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FORMULATION AND EVALUATION OF OSMOTIC CONTROLLED RELEASED MATRIX TABLETS OF LOSARTAN POTASSIUM

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Abstract: The oral controlled release formulation system shows a controlled drug release in pre- determined rate for a prolonged period of time, thereby ensuring sustained therapeutic action. Osmotic Controlled drug delivery systems are most promising strategy-based system for controlled drug delivery. The main intention of the present research was to formulate and evaluate the osmotic controlled release matrix tablet of Losartan potassium using different types of osmogens and control releasing polymer. Losartan Potassium is an Angiotensin II receptor (Type AT1) antagonist commonly used in hypertensive patients. The tablets (F1-F9) were formulated using different ratios of osmotic agents such as mannitol and lactose with the combination of control releasing polymer HPMCK15M and compressed by direct compression techniques. The FTIR spectra of pure drug with different polymers and osmogens showed no interaction. The developed powders were subjected for the pre-compression parameters and punched using single head rotatory compression machine. The tablets were formulated with the weight of 550 mg and were subjected for the post- compression evaluation. The matrix tablets were coated by dip coating method using the coating solution composed of cellulose acetate, PEG- 400 and Acetone as solvent. The coated tablets were also evaluated for different parameters. The coated tablets finally drilled by 0.25 mm needle on center of the one side of the tablet. The optimized formulation, showed the pre- compression and post- compression parameters with in standard limit and in- vitro drug release of optimized formulation was found to be 97.71 % at the end of 12 hours.

Keywords: Osmotic, Losartan potassium, Controlled release, Osmogens, Direct compression technique, Angiotensin II, Hypertensive, Dip coating, Drilling.

INTRODUCTION

Oral route of administration is one of the oldest and most extensively used routes for providing convenient method of effectively achieving both local and systemic effect. The tablets are the most widely used dosage form today because of its convenience in self administration, compactness, easy manufacturing, accurate dosing, stability and better patient compliance. Controlled release dosage form cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate. A number of design options of per oral CR dosage forms are available to control or modulate the drug release from a dosage form which falls in the category of matrix, reservoir, or osmotic systems. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. However, factors such as pH, presence of food, and other physiological factors may affect drug release from these systems. It has many advantages, such as nearly constant drug level at the site of action, prevention of peak- valley fluctuations, reduction in dose of drug, reduce dosage frequency, avoidance of side effects and improve patient compliance. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in between the minimum effective concentration(MEC) and maximum safe concentration (MSC) for a prolonged period of time, thereby ensuring sustained therapeutic action.

Osmotic Controlled drug delivery systems are most promising strategy- based system for controlled drug delivery. Among different types of osmotic controlled pumps, elementary osmotic pump system is simplified form and normally comprises of:

1. The core system(drug, osmogen, polymers and other excipients)
2. Semi-permeable membrane
3. Delivery orifice

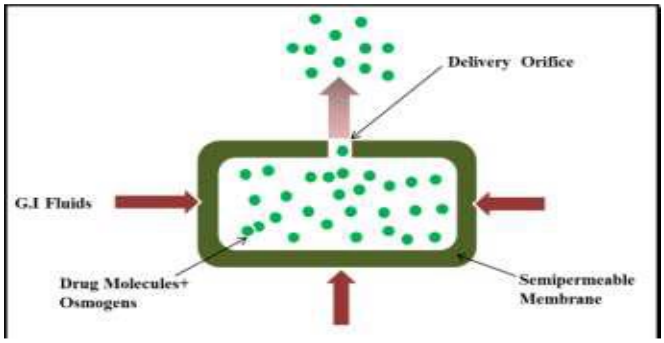

Figure 1: Elementary Osmotic Pump

It is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate. A small orifice is drilled through the membrane coating. When this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semi permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is no extensible and the increase in volume due to imbibitions of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice.

Losartan Potassium is an Angiotensin-II receptor (Type AT1) antagonist. It is a non-peptide molecule of Molecular formula $C_{22}H_{22}CLKN_6O$ and molecular weight 461.01. The elimination half life of Losartan potassium is 1.5- 2 hrs, there by requiring 2-3 times daily dosing in large no. of patients. Oral absorption of Losartan is not affected by food but bioavailability is only 33% due to first pass metabolism, there by requiring two or three times daily dosing in large number of patients, which often leads to non-compliance.

