2.5849	2.0613	27.212	0.9902
	b	6.7944	0.0605	30.432	1.1392
F2	r	0.9989	0.9362	0.9725	0.9971
	a	2.0895	2.0838	35.8570	0.7068
	b	7.0716	0.0604	32.6410	0.9937
F3	r	0.9970	0.9790	0.9801	0.9974
	a	2.0057	2.0376	25.8220	0.9074
	b	6.2290	0.0485	28.097	0.8954
F4	r	0.9856	0.9915	0.9895	0.9917
	a	1.3461	2.0298	27.019	0.7578
	b	6.0802	0.0446	27.898	0.9517
CF1	r	0.9974	0.9958	0.9916	0.9816
	a	1.1986	1.9914	14.688	1.1066
	b	3.9245	0.0519	26.967	0.7589
CF2	r	0.9634	0.9910	0.9894	0.9844
	a	6.0763	2.0072	26.902	0.9642
	b	6.0136	0.0466	19.899	0.8685
CF3	r	0.9769	0.9943	0.9951	0.9864
	a	4.4538	2.0110	20.93	0.8855
	b	5.7588	0.0424	25.924	0.9214
SA1	r	0.9802	0.9896	0.9918	0.9926
	a	5.4468	2.0447	25.412	1.0236
	b	7.0678	0.0653	31.695	0.8614
SA2	r	0.9962	0.9486	0.9666	0.996
	a	3.6179	2.0726	36.349	0.6079
	b	6.6899	0.0518	31.145	1.1973
SA3	r	0.9955	0.9434	0.9707	0.9926
	a	3.887	2.0684	35.987	0.4615
	b	6.4825	0.0487	30.324	1.3482
FA	r	0.9975	0.9323	0.9736	0.9938
	a	3.5839	2.0983	39.629	0.5929
	b	7.3637	0.0643	34.303	0.9727
FB	r	0.9795	0.9606	0.9601	0.9852
	a	2.7436	2.0472	27.36	0.9832
	b	6.7949	0.0579	30.565	0.8554
FC	r	0.9892	0.9837	0.9748	0.9843
	a	5.6742	2.0124	17.57	1.0722
	b	5.7323	0.0442	25.017	0.7104
FD	r	0.9987	0.9604	0.9841	0.9861
	a	0.1844	2.0603	31.569	0.7313
	b	6.6929	0.0545	30.718	1.1104

Table-7: Stability data of GRDDS formulation (FA) at 40±1°C

Sl. No.	Time in days	Physical changes	Mean ± SD (40±1°C)
1.	01	--	84.24±1.46
2.	07	No change	83.00±1.27
3.	14	No change	82.51±1.26
4.	21	No change	83.98±1.08

Table-8: *In vitro* floating studies of formulation (FA)

Sl. No.	Formulation code	Floating lag time (seconds)	Floating time (hrs)
1.	FA	16	24
2.	FA	15	24
3.	FA	18	24

Fig 1. IR spectrum of the pure drug Losartan potassium

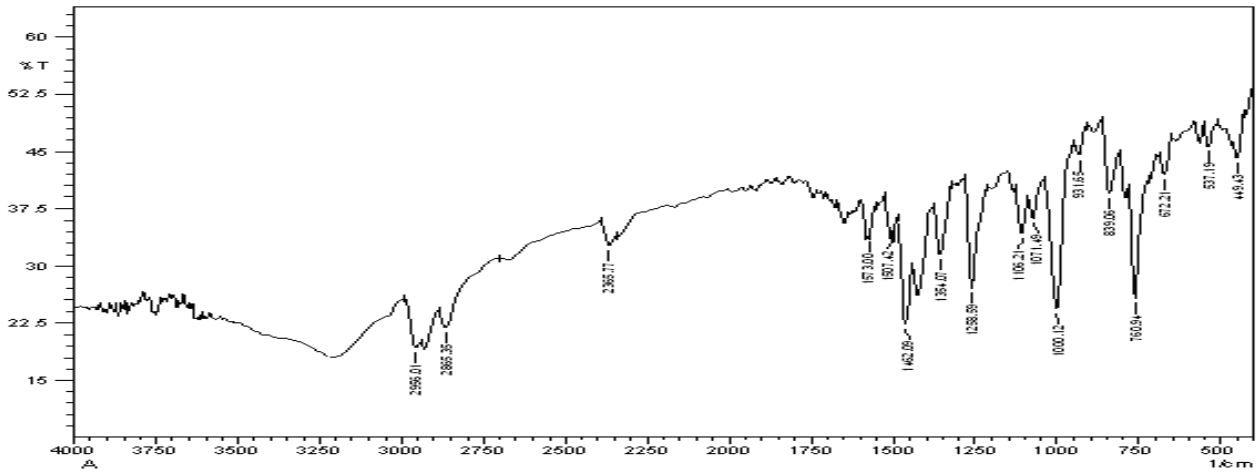

Fig 2. IR spectrum of HPMC K4M.

