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Formulation and Evaluation of Prulifloxacin Sustained Release Matrix Tablets

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ABSTRACT

Prulifloxacin is a chemotherapeutic antibiotic of Fluor quinolone drug used to treat a various urinary tract infections. It has short half-life, makes the sustained release (SR) forms extremely advantageous. Sustained release tablets results in increased bioavailability. The purpose of the present study was to develop a sustain release matrix drug delivery system (SR) containing Prulifloxacin as a model drug by using various proportions of polymers such as HPMC E15, HPMC K15. The sustained release formulations of Prulifloxacin were prepared by direct compression method. Optimization of formulation was done by studying effect of drug to polymer ratio on drug release. FT-IR studies indicated absence of any interaction between Prulifloxacin, polymers (HPMC E15 and HPMC K15) and excipients. Ten formulations were prepared and Formulation F8 possesses good drug release property. The tablets were also evaluated for its hardness, friability and other *In-vitro* evaluation tests. All parameters complied with IP limits. Drug release was diffusion controlled and followed Zero order kinetics. Non-Fickian diffusion was the drug release mechanism for all the tablets formulated.

Keywords: Sustained drug delivery system, Prulifloxacin, HPMCE15, HPMCK15

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INTRODUCTION

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure/treatment of the disease is achieved. Oral sustained release (SR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetics and pharmacodynamics properties of drugs in such a way that it reduce dosing frequency to an extent that once daily dose is sufficient for penetration, polymer swelling, drug dissolution, drug diffusion and Matrix erosion . The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers[1].

Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems[2].

MATERIALS:

Prulifloxacin was obtained as gift sample from DR.Reddys Laboratory, Hyderabad, other Chemicals like

Microcrystalline cellulose from SD Fine Chemicals Ltd., Mumbai, Magnesium Stearate and Talc were procured from Nice Chemicals Pvt. Ltd., Cochin, Polymers like HPMC E15, HPMC K15 were procured from S.Kant.Health Care Ltd., Gujarat and all other chemicals used for this study was analytical grade.

METHODS:

Compatibility studies

The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2 mg sample in 200 mg KBr (Bruker spectrum-100). The scanning range was 600 to 4000 cm^{-1} and the resolution was $1cm^{-1}$. This spectral analysis was employed to check the compatibility of drugs with the excipients used5.

Pre-Compression Characteristics

The pre-compression characteristics like angle of repose, bulk density, tapped density Hauser's ratio, Carr's index, Scale of Flow ability were determined and tabulated in the table no 3.

Angle of Repose:

The angle of repose of powder mix was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted to a height of 2 cm in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where h and r are the height and radius of the powder cone, θ is the angle of repose.

Angle of repose values less than 25, 25-30, 30-40, and more than 40 indicates excellent, good, passable, and poor flow properties respectively[3, 7].

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula[4, 5].

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing.

Compressibility index:

The compressibility index of the granules was determined by Carr's Compressibility index.

Carr's index (%) = [(TBD-LBD) * 100] / TBD

Where, LBD: Weight of the powder/volume of the packing.
TBD: Weight of the powder/Tapped volume of the packing.

Hausner's ratio:

Hausner's ratio can be determined by the following equation[5],

Hausner's ratio = TBD / LBD

Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

Formulation Prulifloxacin Matrix Tablets

All the formulations were prepared by direct compression method using HPMC E15, HPMC K15 polymers in various ratios and other excipients microcrystalline cellulose, Magnesium Stearate and talc are used. Prulifloxacin and all other ingredients were individually passed through sieve ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with magnesium stearate and talc.

Table 1: Formulation of Prulifloxacin Matrix Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Prulifloxacin	200	200	200	200	200	200	200	200	200
HPMC E15	100	200	300	-	-	-	150	200	100
HPMC K15	-	-	-	100	200	300	150	100	200
MCC	330	230	130	330	230	130	130	130	130
Mg stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Total weight	650	650	650	650	650	650	650	650	650

Post-Compression Characteristics

The post-compression characteristics like Weight Variation, Thickness, Hardness, and Friability were determined and tabulated in the table no 4.

