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DESIGN AND EVALUATION OF ONCE DAILY LOSARTAN POTASSIUM SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT: The aim of the study was to develop sustained release matrix tablet of Losartan potassium and to evaluate its efficacy in reducing hypertension. In this experiment, sustained release matrix tablets were prepared by direct compression method and Methocel K4M CR and Methocel K100M CR were used as polymer. The evaluation involves three stages: the micromeritic properties evaluation of powder blend, physical property studies of tablets and in-vitro release kinetics studies. The powder blend was evaluated for angle of repose, loose bulk density, tapped bulk density, Carr's index, Hausner's ratio, moisture content and total porosity and the tablets were evaluated for hardness, friability, thickness, drug content and in vitro dissolution parameters. The weight variation was observed to be within the prescribed limits for each formulation. *In vitro* release studies were carried out using USP apparatus type II at 100 rpm and dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 24 hours, maintained at 37±0.5°C. Drug release at different intervals was measured by UV-visible spectrophotometer at 205 nm. In this study the F9, F10 and F12 formulations showed better drug release compared to others. The release of drug was plotted in zero order, 1st order, Higuchi, Korsemeyer-Peppas and Hixson-Crowell release pattern. Kinetic modeling of in vitro dissolution profiles revealed that the drug release mechanism from all proposed formulations followed anomalous type or non-Fickian transport. The release of drug was extended for 24 hour by polymer combination which indicated the usefulness of the formulations for sustained release drug delivery.

INTRODUCTION: An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not longer lasting in the body and require multiple daily dosing to achieve the desired therapeutic results [1].

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An appropriately designed sustained or controlled release drug delivery system can be a major advance towards solving this problem [2]. Losartan potassium is an orally active angiotensin II receptor antagonist used in the treatment of hypertension. The main limitation of the drug is its low therapeutic effectiveness which is due to narrow therapeutic index, poor bioavailability (25-35%) and short biological half- life (1.5 to 2.5 hr) [3, 4]. Conventional tablets should be administered 2-3 times to maintain plasma drug concentration. So, to increase therapeutic efficacy, reduce frequency of administration and for better patient compliance once daily sustained release Losartan potassium

matrix tablets were prepared [5, 6]. Extended release technology can be categorized either as matrix or membrane system, depending on the formulation technique and release mechanisms. Membrane systems control the release rate by using osmotic pumping or solution diffusion mechanism and the matrix systems can be attained by swelling and erosion control [7].

Matrix systems offer several advantages relative to other extended release dosage form like easy to manufacture, versatile, effective and can be made to release high molecular weight compounds. Since the drug is dispersed in the matrix system, accidental leakage of the total drug components is less likely to occur [8].

The current study aims at developing oral controlled release tablets of losartan potassium using HPMC as release controlling polymer. HPMC has always been a first choice for formulation of hydrophilic matrix systems because of providing robust mechanism, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipments and methods [9, 10].

Here, the polymers mainly used are Methocel K4M CR and Methocel K100M CR. The ratio of these two polymers is changed gradually and the effect of this change on the release of drug is observed very carefully.

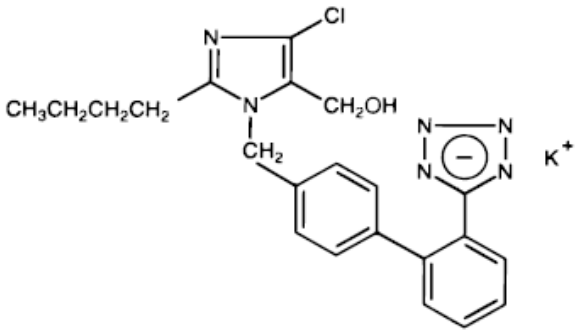


FIGURE 1: STRUCTURE OF LOSARTAN POTASSIUM[11]

MATERIALS AND METHODS [12-16]:

Materials: Losartan Potassium was obtained as a gift sample from Incepta Pharmaceuticals Ltd., Methocel K4M CR and Methocel K100M CR were obtained as a gift sample from Colorcon, Talc, Microcrystalline Cellulose (Avicel-101) and Magnesium Stearate were purchased from Taj Laboratories Ltd. Other materials used were of analytical grade.