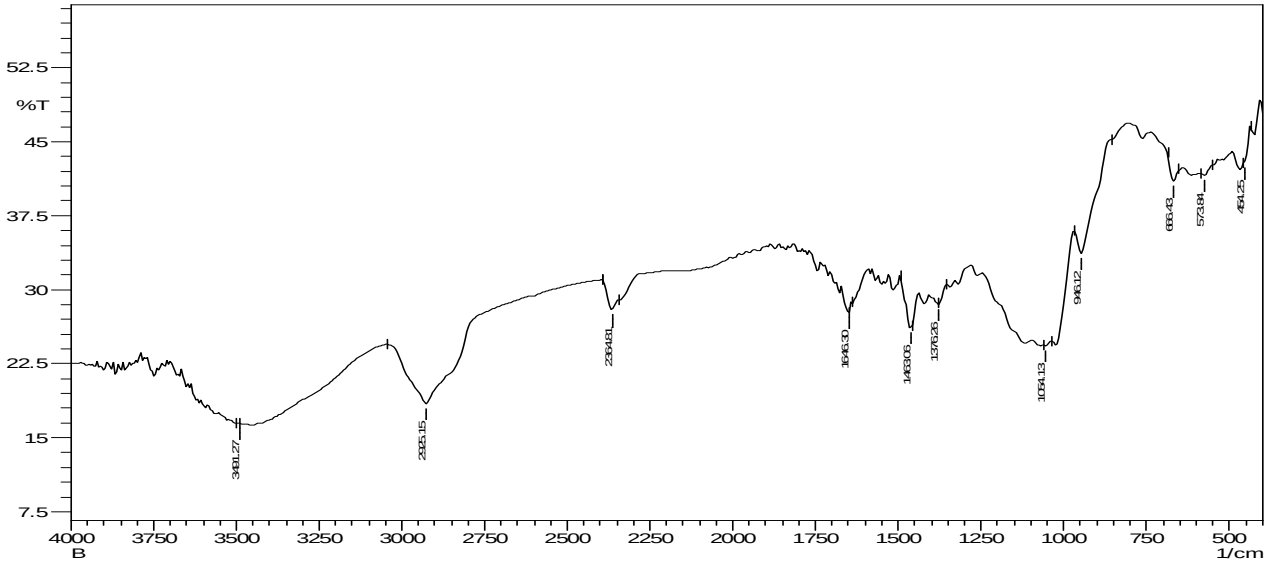

Fig 3. IR spectrum of formulation FA

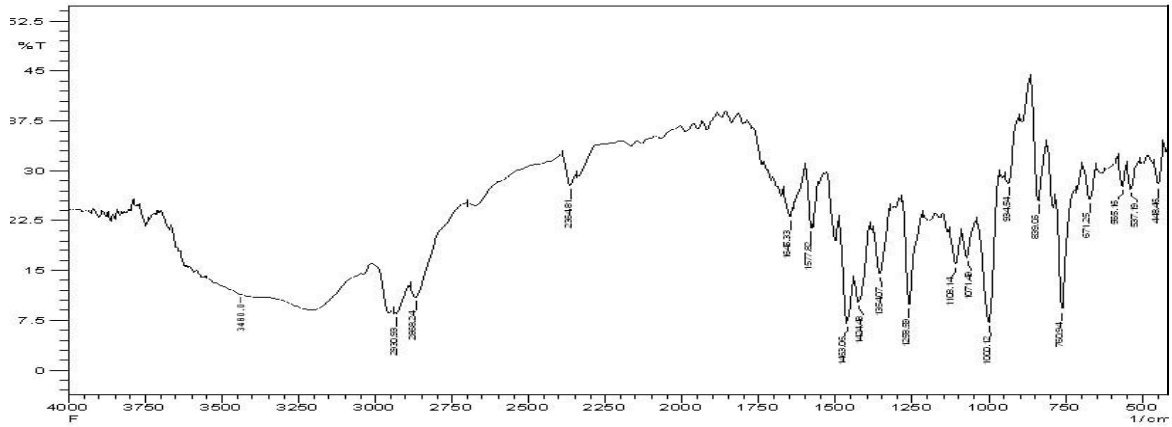

Fig 4. Cumulative Percent Drug Released Vs Time Plots (Zero Order) of F1 and F2

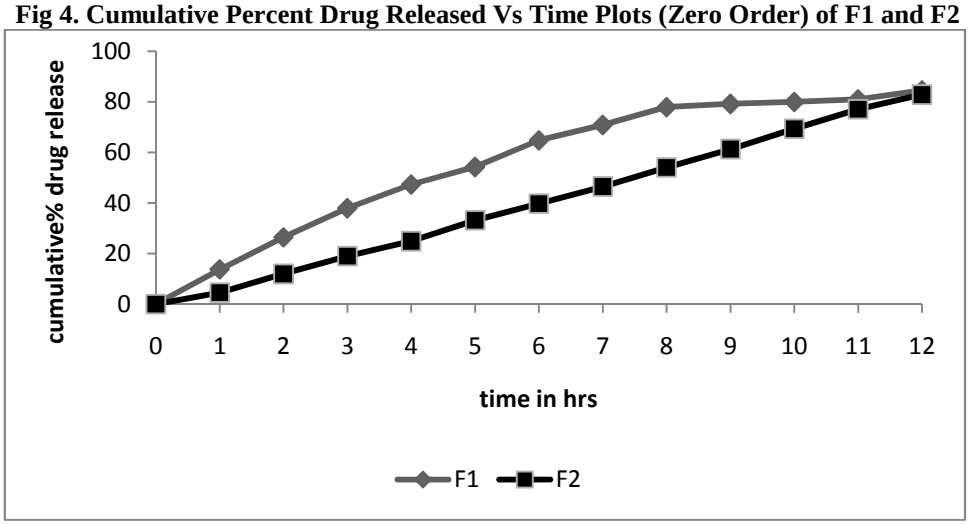

Fig 5. Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of F1 and F2

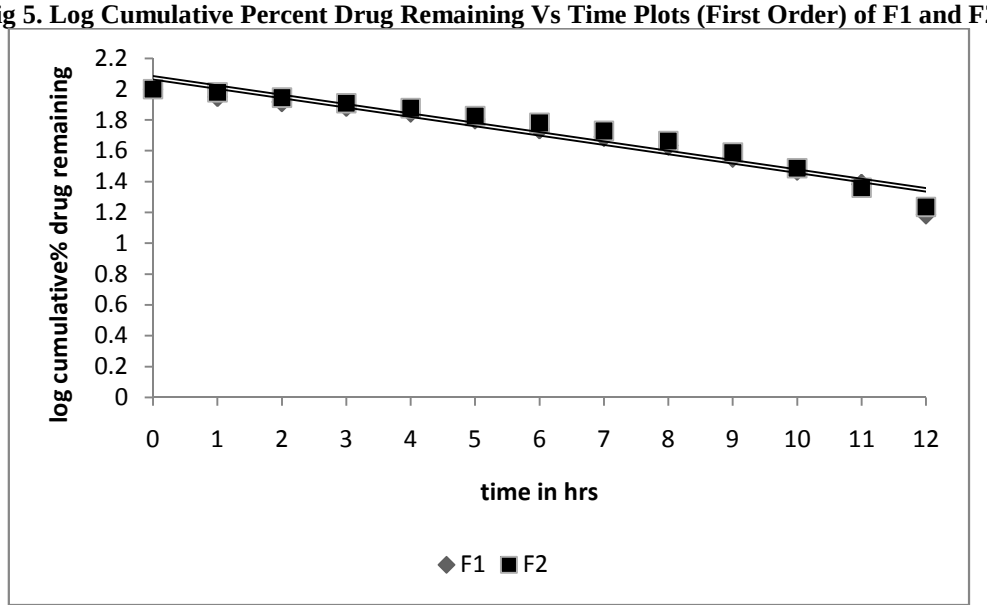

Fig 6. Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of F1 and F2

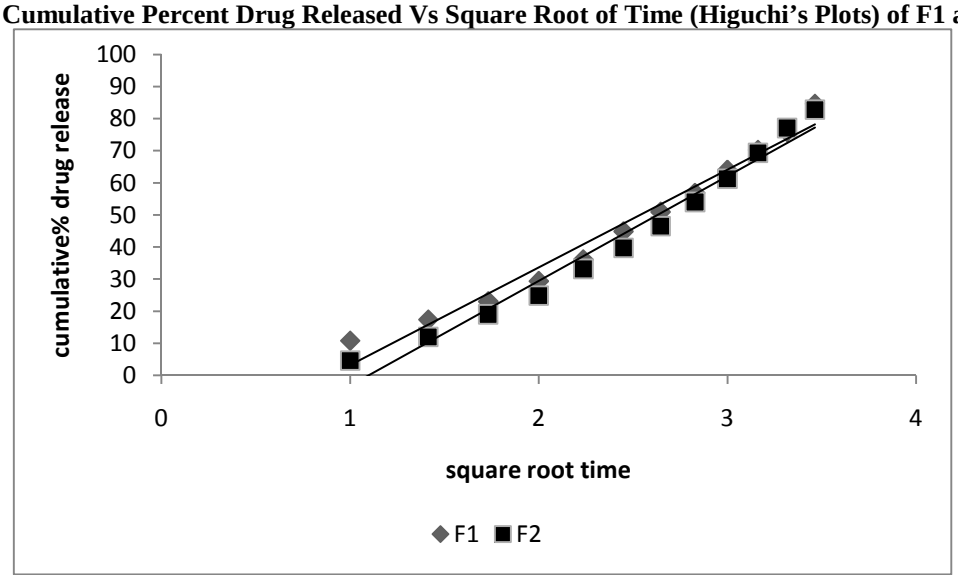

Fig 7. Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of F1 and F2