Thickness and Diameter:

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm[6].

Tablet hardness:

Tablet hardness of the tablets for shipping or breakage under conditions of storage, transportation and handling depends on hardness which was determined using Monsanto hardness tester. For each formulation, the hardness of 10 tablets was determined. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/ cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2[7, 8].

Weight variation:

This is an important In-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated using the following formula. The limits are mentioned in the below table as per Indian pharmacopoeia (I.P) [9, 10].

Friability Test:

For each formulation, 6 tablets were weighed. The tablets were placed in a Friabilator (Roche Friabilator) and subjected to 100 rotations in 4 minutes at 25 rpm. The tablets were then reweighed. The friability was calculated as the percentage weight loss.[11, 12]

%Friability = (Loss in weight/Initial weight) x 100

***In vitro* drug release studies1**[3, 14]**:**

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Lab India) at a rotational speed of 50 rpm at 37±0.5°. The dissolution media used were 900 ml of 0.1 mol / l HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 22h. Sink condition was maintained for the whole experiment. Samples (10 ml) were withdrawn at regular intervals and the same volume of pre-warmed (37±0.5°) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 276nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve and results obtained were tabulated in table no 5 .

RESULTS AND DISCUSSION

Table 2: Calibration curve for Estimation of Prulifloxacin

S.NO	Concentration(µg/ml)	Absorbance	
		0.1 N HCl	6.8pH
1	0	0	0
2	5	0.134	0.127
3	10	0.261	0.245
4	15	0.382	0.388
5	20	0.512	0.523
6	25	0.628	0.641