Thus, objective of present investigation was to develop a osmotic controlled released matrix tablet of Losartan potassium that can fulfill strong clinical need and Market potential for a single dose resulting in a better patient compliance.

MATERIALS AND METHODS

Losartan potassium was obtained as a gift sample from **Micro Labs. Ltd,** and all other reagents used were of analytical grade. Osmotically controlled matrix tablet of Losartan potassium were prepared by using different ratios of osmotic agents such as mannitol and lactose with the combination of control releasing polymer $HPMCK_{15}M$ and compressed by direct compression techniques. The Matrix Tablets were coated by dip coating method. The Coating solution was made by dissolving cellulose acetate and PEG- 400 in Acetone. The coated tablets were drilled through needle of diameter 0.25mm on center of the one side of the tablets. After Pre-formulation study the micromeritic property of the blend is characterized with respect to the angle of repose, bulk density, tapped density and Carr's index.The tablets were compressed using 12 mm punch in single headed 16 station tablet punching machine. Tablets from different formulations were evaluated for post- compression parameters like general appearance, hardness, thickness, weight uniformity, friability, drug content and in-vitro dissolution test. The coated tablets were also evaluated for different Parameters such ass thickness, weight uniformity, percentage weight gain, drug content and in-vitro dissolution test.

Preparation Osmotically Controlled Matrix Tablet

Losartan potassium was blended with $HPMCK_{15}M$ in a air- tight plastic container for 10 minutes and were passed through a sieve #40. The osmotic agent (mannitol or lactose) and micro crystalline cellulose (MCC) were added in geometric dilution and blending was continued for additional 10 min. To this mixture talc and magnesium stearate which were passed through #60 mesh sieve were added and blending was continued for additional 5 minute. The blend was evaluated for pre- compression parameters, followed by direct compression. The weight of the tablet was adjusted to 550 mg using 12 mm punch in single headed 16 station tablet punching machine. After compression, the formulated tablets were evaluated for post- compression parameters. The Matrix Tablets were coated by dip coating method. The Coating solution was made by dissolving cellulose acetate and PEG- 400 in Acetone. All the coated tablets dried at 50° C for 6 hours. The Coated Tablets were drilled through needle of diameter 0.25mm on center of the one side of the tablets.

Table 1: Formulation Development of Osmotically Controlled Matrix Tablet of Losartan Potassium by Direct Compression.

FORMULATION CODE	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Losartan Potassium	109	109	109	109	109	109	109	109	109
Mannitol	50	100	150	-	-	-	50	75	100
Lactose	-	-	-	50	100	150	100	75	100
Hydroxy Propyl Methyl Cellulose ($HPMCK_{15}M$)	75	75	75	75	75	75	75	75	75
Micro- Crystalline Cellulose (MCC)	308	258	208	308	258	208	208	208	208
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Total	550	550	550	550	550	550	550	550	550

Table 2: Coating Solution Composition

Ingredients	Coating Code				
	C1	C2	C3	C4	C5
Cellulose Acetate	5	5.5	6	6.5	7
PEG- 400	2	2.5	3	3.5	4
Acetone(ml)	100	100	100	100	100

EVALUATION TEST

Pre-compression evaluation

Before formulation development FT- IR spectrum, solubility, melting point of drug sample, drug-polymer compatibility and compatibility of drug with other excipients were evaluated. 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.

Post-compression evaluation

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 were measured using Vernier calipers. The uniformity of weight using 20 tablets, Hardness (Monsanto) using 10 tablets, Friability using 15 tablets (Roche Friabilator) were evaluated.

Drug Content

Ten tablets were selected randomly and weighed. The weighed tablets were crushed and powdered to get fine powder. An amount of powder equivalent to one tablet was taken and was allowed to dissolve in 100 ml of distilled water and kept to overnight. The solution was filtered and diluted suitably. The absorbance of the final solution was measured at wavelength 250 nm using distilled water as blank in UV- spectrophotometer. The content of drug was calculated using standard calibration curve of the drug.