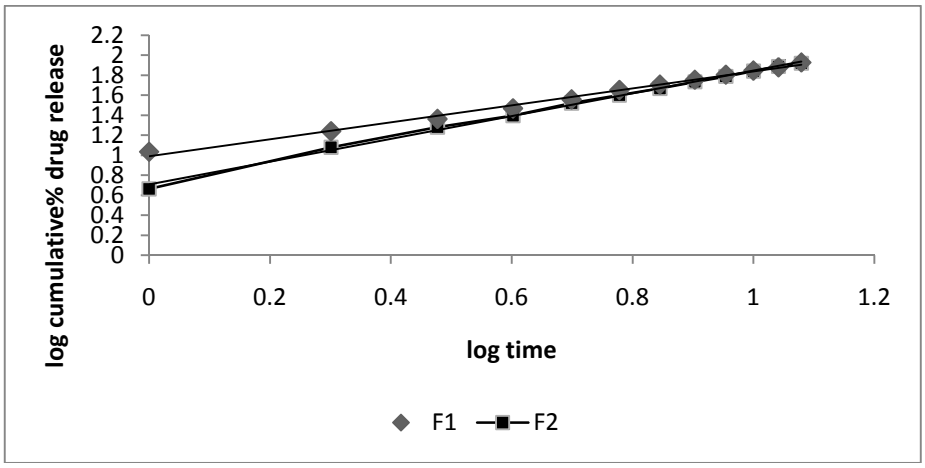

Fig 8. Cumulative Percent Drug Released Vs Time Plots (Zero Order) of F3 and F4

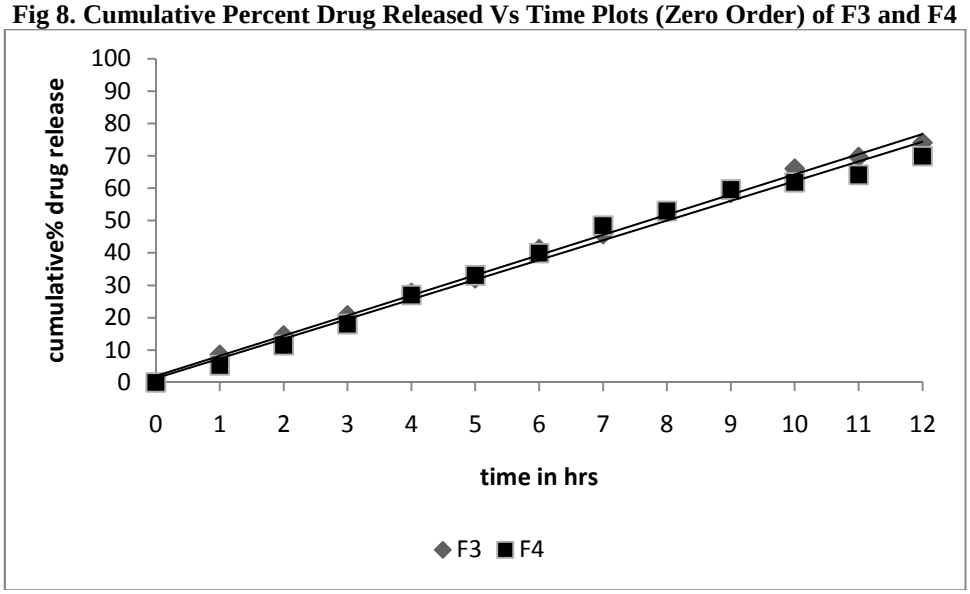

Fig 9. Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of F3 and F4

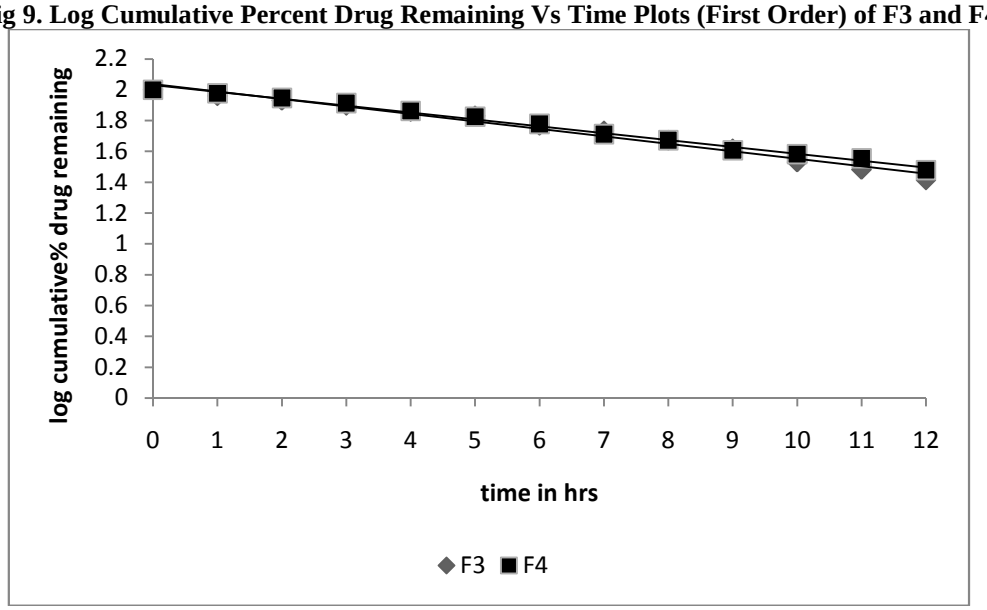

Fig 10. Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of F3 and F4

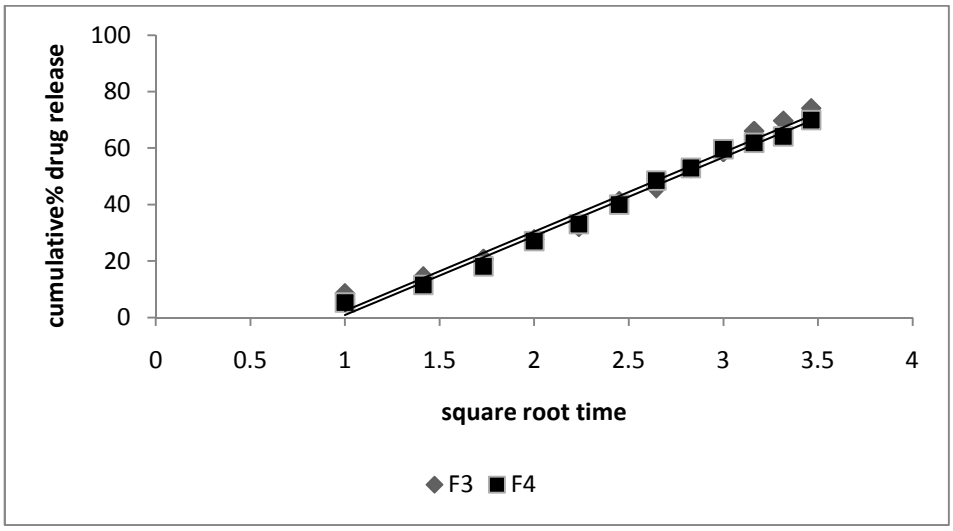

Fig 11. Log Cumulative Percent Drug Released Vs Log Time (Korsemeyer Plots) of F3 and F4