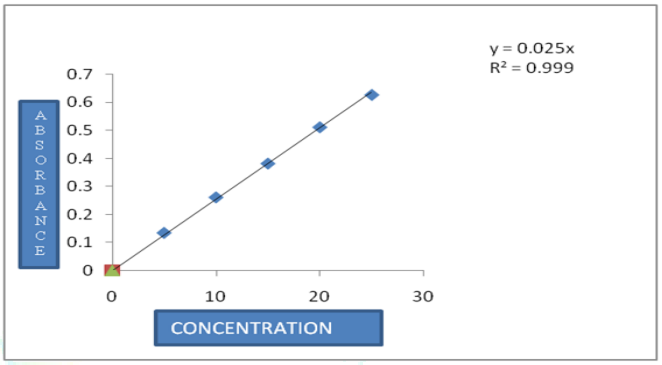

Fig no 1: Calibration curve of Prulifloxacin in 0.1 N HCl

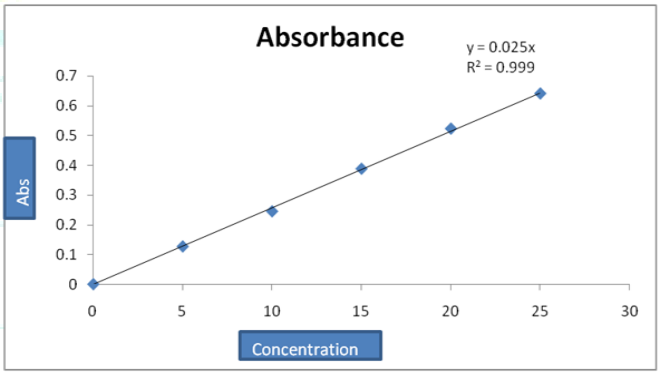

Figure.no:2 Calibration curve of Prulifloxacin in 6.8pH

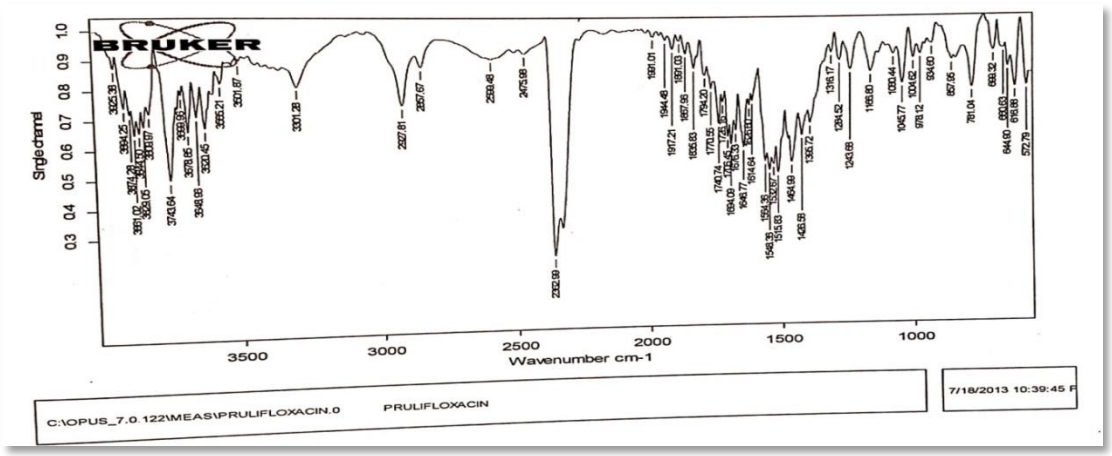

Figure.no:3 FTIR of Prulifloxacin

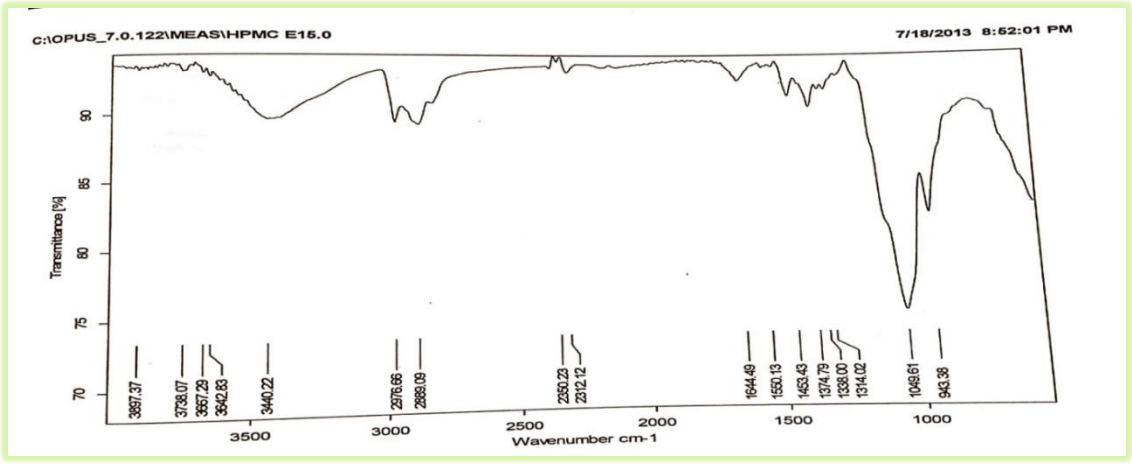

Figure.no 4: FTIR of HPMC E15

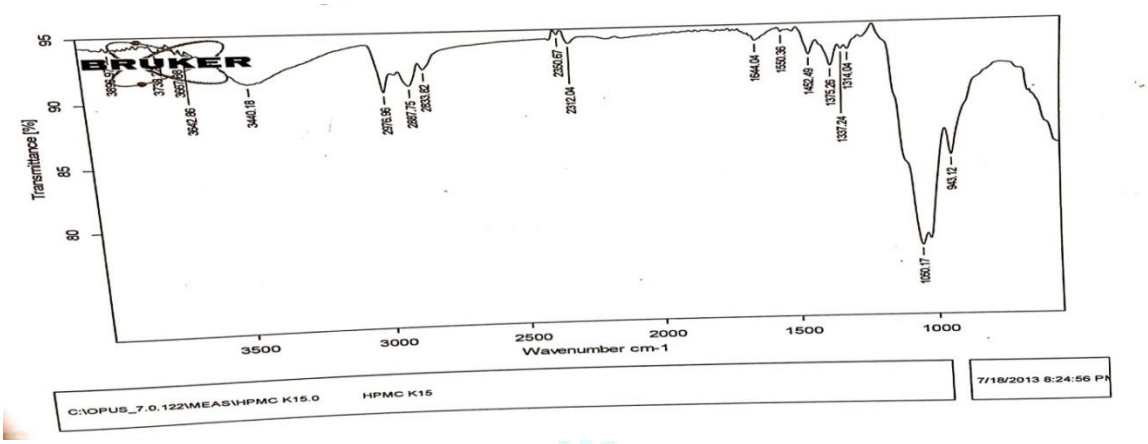

Figure.no 5: FTIR of HPMC K15

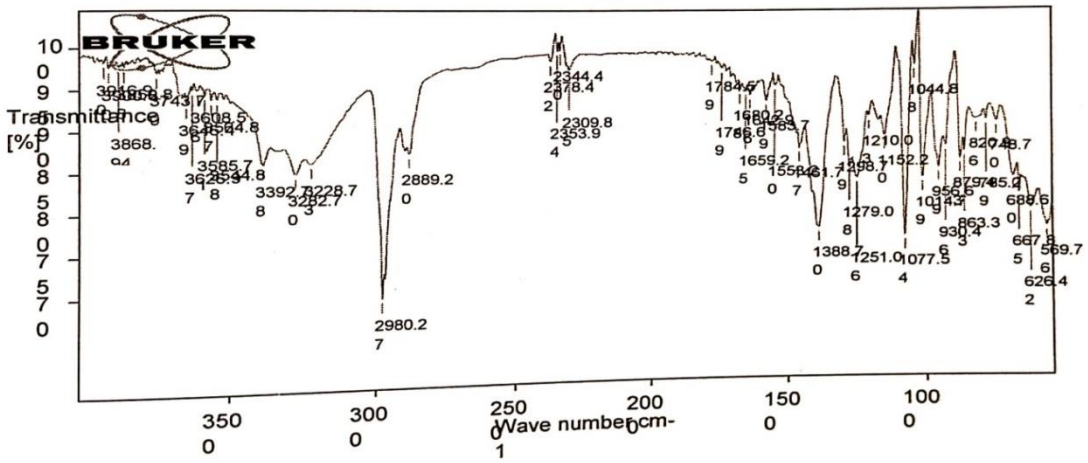

Figure.no 6: FTIR of Best Formulation

Table 3: Physical properties of blend

F.CODE	Angle of Repose± SD*	Bulk Density (g/ml) ±SD*	Tapped Density (g/ml) ±SD*	Carr's Index (%)±SD*	Hausner's Ratio ±SD*
F1	26.25±0.23	0.488±0.0202	0.5091±0.0252	8.61±1.9083	1.0416±0.0088
F2	27.96±0.15	0.5055±0.0055	0.5170±0.012	8.222±0.2266	1.02227±0.0052
F3	26.65±0.34	0.4859±0.0069	0.5329±0.0051	8.8235±0.3054	1.0967±0.0321
F4	28.93±0.12	0.3463±0.068	0.3810±0.0093	9.0909±0.1994	1.1000±0.004