In- vitro Dissolution Test

Dissolution is defined as a process where solid part i.e. solute dissolve in a solution i.e. medium. Dissolution test was carried out in dissolution USP type I apparatus i.e. basket apparatus at 50 rpm for 12 hours. Dissolution mediums used were 0.1N HCl and 6.8 pH phosphate buffer. The first 2 hours dissolution was carried out using 0.1 N HCl of 900 ml and remaining 10 hours was carried out by using 6.8 pH phosphate buffer at the temperature of 37°C± 0.5°C. The samples were withdrawn (5 ml) at every 1 hour and replaced with equivalent amount of fresh medium. The dissolution samples were analyzed using validated UV- Vis spectrophotometer at 205 nm and 225 nm for 0.1 N HCl and 6.8 pH phosphate buffer respectively.

Release kinetics

The cumulative amount of Losartan potassium release from the formulated osmotic controlled matrix tablet at different time intervals were fitted to zero order kinetics, first order kinetics, Higuchi's model and Korsmeyer- Peppas model to characterize mechanism of drug release.

Stability Studies

Selected formulation was tested for its stability. Short-term stability studies were performed at temperature 40±2°C, 75±5% relative humidity 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, 75±5% RH. 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.

RESULTS AND DISCUSSION

Pre-compression parameters of Granules

The bulk density was found in the range 0.388 to 0.458 and tapped density in the range 0.468 to 0.568. Hausner's ratio was found to be in the range of 1.16 to 1.27, showing good to passable range and Carr's index was found in the range 14.28 to 21.70, showing good to passable range. The angle of repose of blend of all formulations was found in the range 25.44° to 29.40° (Table 4), showing good flow properties. Hence all the data obtained were found to be within the limit as prescribed by the Pharmacopoeia.

Post compression parameters

The average weight of all the formulations (uncoated tablets) were within the range 546.77 to 549.42 (Table 5) and coated tablets were within the range 563.26 to 569.46 as shown in Table 6. Hence, all the tablets passed the weight variation test, i.e, the average percentage weight variation was found to be within the prescribed pharmacopoeial limits of ±5%. The thickness of all the formulations of uncoated tablets were found in the range 4.92 to 5.00 mm (Table 5). The thickness of all the formulations of coated tablets was found in the range 5.09 to 5.15 (Table 6). The thickness of all the formulations (uncoated and coated) was found to be within the accepted limit of deviation. The hardness of the developed tablets ranges from 6.20 to 6.76 kg/cm^2 (Table

5). Hence hardness of all the tablets was within the limit and good mechanical strength. The friability of all the formulations ranges from 0.36 to 0.51 which implies that, the friability of all the tablets are within the pharmacopoeial limit i. e. less than 1%. All the formulated osmotic controlled matrix tablets were evaluated for uniformity drug content and it was found to be between 96.45 to 98.21%. All the coated tablets were evaluated for percentage weight gained and found to be within the range of 3.10 to 3.59, as shown in the Table 6.

***In- vitro* drug release**

The entire formulated osmotic controlled matrix tablets were evaluated for *in- vitro* dissolution as described in the methodology section. The optimized formulation F7 showed the best drug release of 97.71%. *In-vitro* dissolution studies showed that the formulation containing the mixture of both osmogen mannitol and lactose and drug ratio (0.5+ 0.5: 1) showed the best release of drug at the end of 12 hours.

Drug release kinetics

The data obtained from the *in-vitro* dissolution studies were fitted to mathematical model viz. Zero order, First order, Higuchi and Korsmeyer- Peppas equation as shown in Table 8. The release coefficient of the optimized formulation F7 was found to be 1.015 which indicates that the drug release follows Super Case –II Transport Release.

Stability study

The short term stability study of the optimized formulation F7 was carried out for 90 days at 40± 2° C and 75±5 % RH. The results of the stability study are given in the Table 9. There was no significant change in colour and odour, hardness, drug content and % CDR. 90 day's stability study revealed that, there was no any significant degredation of the drug and results were found to be satisfactory.