METHOD:

Preparation of Matrix Tablet: The tablets were prepared by direct compression method. The corresponding amount of drug and excipients such as HPMC K4M CR, HPMC K100M CR, lactose monohydrate, microcrystalline cellulose, talc, magnesium stearate, starch were accurately weighed and mixed properly and the matrix tablets were prepared by direct compression using single station tablet press. Each tablet contains 100 mg of Losartan potassium and other pharmaceutical ingredients as listed in **table 1**.

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS (Here all weights are in mg)

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
Losartan Potassium	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M	95	90	70	67.5	68	45	45	45	54	45	54	36
HPMC K100M	95	80	80	67.5	45	68	45	68	36	45	36	54
Lactose Monohydrate	108	128	148	163	185	185	158	134	158	208	208	208
MCC	45	45	45	45	45	45	45	45	45	45	45	45
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Starch	-	-	-	-	-	-	50	50	50	-	-	-
Total	450	450	450	450	450	450	450	450	450	450	450	450

Evaluations of Powder blend [17-20]:

Bulk density:

Loose bulk density: 2 gm of powder blend was transferred in 10 ml graduated cylinder. Without compaction the unsettled apparent volume (V_0) was read. The apparent bulk density was calculated in gm/ml by the following formula.

Bulk density = Weight of powder/ Bulk volume

Tapped bulk density: After the initial volume was observed, the cylinder was placed into the tap density tester and the machine was set to a fixed rpm. The reading of tapping was continued until no further change in volume was noted. The tapped bulk density was calculated in gm/ml by the following formula.

Tapped density = Weight of powder / Tapped volume

Carr's Index: Compressibility index of the powder blend was determined by Carr's index. The formula for Carr's index is as below:

Carr's index (%) = [(TBD – LBD) X 100]/TBD

Angle of Repose: The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. Powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Angle of repose, } \theta = tan^{-1} (h/r)$$

Where, h = Height in cm of the powder cone, *r* = Radius in cm of the powder cone.

Hausner's Ratio: It is a number that is correlated to the flowability of a powder.

Hausner's Ratio = TD / BD

Moisture content: Moisture content of granules was determined using Mettler Karl Fischer Titrator.

The results of angle of repose ($<30^0$) indicated good flow properties of the granules. This was further supported by lower Carr's index and Hausner's ratio values (**table 2**).

TABLE 2: EVALUATION OF PHYSICAL PROPERTIES OF LOSARTAN POTASSIUM POWDER BLEND

Loose bulk density (gm/ml)	0.44 ± 0.03 to 0.49±0.02
Tapped bulk density (gm/ml)	0.57 ± 0.03 to 0.58±0.04
Carr's index (%)	15.65 ± 0.02 to 23.60±0.02
Hausner's ratio	1.16 ± 0.01 to 1.31±0.03
Total porosity (%)	13.58 ± 0.01 to 17.65±0.06
Angle of repose (°)	13.58 ± 0.01 to 17.65±0.06
Moisture content (%)	0.93 to 1.01

Evaluation of Losartan Potassium matrix tablets [17-20]:

Thickness: Thickness of the tablets was determined using a Vernier caliper.

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.

Drug content uniformity: Drug content was determined by taking an accurately weighted amount of powdered Losartan potassium with water and solution was filtered through 45µ membrane. The absorbance was measured at 205nm by UV visible spectrophotometer.

Hardness: Hardness of the tablets was determined using a hardness testing apparatus (Monseto Type). A tablet hardness of about 5-6 kg/cm^2 is considered adequate for mechanical stability.

It was found that all the formulations showed uniform thickness. The average percentage of deviation of all tablet formulations was found to be within the limit. In this study the percentage friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits.

All the tablet formulations are complied with the specifications for weight variation, drug content, hardness and friability (**table 3**).