F5	27.36±0.15	0.3127±0.056	0.3528±0.0009	9.3636±0.6143	1.1082±0.0481
F6	29.45±0.64	0.4650±0.0019	0.5093±0.001	8.6956±0.1499	1.0952±0.1191
F7	27.54±0.15	0.5161±0.0050	0.5704±0.0014	9.6774±0.4180	1.1071±0.021
F8	28.62±0.17	0.5000±0.0007	0.5577±0.0008	9.5750±0.3041	1.1034±0.0071
F9	28.74±0.25	0.4706±0.0031	0.5333±0.0017	8.7647±0.9171	1.0933±0.0025

*n = 3

Table 4: Evaluation of post compression parameters

Trial	Weight variation ±SD***	Thickness (mm) ±SD**	Hardness (Kg/cm^2) ±SD*	Friability (%w/w) ±SD**
F1	649±1.422	5.81±0.049	8±0.331	0.32±0.02
F2	659±2.772	5.84±0.036	8.5±0.338	0.44±0.01
F3	650±1.631	6.68±0.033	9±0.378	0.37±0.05
F4	658±1.744	6.04±0.029	9±0.318	0.49±0.03
F5	657±1.713	5.9±0.027	11±0.347	0.51±0.01
F6	654±1.313	6.01±0.025	8.5±0.314	0.53±0.05
F7	659±1.080	5.9±0.027	9.5±0.313	0.54±0.03
F8	651±1.005	6.1±0.032	10.5±0.383	0.52±0.02
F9	649±1.426	5.8±0.028	9.5±0.357	0.47±0.05