CONCLUSION

The osmotic controlled matrix tablets of Losartan potassium were prepared by direct compression technique incorporating polymer and various concentration of osmogens. The polymer (release rate retardant) was $HPMCK_{15}M$ and osmogens were mannitol and lactose. Total nine formulations were developed in which three formulations were developed using different concentration of mannitol, three formulations using different concentration of lactose and three formulations using both mannitol and lactose. The FTIR studies reveled that there was no chemical interaction of pure drug with polymers, osmogens and other excipients. The pre- compression parameters and the post- compression parameters were within the standard Pharmacopoeial limits. The formulation F7 containing drug and $HPMCK_{15}M$ ratio of 1:0.75 and combination of mannitol and lactose as osmogen showed 97.71 %of drug release with in 12 hours, so it is considered as the best formulation. All the formulations were subjected to drug release kinetics and the optimized formulation F7 followed Korsmeyer- Peppas model with Super Case- II Transport Release. The formulation F7 was selected for short term stability studies on the basis of t heir better and satisfactory evaluation study parameter. Results showed that there was not much variation in parameters even after the period of 90 days. From the results obtained, it was concluded that formulation F7 containing drug and $HPMCK_{15}M$ ratio in 1:0.75 and combination of mannitol and lactose as osmogen was found to be stable and retained the original properties during the study period.

Table 03: FT-IR Characteristic peak of pure drug (Losartan Potassium) with excipients.

SN. NO.	Functional Group	IR Range (cm^{-1})	IR Observed Peaks				
			Pure Drug (Losartan Potassium)	Drug + Micrcrystalline Cellulose	Drug + HPMCK15M	Drug + Mannitol	Drug+ Lactose
1	C–Cl	600 – 800	759.98	759.98	665.47	630.74	761.91
2	–OH	3200 – 3600	3209.66	3279.10	3414.12	3400.62	3379.4
3	C═C	1400 – 1600	1460.16	1460.16	1458.23	1421.58	1460.16
4	Ar–CH	2850 – 3000	2951.19	2945.40	2941.54	2953.12	2933.83
5	C═N	1600– 1690	1635.69	1633.76	1637.62	1631.83	1645.33

Table 4: Results of pre-compression flow properties of Granules of Losartan Potassium

SL. No.	Formulation code	Loose Bulk Density(g/ml)	Tapped Bulk Density(g/ml)	Compressibility Index(%)	Hausners's Ratio	Angle of Repose(θ)
1	F1	0.441±0.001	0.536±0.003	17.57±0.25	1.21±0.031	28.75±1.08
2	F2	0.436±0.002	0.556±0.005	21.62±0.31	1.27±0.060	27.28±1.22
3	F3	0.458±0.005	0.568±0.002	19.00±0.24	1.24±0.060	26.36±1.33
4	F4	0.440±0.010	0.562±0.003	21.70±0.22	1.27±0.018	25.93±1.37
5	F5	0.444±0.007	0.521±0.011	14.77±0.23	1.17±0.130	28.35±0.34
6	F6	0.444±0.007	0.518±0.002	14.28±0.27	1.16±0.061	27.31±1.18
7	F7	0.410±0.005	0.509±0.004	19.44±0.34	1.24±0.041	25.44±1.23
8	F8	0.388±0.003	0.468±0.061	17.09±0.09	1.20±0.051	29.40±1.15
9	F9	0.401±0.011	0.499±0.002	19.63±0.20	1.24±0.041	25.69±1.49

Table 5: Post- compression evaluation of uncoated osmotic controlled matrix tablet of Losartan potassium

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation(mg)	Drug Content (%)
F1	4.94 ±0.054	6.70±0.10	0.45	549.20±0.001	97.85±1.28
F2	5.00 ±0.070	6.06±0.15	0.36	547.28±0.002	96.89±1.12
F3	4.94 ±0.054	6.66±0.32	0.40	548.37±0.003	97.55±1.33
F4	4.94 ±0.054	6.26±0.15	0.48	548.71±0.005	97.63±1.24
F5	4.92 ±0.044	6.63±0.25	0.41	547.17±0.002	97.47±1.16
F6	4.92 ±0.044	6.33±0.05	0.37	546.91±0.002	96.97±1.29
F7	4.98± 0.044	6.20±0.10	0.36	549.42±0.002	98.87±1.36
F8	4.94 ±0.054	6.76±0.15	0.51	546.77±0.002	98.13±1.31
F9	4.96± 0.054	6.56±0.15	0.42	548.83±0.002	97.64±1.34