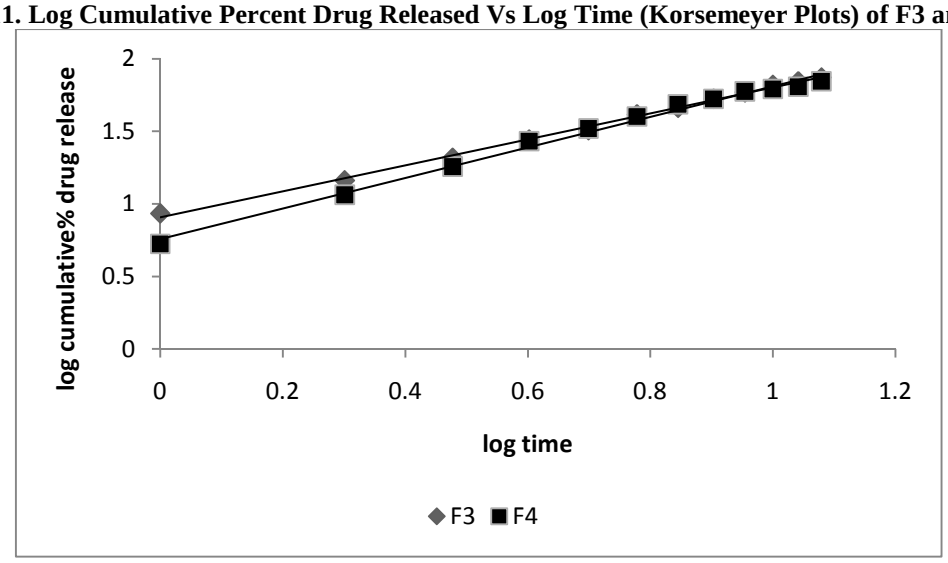

Fig 12. Cumulative Percent Drug Released Vs Time Plots (Zero Order) of CF1, CF2 and CF3

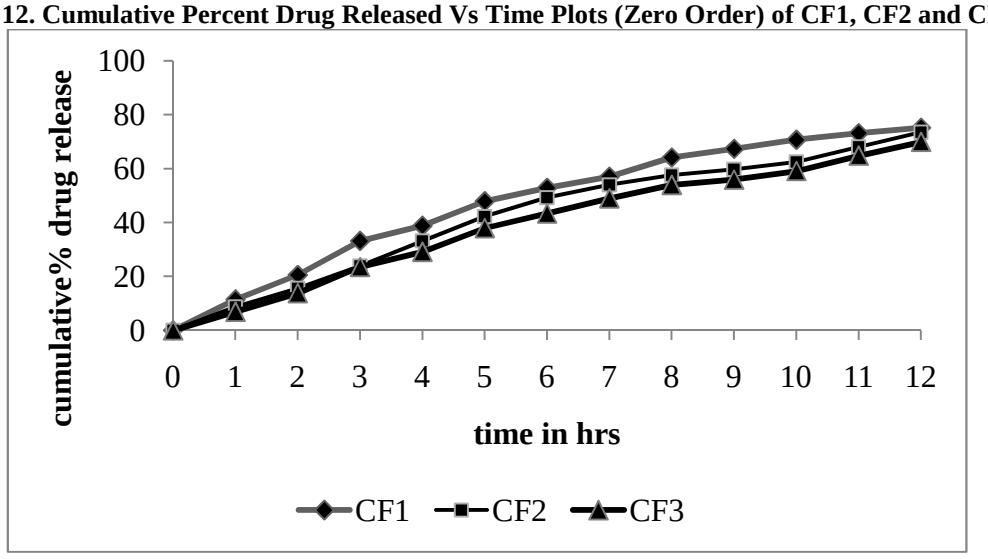

Fig 13. Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of CF1, CF2 and CF3

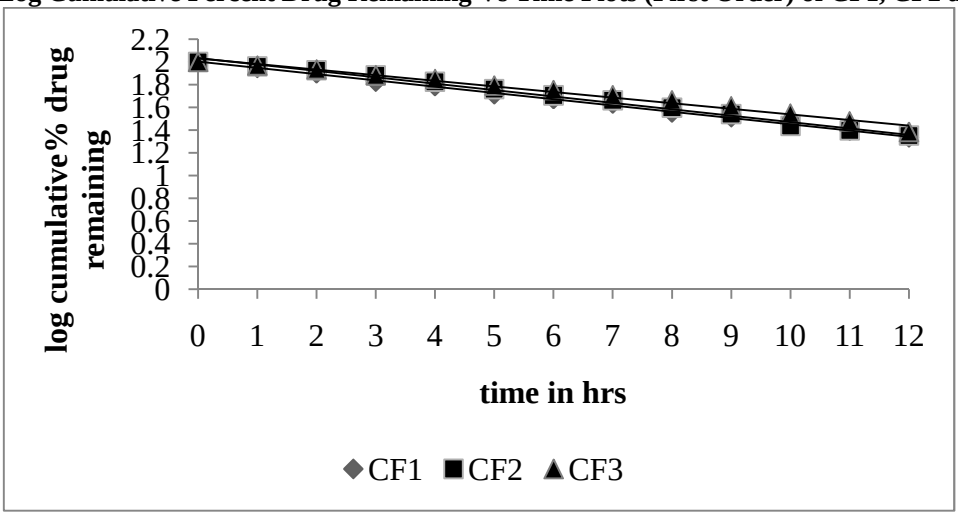

Fig 14. Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of CF1, CF2 and CF3

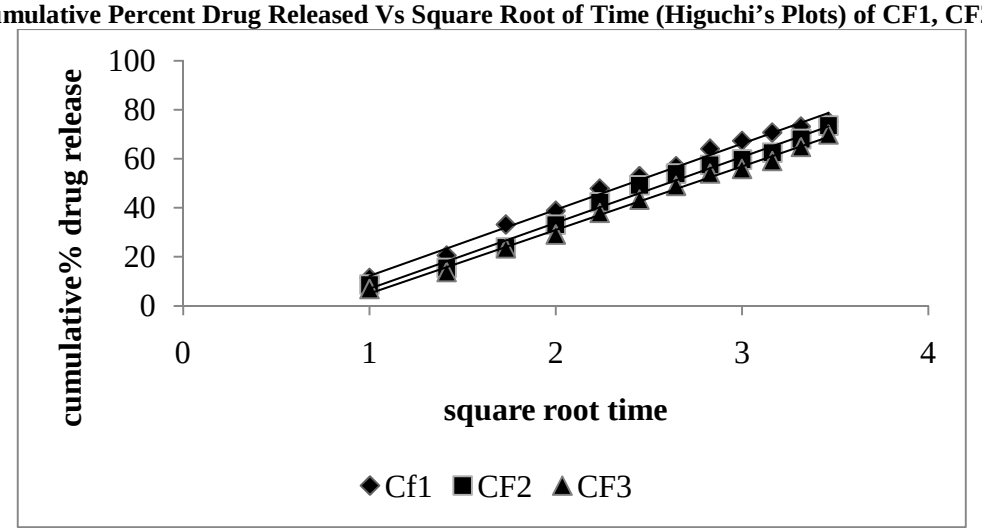

Fig 15. Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of CF1, CF2 and CF3

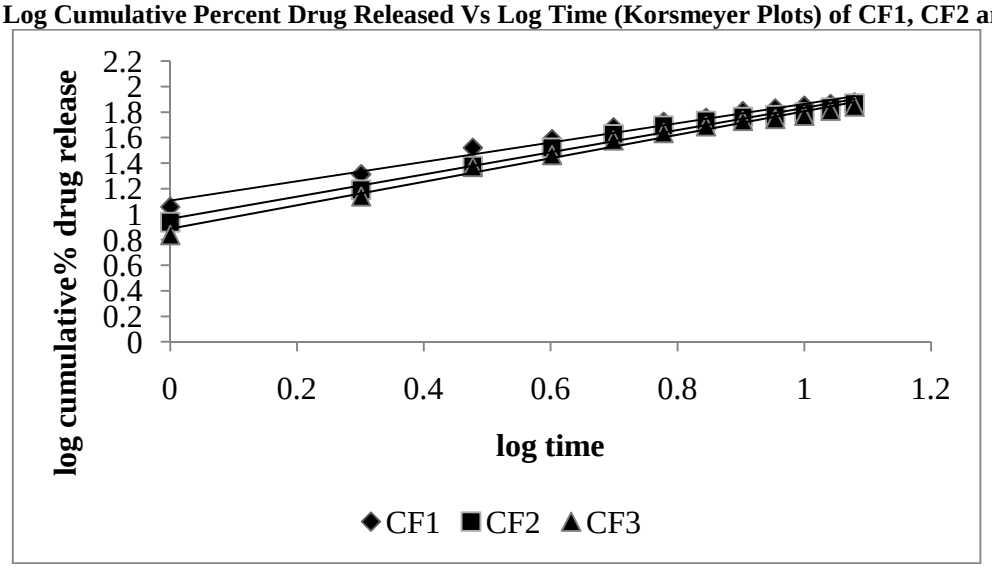

Fig 16. Cumulative Percent Drug Released Vs Time Plots (Zero Order) of SA1, SA2 and SA3