*n=6 **n=10 ***n=20

Table 5: *In vitro* Drug Release Studies for different Trials Formulations

Time (hrs.)	% Cumulative Drug Released ±SD*								
	F 1	F2	F3	F4	F5	F6	F7	F8	F9
1	27.13± 0.4676	23.03± 0.1869	18.083± 0.1329	12.08± 0.343	9.1166± 0.1834	83± 0.4195	10.1± 0.2756	9± 0.1897	10.12± 0.2316
2	41.96± 0.4956	34.03± 0.1861	27.06± 0.1966	23.083± 0.2994	18.13± 0.2338	16.2± 0.3326	29± 0.1897	23.98± 0.3311	23.06± 0.2804
4	55.966± 0.1966	47.01± 0.1940	38.95± 0.4086	34.1± 0.5176	26.95± 0.3563	25± 0.2366	36.1± 0.3033	32.15± 0.3728	30.08± 0.3125
6	69.2± 0.129	58.06± 0.1972	46.56± 1.284	42.03± 0.464	36.58± 1.099	32.1± 0.2581	49.13± 0.3771	38.91± 0.384	48.16± 0.4109
8	80.96± 0.1940	64.16± 0.1505	56.85± 0.4636	54.11± 0.3544	45.1± 0.2683	38.86± 0.4273	53.13± 0.388	45.05± 1.952	55.16± 0.366
10		82± 0.1095	68.13± 0.2065	69.18± 0.4622	57.2± 0.2607	54.18± 0.2401	68.98± 0.2786	57.06± 0.3204	61.1± 0.2828
12			78.98± 0.2786	77.06± 0.2804	68.95± 0.4549	62.95± 0.5890	75.15± 0.3146	64.15± 0.3016	76.08± 0.134
16			98.08± 0.240	86.133± 0.388	80.56± 15.75	74.11± 0.285	83.23± 0.2338	79.21± 0.2857	82.21± 0.2857
20				90.2± 0.259		86.16± 0.4033	97.03± 0.233	86.05± 0.288	87.56± 0.4844
24				94.133± 0.163		92± 0.2756		99.08± 0.183	93.23± 0.1966