TABLE 3: EVALUATION OF PHYSICAL PROPERTIES OF LOSARTAN POTASSIUM TABLETS

Average weight (mg)	450 ± 5%
Diameter (mm)	10.0
Thickness (mm)	3.59 ± 0.02 to 3.84±0.02
Hardness (Kp)	8.4 ± 0.04 to 9.7±0.05
Friability (%)	0.17 to 0.44

***In-vitro* dissolution studies:** *In vitro* drug release studies of the matrix tablets were carried out using a six-station USP XXII type II dissolution test apparatus (Eurolab, Germany) at 37°C (± 0.5°C) and 100 rpm speed in 900 ml of 0.1 N hydrochloric acid (gastric simulated fluid, pH 1.3) as a dissolution medium for first 2 hours and next 3 to 24 hours in intestinal simulated fluid (buffer solution, pH 6.8). The amount of drug dissolved after 1hr, 2hr, 4hr, 8hr, 10hr, 12hr and 24hr in the surrounding dissolution medium were determined by UV visible spectrophotometer at 205 nm[21].

Kinetic analysis of release data and mechanism of drug release [22]**:** In order to evaluate the kinetics and the mechanism of drug release from the formulations, the data obtained from the in vitro drug release studies were analyzed by zero order, first order, Higuchi, Korsemeyer-Peppas and Hixson-Crowell models.

Zero order: To determine the mechanism of drug release from the formulations the zero order equation expressed as cumulative amount of drug release vs time **(table 4 and graphed in graph 1).**

First order: To determine the mechanism of drug release from the formulations the first order equation expressed as log cumulative amount of drug remaining vs time **(table 5 and graph 2).**

Higuchi square root law: The Higuchi release model describe as cumulative percentage of drug release vs square root of time **(table 6 and graph 3).**

Korsemeyer-Peppas model: The dissolution data were also fitted according to the well-known exponential equation of Peppas *et al* (Eq. 3) which is often used to describe drug release behavior from polymeric systems.

$$M_t / M_\infty = Kt^n \text{ ---------- (3)}$$

Where, M_t / M_∞ is the fraction of drug released at time, t, k is the kinetic constant, and n is the diffusional exponent for drug release **(table 7 and graph 4).**

Hixson-Crowell cube root law: It is the law that provides idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets **(table 8 and graph 5).** The diffusional exponent, n, is dependent on the geometry of the device as well as the physical mechanism for release. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release **(Table 9).**

TABLE 4: ZERO ORDER RELEASE PROFILE OF TWELVE FORMULATIONS (F-1 TO F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS

Time (hrs)	Cumulative amount of drug released (%)											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	7.23	9.43	8.36	8.21	10.23	9.37	8.93	7.56	8.34	12.59	15.26	11.56
2	11.89	13.71	14.91	14.57	17.56	16.45	15.32	14.14	16.2	22.57	25.31	19.93
4	19.89	24.36	31.34	32.54	34.36	32.73	31.49	31.23	32.8	36.34	39.16	34.91
8	31.46	37.45	42.63	44.71	51.34	47.56	45.68	43.26	48.5	52.41	55.31	49.65
12	45.86	47.27	48.59	52.37	60.57	59.46	54.36	51.23	57.9	65.15	68.57	62.32
24	71.39	72.36	75.81	82.93	88.76	86.34	85.39	82.74	87.5	93.63	94.97	92.75

TABLE 5: FIRST ORDER RELEASE PROFILE OF TWELVE FORMULATIONS (F-1 TO F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS

Time (hrs)	Log cumulative amount of drug remaining (%)											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
0	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
1	1.97	1.96	1.96	1.96	1.95	1.96	1.96	1.97	1.96	1.94	1.93	1.95
2	1.95	1.94	1.93	1.93	1.92	1.92	1.93	1.93	1.92	1.89	1.87	1.90
4	1.90	1.88	1.84	1.83	1.82	1.83	1.84	1.84	1.83	1.80	1.78	1.81
8	1.84	1.80	1.76	1.74	1.69	1.72	1.73	1.75	1.71	1.68	1.65	1.70
12	1.73	1.72	1.71	1.68	1.60	1.61	1.66	1.69	1.62	1.54	1.50	1.58
24	1.46	1.44	1.38	1.23	1.05	1.14	1.16	1.24	1.10	0.80	0.70	0.86

TABLE 6: HIGUCHI RELEASE PROFILE OF TWELVE FORMULATIONS (F-1 to F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS.