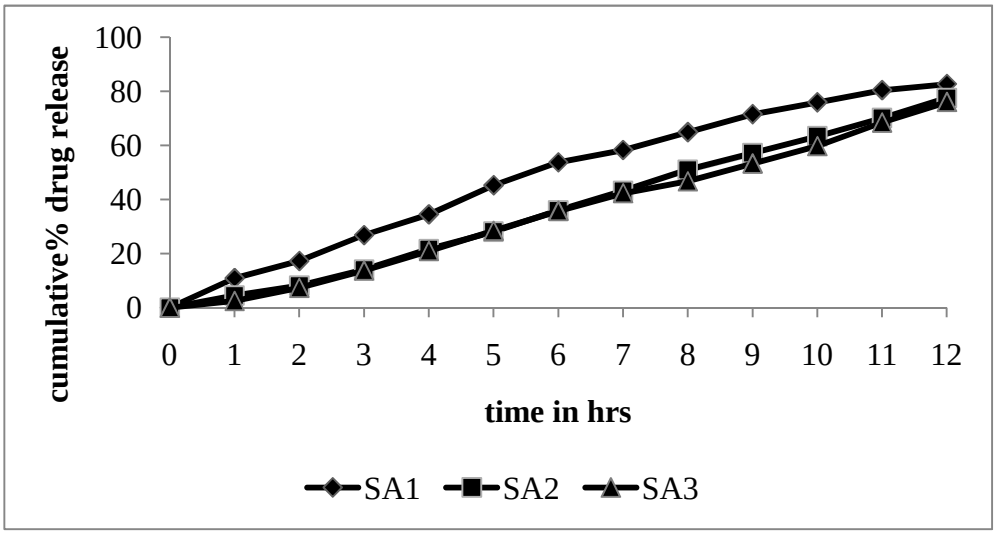

Fig 17. Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of SA1, SA2 and SA3

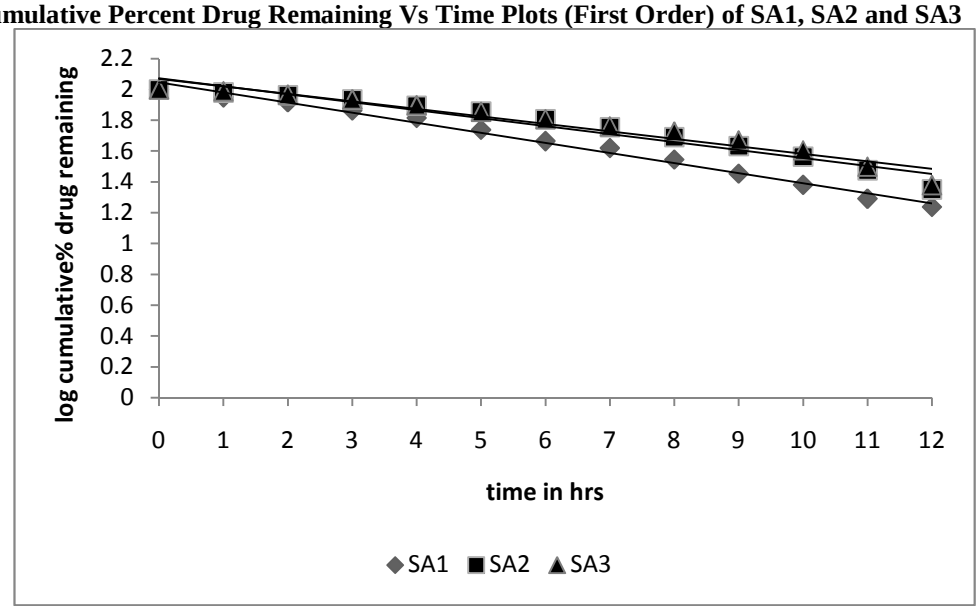

Fig 18. Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of SA1, SA2 and SA3

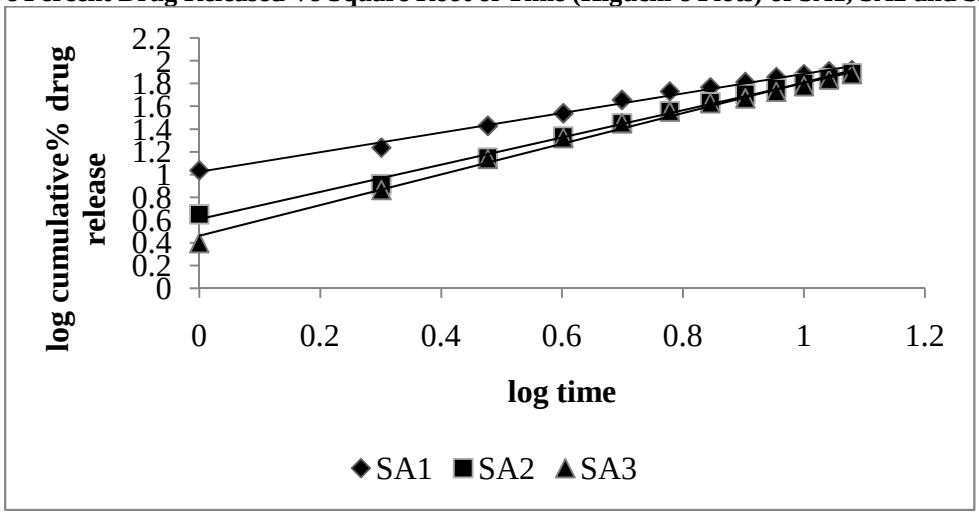

Fig 19. Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of SA1, SA2 and SA3

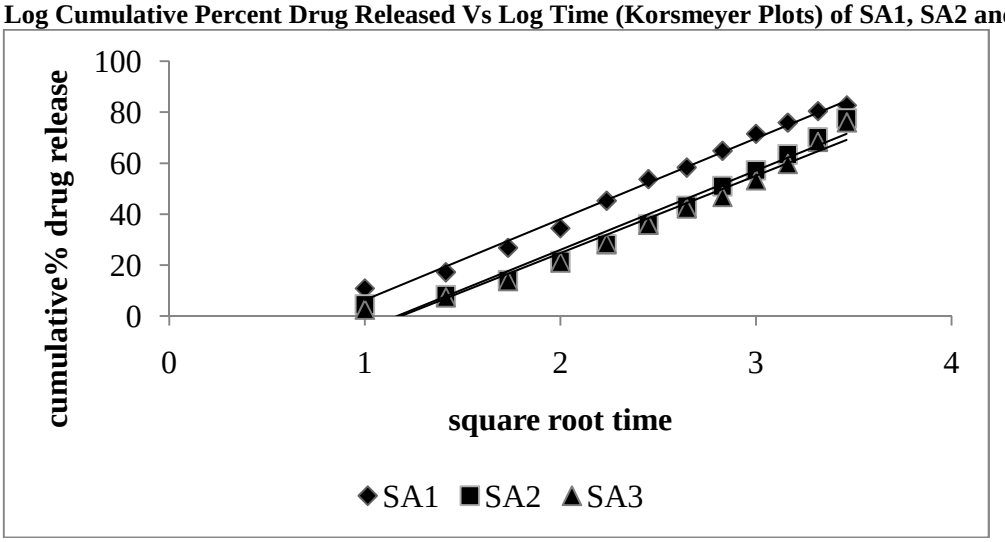

Fig 20. Cumulative Percent Drug Released Vs Time Plots (Zero Order) of FA and FB

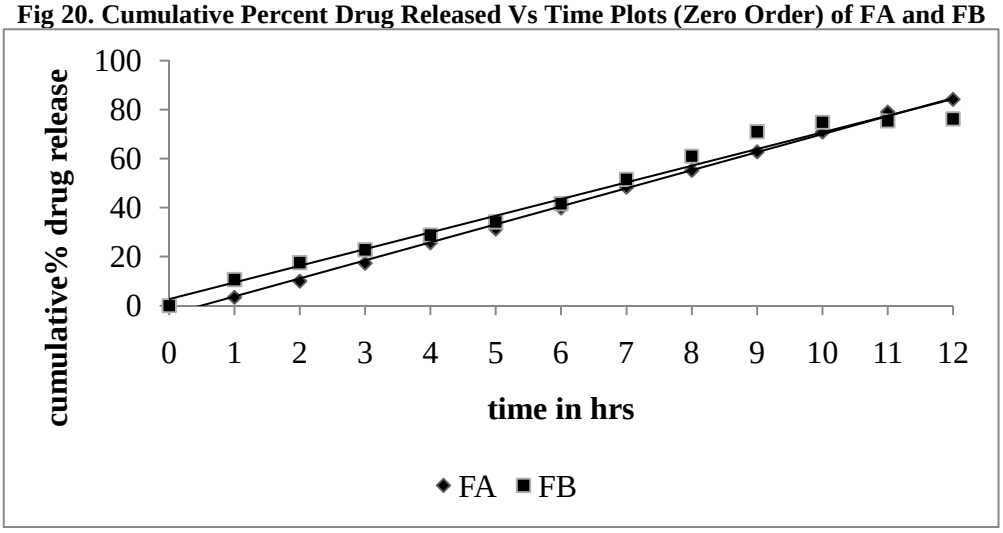

Fig 21. Log Cumulative Percent Drug Remaining Vs time Plots (First Order) of FA and FB