*n=6

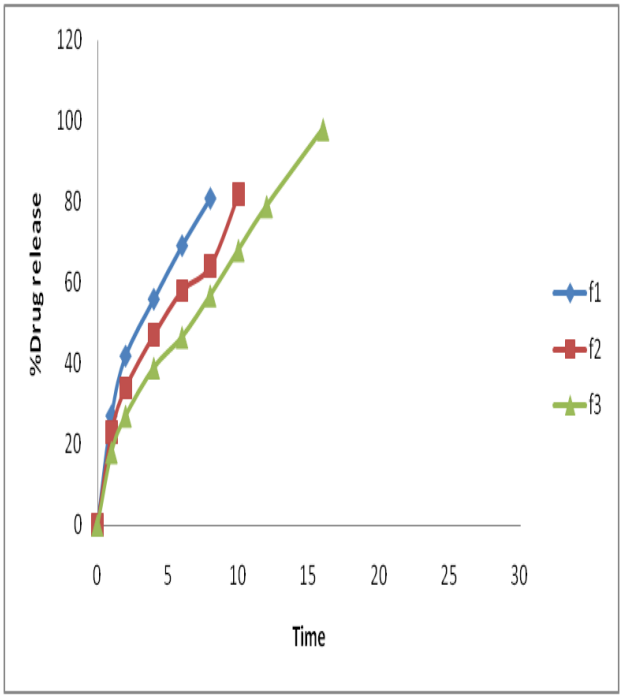

Fig No.7: *In vitro Drug Release Studies for* F1, F2, F3

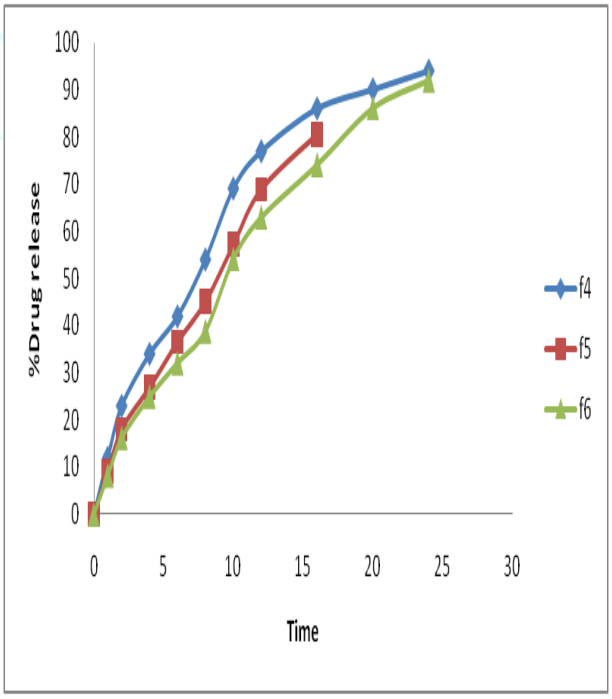

Fig 8: *In vitro* Drug Release Studies for F4, F5 and F6

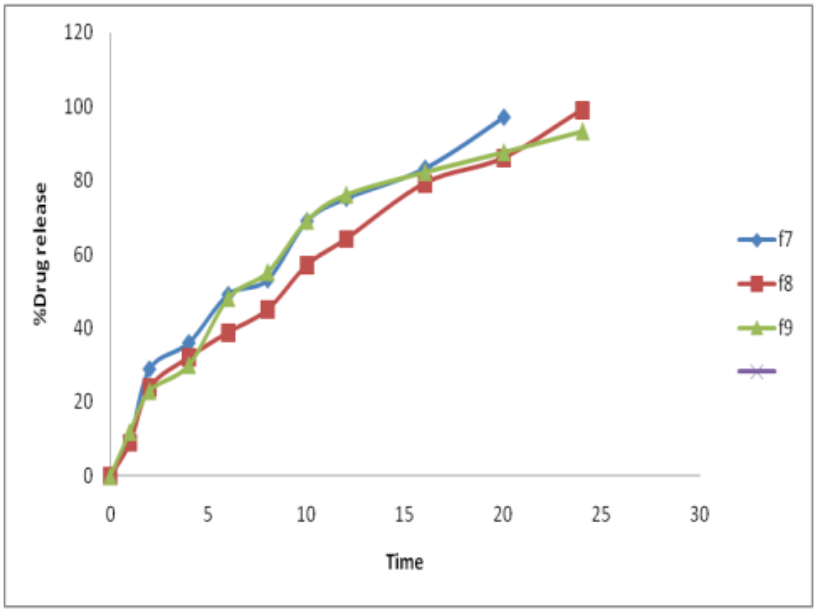

Fig 9: *In vitro* Drug Release Studies for F7, F8 andF9 Formulations