SQRT Time (hrs)	Cumulative amount of drug released (%)											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
0	0	0	0	0	0	0	0	0	0	0	0	0
1.00	7.23	9.43	8.36	8.21	10.23	9.37	8.93	7.56	8.34	12.59	15.26	11.56
1.41	11.89	13.71	14.91	14.57	17.56	16.45	15.32	14.14	16.2	22.57	25.31	19.93
2.00	19.89	24.36	31.34	32.54	34.36	32.73	31.49	31.23	32.8	36.34	39.16	43.91
2.83	31.46	37.45	42.63	44.71	51.34	47.56	45.68	43.26	48.5	52.41	55.31	49.65
3.46	45.86	47.24	48.59	52.37	60.57	59.46	54.36	51.23	57.8	65.15	68.57	62.32
4.90	71.39	72.36	75.81	82.93	88.76	86.34	85.39	82.74	87.4	93.63	94.97	92.75

TABLE 7: KORSMEYER-PEPPAS RELEASE PROFILE OF TWELVE FORMULATIONS (F-1 to F-12) OF LOSARTAN POTASSIUM TABLETS

Log of time (hrs)	Log fraction released (%)											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
0.00	0.86	0.97	0.92	0.91	1.01	0.97	0.95	0.88	0.92	1.10	1.18	1.06
0.30	1.08	1.14	1.17	1.16	1.24	1.22	1.19	1.15	1.21	1.35	1.40	1.30
0.60	1.30	1.39	1.50	1.51	1.54	1.51	1.50	1.49	1.52	1.56	1.59	1.54
0.90	1.50	1.57	1.63	1.65	1.71	1.68	1.66	1.64	1.69	1.72	1.74	1.70
1.08	1.66	1.67	1.69	1.72	1.78	1.77	1.74	1.71	1.76	1.81	1.84	1.79
1.38	1.85	1.86	1.88	1.92	1.95	1.94	1.93	1.92	1.94	1.97	1.98	1.97

TABLE 8: HIXSON-CROWELL RELEASE PROFILE OF TWELVE FORMULATIONS (F-1 TO F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS

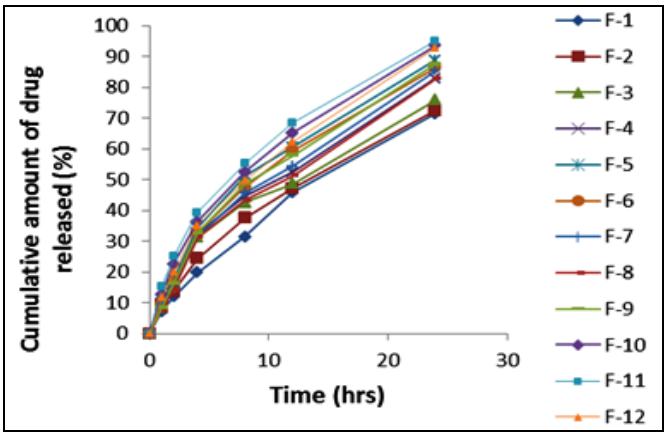
Time (hrs)	Cubic root of drug remaining (%)											
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
0	4.64	4.64	4.64	4.64	4.64	4.64	4.64	4.64	4.64	4.64	4.64	4.64
1	4.53	4.49	4.51	4.52	4.48	4.49	4.49	4.52	4.51	4.44	4.39	4.45
2	4.45	4.42	4.39	4.4	4.35	4.37	4.39	4.41	4.38	4.26	4.21	4.31
4	4.31	4.23	4.09	4.07	4.03	4.07	4.09	4.09	4.06	3.99	3.93	4.02
8	4.09	3.97	3.85	3.81	3.65	3.74	3.79	3.84	3.72	3.62	3.55	3.69
12	3.78	3.75	3.72	3.62	3.4	3.43	3.57	3.65	3.48	3.27	3.15	3.35
24	3.06	3.02	2.89	2.57	2.24	2.39	2.44	2.58	2.32	1.85	1.71	1.93