Table 6: Evaluation of Coated Tablets

Formulation code	Weight variation	Thickness	Percentage weight gained
F1	568.30±0.001	5.13±0.067	3.51±0.23
F2	568.20±0.002	5.10±0.061	3.59±0.08
F3	566.40±0.002	5.15±0.070	3.10±0.11
F4	566.22±0.002	5.11±0.054	3.37±0.09
F5	564.34±0.005	5.09±0.065	3.30±0.06
F6	564.50±0.003	5.11±0.054	3.58±0.39
F7	565.64±0.003	5.12±0.075	3.30±0.12
F8	563.26±0.002	5.09±0.065	3.26±0.02
F9	569.46±0.003	5.11±0.054	3.32±0.11

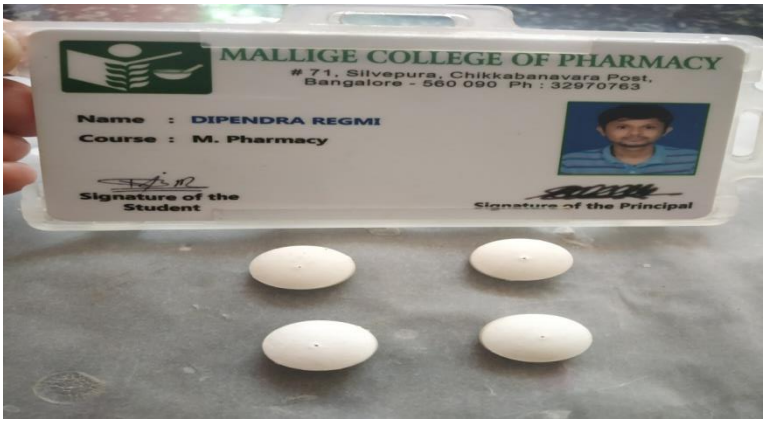

Figure 2: Formulated Coated Osmotic Matrix Tablets with Delivery Orifice

Table 7: Dissolution Data of all Formulation

Time (hrs)	Cumulative % Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
In 0.1 N HCl (Absorbance at 205 nm)									
0	0	0	0	0	0	0	0	0	0
1	7.19	7.27	8.11	6.52	7.70	7.24	8.05	7.60	8.29
2	14.58	15.31	13.84	14.67	16.01	15.31	15.70	13.95	15.41
In 6.8 p^H Phosphate Buffer(Absorbance at 225 nm)									
3	23.36	23.25	22.02	23.41	23.37	23.42	24.25	23.28	23.43
4	30.79	32.22	30.47	32.69	31.20	31.43	31.53	30.48	30.49
5	38.27	41.84	39.60	41.05	38.82	39.86	38.52	38.81	39.62
6	47.50	50.80	46.41	51.04	50.63	48.94	47.52	46.41	47.52
7	57.47	62.51	54.52	59.97	62.97	59.40	55.83	55.79	57.48
8	67.46	72.30	64.71	69.34	70.78	68.85	64.78	63.23	64.76
9	75.37	80.96	73.80	76.86	80.28	75.57	73.86	73.82	72.60
10	85.94	87.90	84.99	86.01	87.88	84.55	83.39	84.46	80.61
11	92.99	93.21	93.55	93.06	95.01	93.50	93.60	92.93	93.42
12	95.64	95.39	96.35	95.86	95.98	95.67	97.71	97.28	96.93

Table 8: Mathematical Modeling and Drug Release

Formulation Code	KINETIC MODELS					
	Zero Order	First Order	Higuchi	Korsmeyers- Peppas		Best Fit Model
	R^2	R^2	R^2	R^2	N	
F1	0.9960	0.8845	0.9715	0.9991	1.0707	Super case II Transport
F2	0.9898	0.9268	0.9792	0.9976	1.0756	Super case II Transport
F3	0.9872	0.8527	0.9492	0.9961	1.0440	Super case II Transport
F4	0.9957	0.8970	0.9824	0.9977	1.0982	Super case II Transport
F5	0.9906	0.8981	0.9730	0.9967	1.0535	Super case II Transport
F6	0.9964	0.8810	0.9768	0.9990	1.0606	Super case II Transport
F7	0.9979	0.8106	0.9786	0.9987	1.0158	Super case II Transport
F8	0.9974	0.8285	0.9663	0.9982	1.0548	Super case II Transport
F9	0.9979	0.8249	0.9690	0.9943	1.0185	Super case II Transport