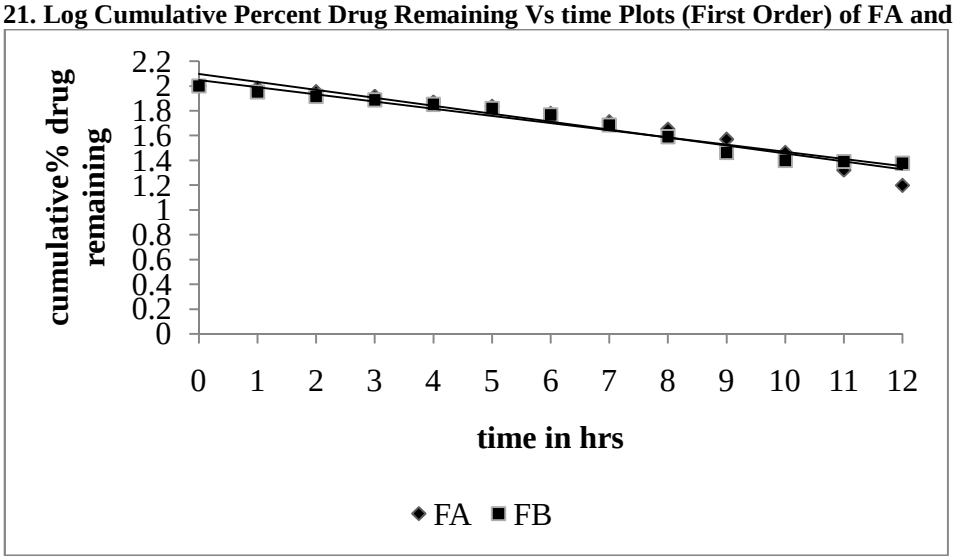

Fig 22. Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of FA and FB

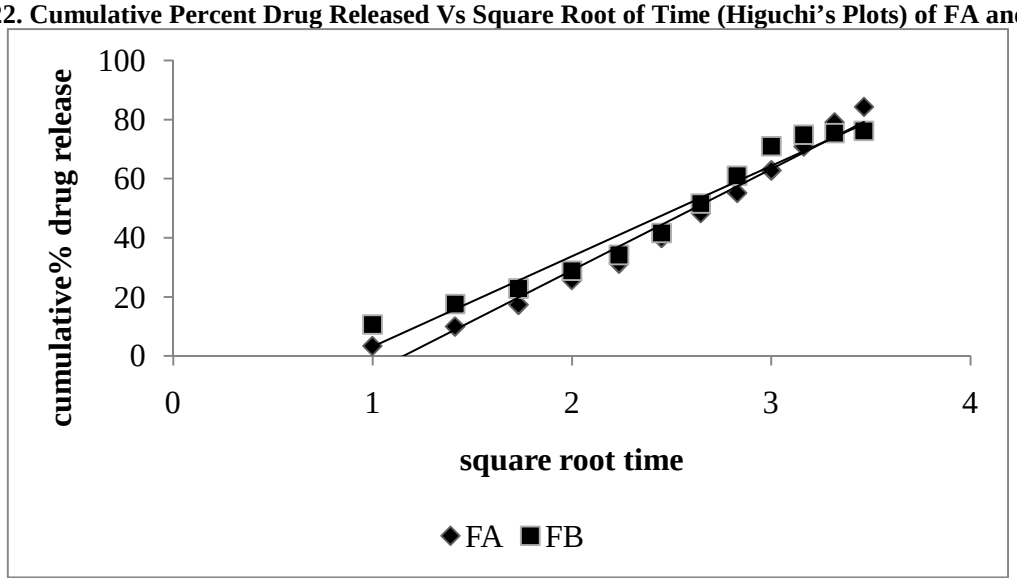

Fig 23. Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of FA and FB

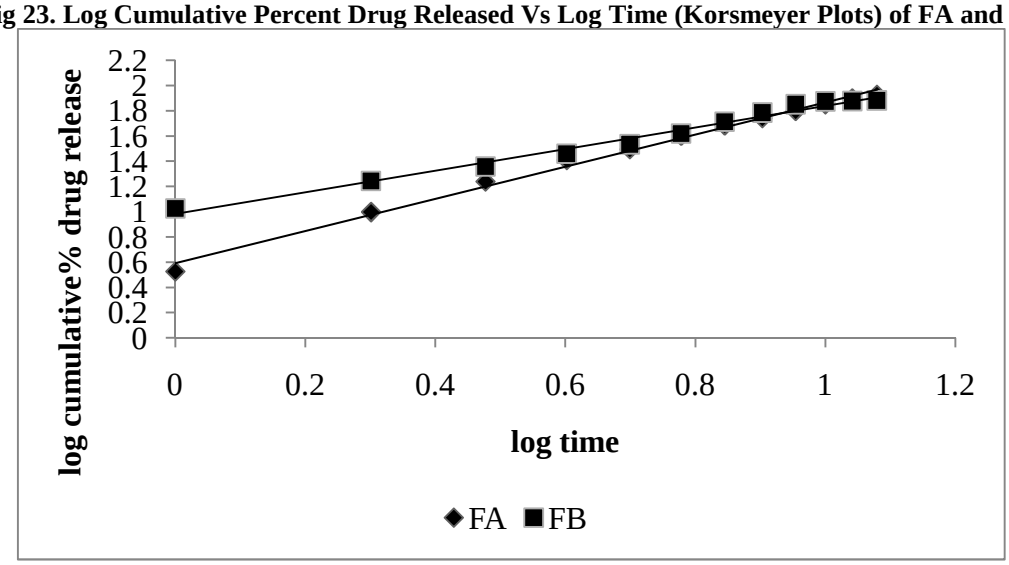

Fig 24. Cumulative Percent Drug Released Vs Time Plots (Zero Order) of FC and FD