Interpretation of Release rate constants and R-square values for different release kinetics:

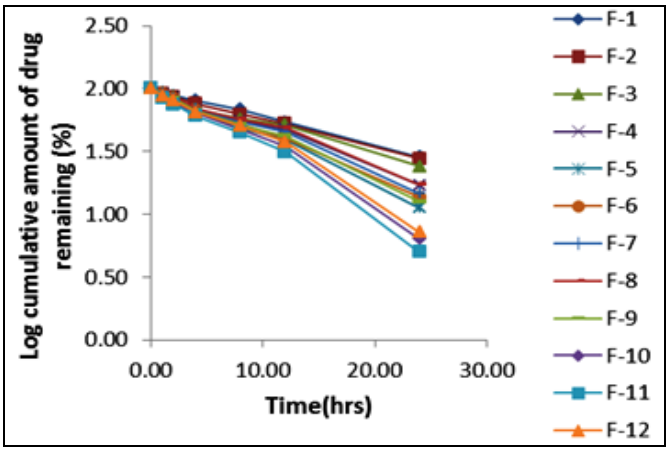
TABLE 9: RELEASE RATE CONSTANTS AND R^2 VALUES FOR DIFFERENT RELEASE KINETICS OF TEN FORMULATIONS OF LOSARTAN POTASSIUM MATRIX TABLETS

Formulation	Zero order		First order		Higuchi		Korsemeyer-Peppas		Hixson- Crowell	
	K_0	R^2	K_1	R^2	K_h	R^2	n	R^2	K_{HC}	R^2
F-1	2.903	0.9755	-0.0223	0.9978	14.986	0.9722	0.7255	0.999	-0.0648	0.9973
F-2	2.8773	0.9536	-0.0226	0.9971	15.151	0.9887	0.6537	0.9968	-0.0653	0.9911
F-3	2.9816	0.9213	-0.0247	0.9861	15.935	0.9842	0.6837	0.9708	-0.0697	0.9738
F-4	3.2979	0.9342	-0.0309	0.9877	18.694	0.9858	0.722	0.9726	-0.0833	0.9858
F-5	3.5433	0.9209	-0.0384	0.9924	18.985	0.9887	0.6844	0.982	-0.0972	0.9902
F-6	3.47	0.9293	-0.0352	0.9959	18.506	0.9884	0.7025	0.9832	-0.0916	0.9919

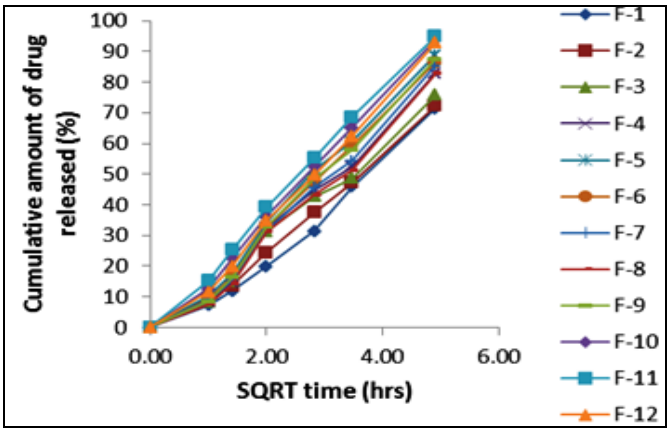
F-7	3.4044	0.9424	-0.0336	0.9885	17.999	0.9852	0.7089	0.9833	-0.0885	0.9914
F-8	3.3004	0.943	-0.0307	0.9868	17.402	0.9804	0.7418	0.9738	-0.0828	0.9874
F-9	3.5144	0.9316	-0.0365	0.9909	18.694	0.9858	0.7326	0.9764	-0.0941	0.9912
F-10	3.6723	0.9234	-0.0479	0.9818	19.716	0.9954	0.6212	0.9895	-0.1117	0.9945
F-11	3.6725	0.9061	-0.0519	0.9819	19.925	0.9974	0.5702	0.9925	-0.1167	0.9939
F-12	3.661	0.937	-0.0457	0.9789	19.485	0.9925	0.6488	0.9909	-0.1086	0.9946