R^2= Regression Constant N= Release Exponent

Table 9: Stability studies of F7 Formulation at (40±2° C/75% RH)

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)	6.2	6.2	6.1	6.1	6	6	5.9
4	Friability (%)	0.36	0.35	0.33	0.32	0.31	0.28	0.26
5	Content Uniformity (%)	98.87	98.86	98.85	98.81	98.78	98.74	98.57

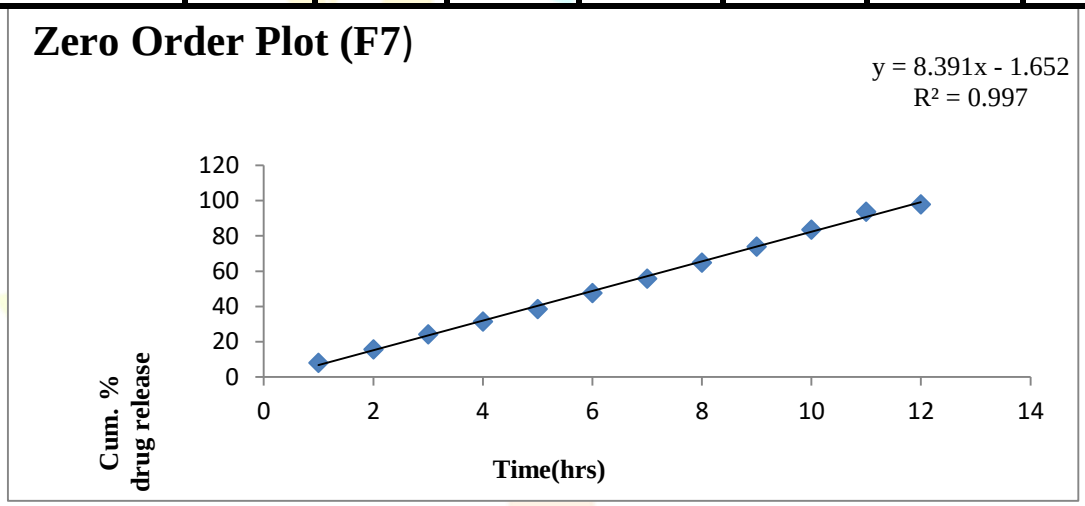

Figure 2: Zero order release kinetics formulation F7