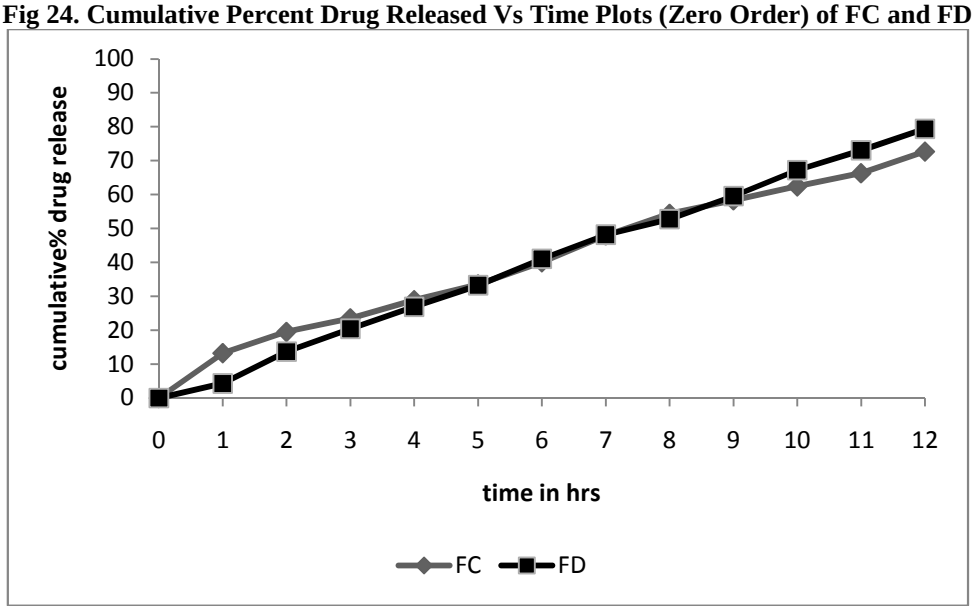

Fig 25. Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of FC and FD

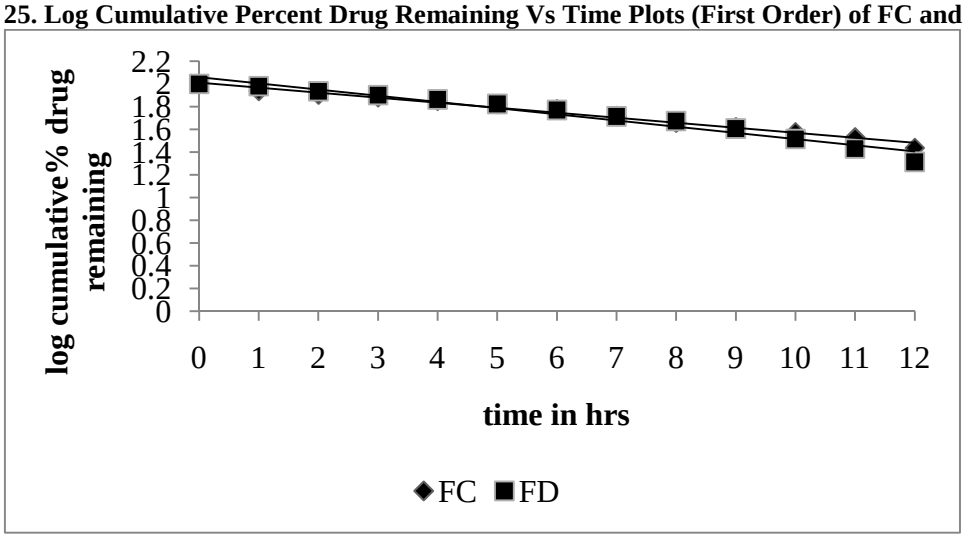

Fig 26. Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of FC and FD

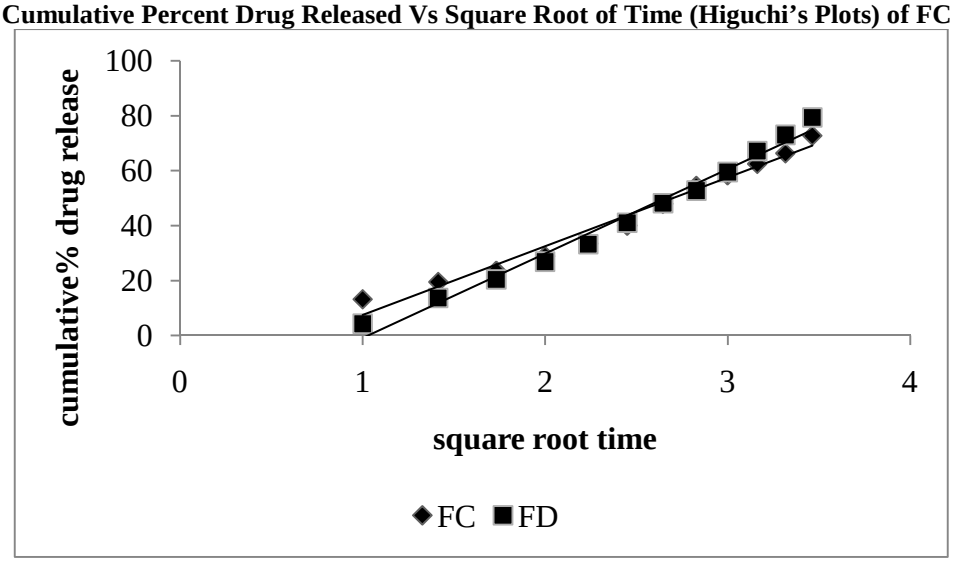

Fig 27. Log Cumulative Percent Drug Released Vs Log Time (Korsmeyer Plots) of FC and FD