GRAPH 1: ZERO ORDER PLOT OF RELEASE KINETICS OF TWELVE FORMULATIONS (F-1 to F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS



GRAPH 2: FIRST ORDER PLOT OF RELEASE KINETICS OF TWELVE FORMULATIONS (F-1 TO F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS



GRAPH 3: HIGUCHI PLOT OF RELEASE KINETICS OF TWELVE FORMULATIONS (F-1 to F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS

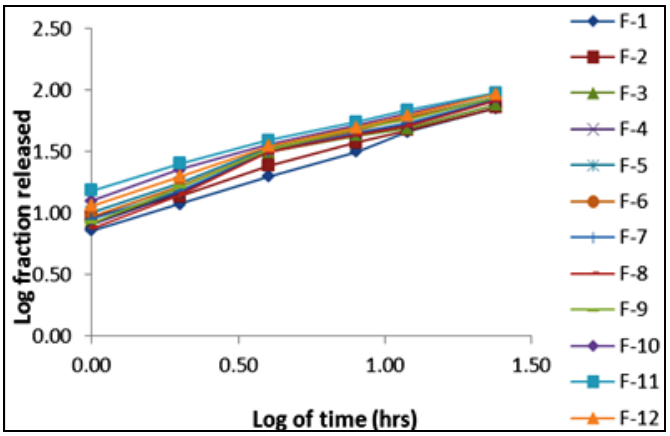


FIGURE 4: KORSMEYER-PEPPAS PLOT OF RELEASE KINETICS OF TWELVE FORMULATIONS (F-1 to F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS

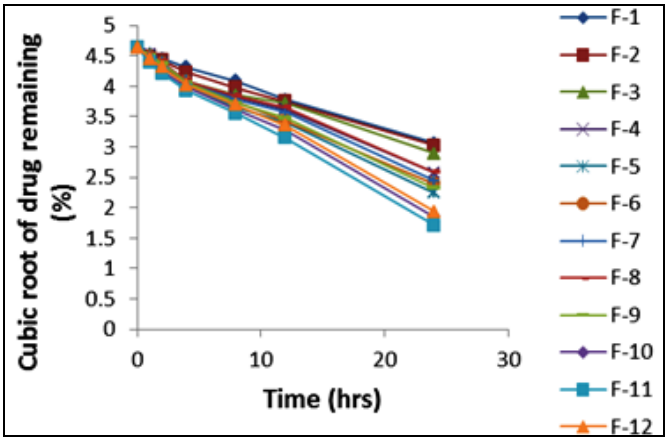


FIGURE 5: HIXSON-CROWELL PLOT OF RELEASE KINETICS OF TWELVE FORMULATIONS (F-1 to F-12) OF LOSARTAN POTASSIUM MATRIX TABLETS

CONCLUSION: The present study was investigated in order to formulate Losartan Potassium sustained release tablet with the addition of two release retarding polymers Methocel K4M and Methocel K100M. Drug release kinetics indicated that the drug release was best explained by Zero order, First Order, Korsemeyer-Peppas and Hixson-Crowell equations as these plots showed the highest value of linearity. Among all three formulations; **F-9** (Methocel K4M: Methocel K100M = 12%: 8%), F-**10** (Methocel K4M: Methocel K100M = 10%: **1**0%), **F-12** (Methocel K4M: Methocel K100M = 8%: 12%) successfully met the official specification for release profile.

Kinetic modeling of *in vitro* dissolution profiles revealed that drug release mechanism from all proposed formulations (F – 1 to F – 12) followed anomalous type or non-Fickian transport.

The release of drug was extended for 24 hour by polymer combinations which indicated the usefulness of the formulations for sustained release drug delivery. The optimized formulations may be used for the development of Losartan Potassium sustained release tablet for commercial production in order to treat hypertension.

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