Zero Order Plots

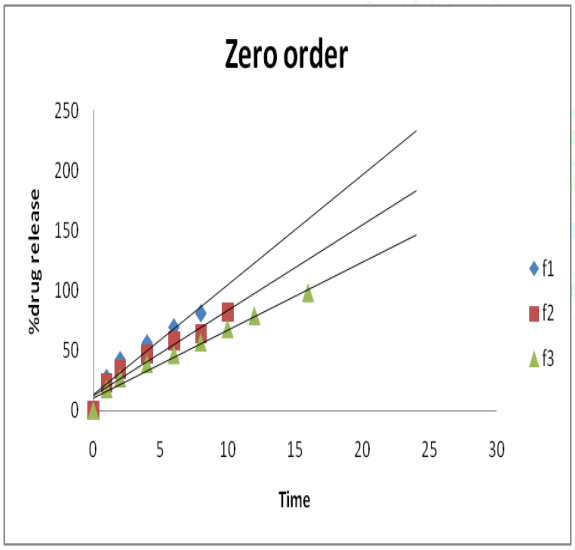

Fig 10: Zero order plots of F1-F3

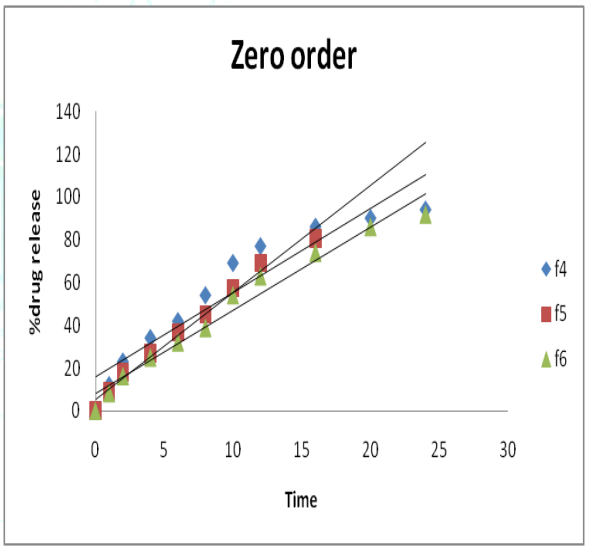

Fig 11: Zero order plots of F4-F6

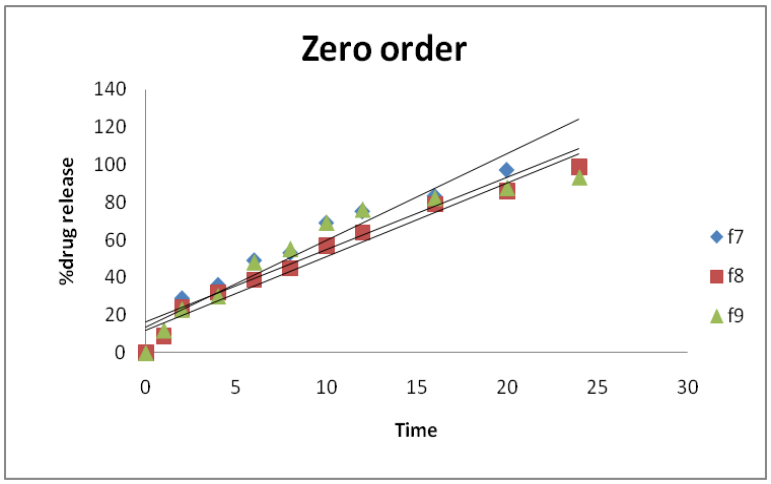

Fig 12: Zero order plots of formulations F7-F9

First Order Plots

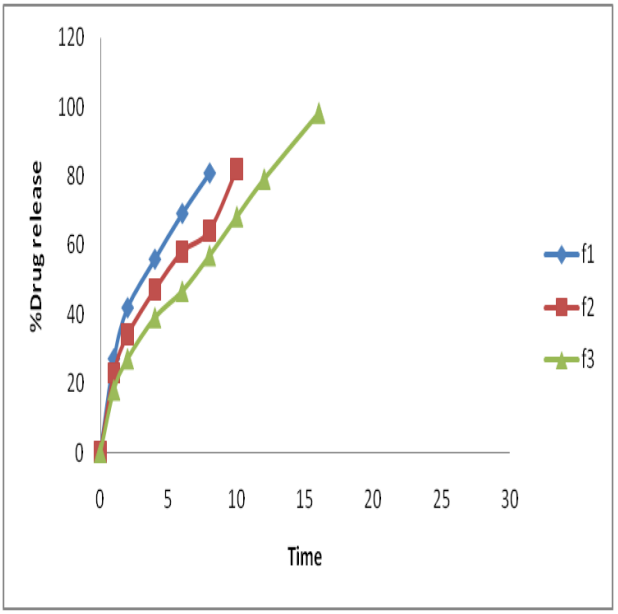