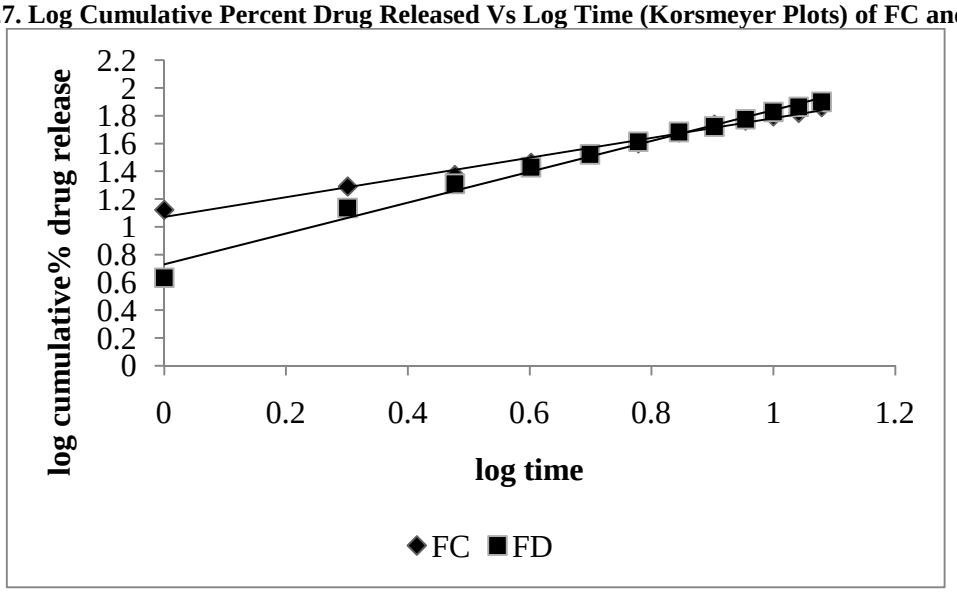

Figure 28: Swelling index (%WU) of F1-FD formulations at the end of 12h

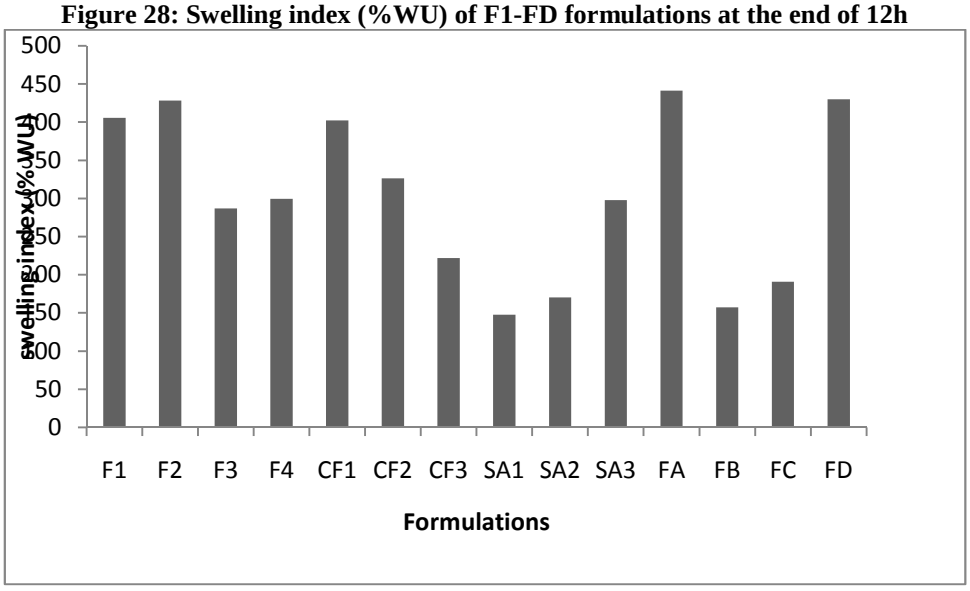

Figure-29: *In vitro* release profile of the formulation FA

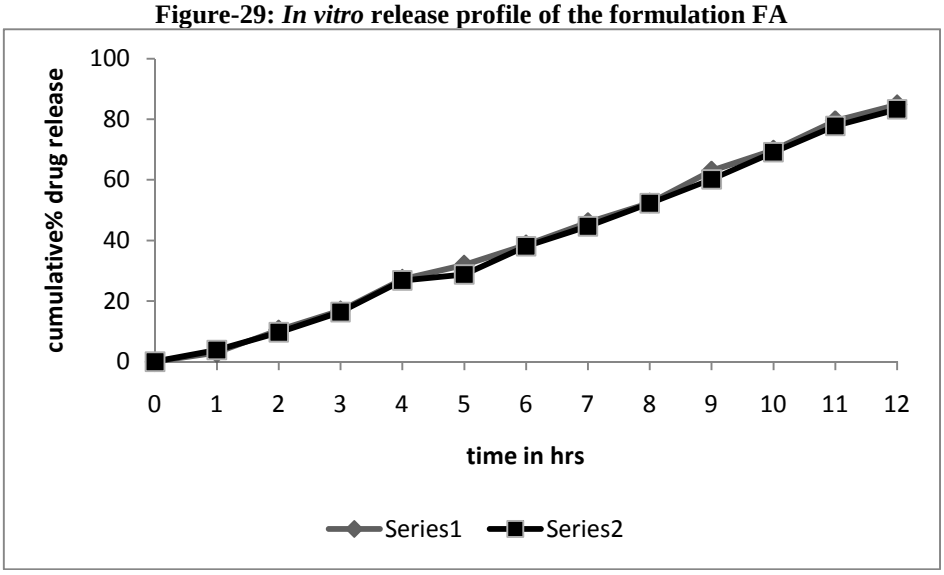

Table-9: *In vitro* Release Data of the Formulation (FA)

Sl. No.	Time (Hrs)	Cumulative * Percent Drug Released ± SD at 40±1°C	
		1st Day	21st Day
1.	01	2.99±0.20	3.87±0.91
2.	02	10.54±0.08	9.70±0.77
3.	03	16.84±0.26	16.37±0.22
4.	04	27.12±0.11	26.80±0.30
5.	05	31.90±2.44	28.78±1.28
6.	06	38.52±0.07	38.03±0.33
7.	07	45.94±0.15	44.66±0.78
8.	08	51.38±1.03	52.25±1.24
9.	09	62.95±0.18	60.12±0.55
10.	10	69.77±0.21	69.11±0.38
11.	11	79.50±0.11	77.74±1.60
12.	12	84.24±1.46	83.98±1.08

**Average of three determinations.*

CONCLUSION

The following conclusions can be drawn from the results obtained in this study

- The GRDDS of Losartan potassium prepared tablets were found to be good without chipping, capping and sticking.
- The drug content was uniform and well within the accepted limits with low values of standard deviation indicating uniform distribution of drug within the GRDDS.
- IR spectroscopic studies indicated that the drug is compatible with polymer and co-excipients.
- The drug – polymer ratio, viscosity of HPMC K4M, HPMC K15M, Carbopol 934P and Sodium alginate , different diluents and gas generating agents were found to influence the release of drug and floating characteristics from the prepared GRDDS of Losartan potassium.
- The prepared GRDDS of Losartan potassium showed excellent *In vitro* floating properties. Addition of less quantity of gas generating agent sodium bicarbonate resulted in the reduction of floating lag time. Addition of citric acid and sodium bicarbonate (1:1) has produced a marked reduction in the floating lag time upto 15 seconds. GRDD systems have showed a floating time of 24 hours. The floating lag time is dependent upon the polymer used, concentration of gas generating agent sodium bicarbonate and citric acid was found to achieve an optimum *In vitro* floating.
- The *In vitro* dissolution profiles of the prepared GRDDS formulations of Losartan potassium were found to extend the drug release over a period of 12 hours and the drug release decreased with an increase in viscosity of polymer.
- The prepared GRDDS formulations were found to have a good swelling property, with HPMC K4M containing formulations showing maximum water uptake.
- Release of Losartan potassium from most of the GRDDS formulations was found to follow zero order kinetics (0.9634 to 0.9989) and derived correlation coefficient 'r' (0.99) indicated good fit of Higuchi model suggesting that diffusion is the predominant mechanism controlling the drug release. When drug release data fitted to Korsmeyer equation, the values of slope 'n' (0.7104 to 0.9937) indicated that the drug release was by Non-Fickian mechanism.
- Among the various GRDDS formulations studied, formulation FA containing drug-polymer ratio (1:0.8) prepared with HPMC K4M showed promising results releasing $\approx$ 70% of the drug in 10.00 hours with a floating lag time of 15sec and floating time of 24 hours has been considered as an ideal formulation and subjected to further short term stability studies.
- Optimized GRDDS of Losartan potassium (FA) was found to be stable at 40^0C/RH75% following a three week stability study.
- Finally, it may be concluded that this novel drug delivery system i.e GRDDS offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The GRDDS of Losartan potassium provides a better option for increasing the bio availability and treating hypertension by allowing a better control of fluctuations observed with conventional dosage forms.

Acknowledgement

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