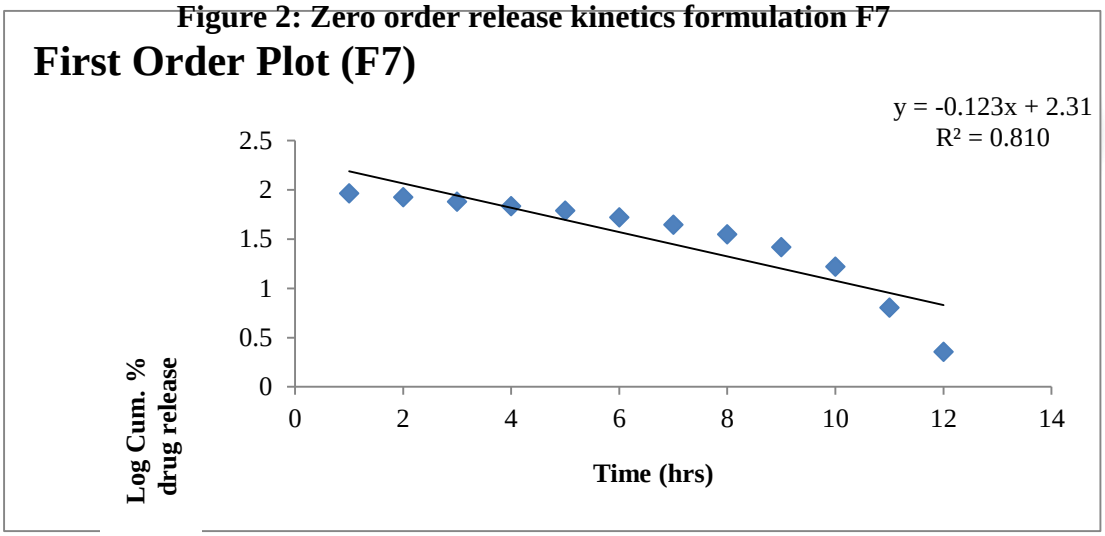

Figure 3: First order release kinetics formulation F7

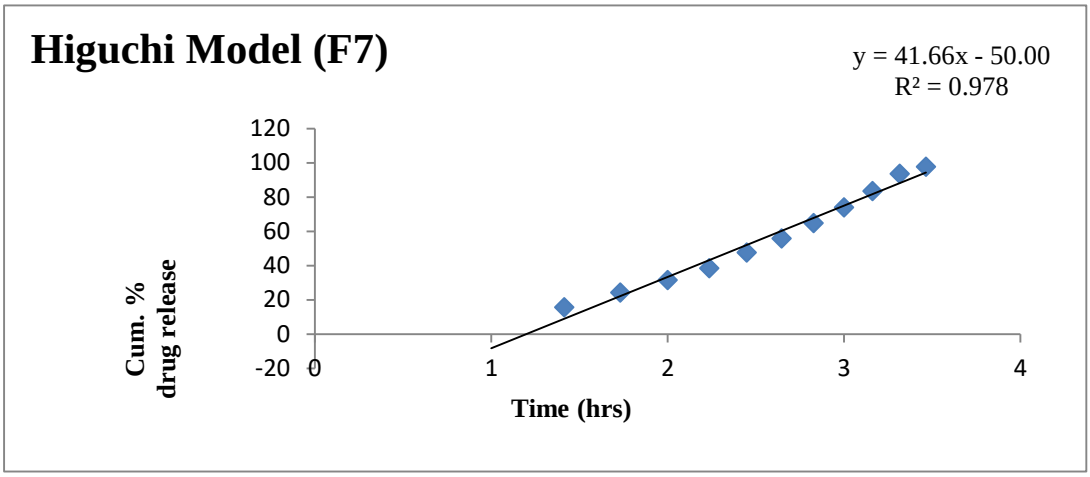

Figure 4: Higuchi release kinetics of formulation (F7)

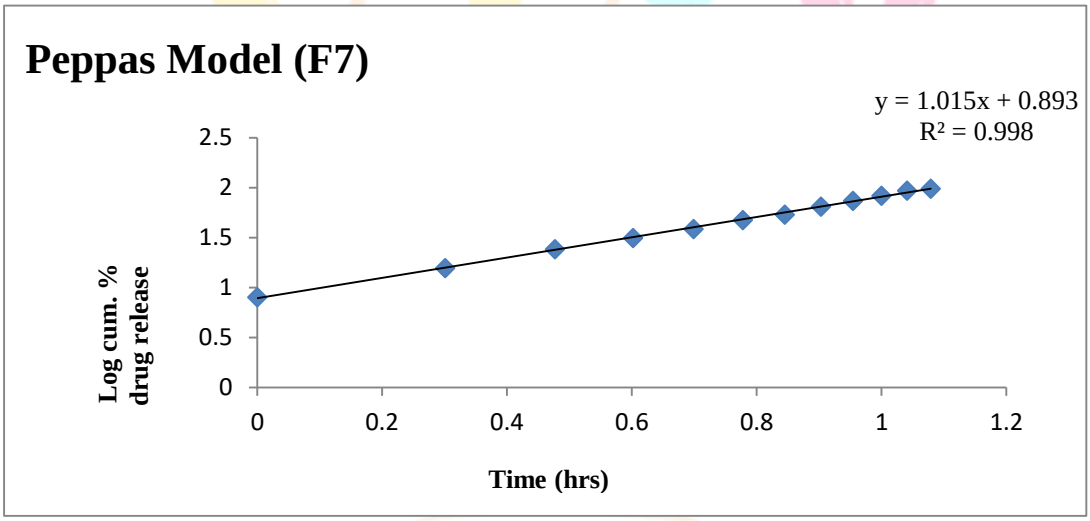

Figure 5: Korsmeyer and peppas release kinetics of formulation (F7)

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