Fig 13: First order plots of F1-F3

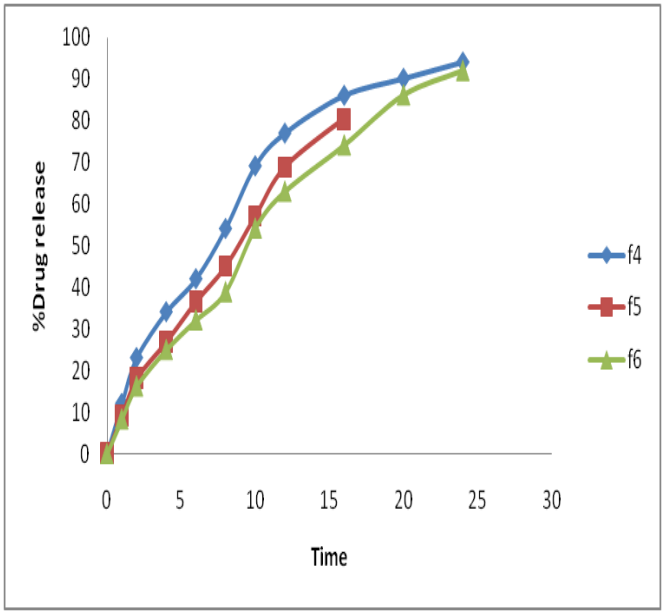

Fig 14: First order plots of F4-F6

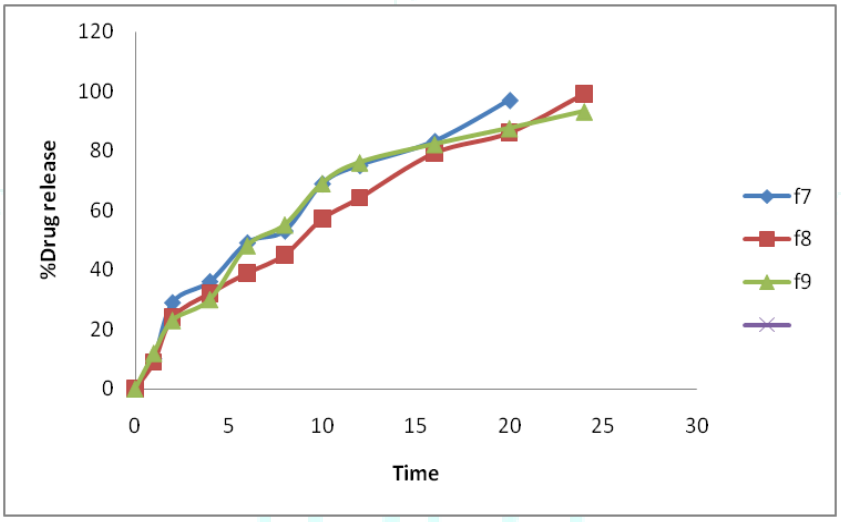

Fig 15: First order plots of formulations F7-F9

Hixso- Crowell Plots

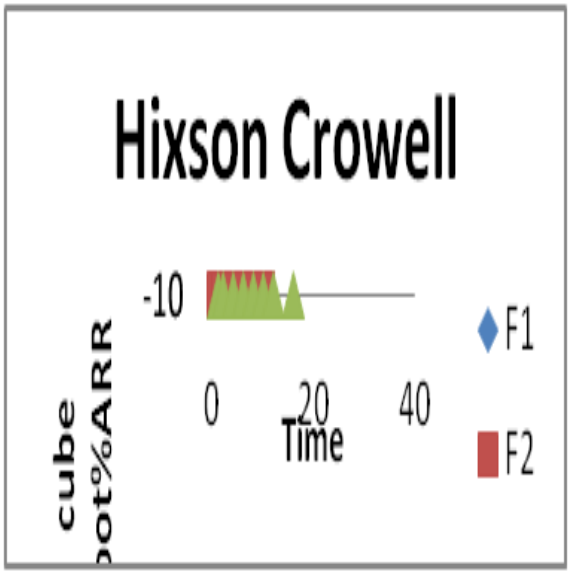

Fig 16: Hixson Crowell plots of F1-F3

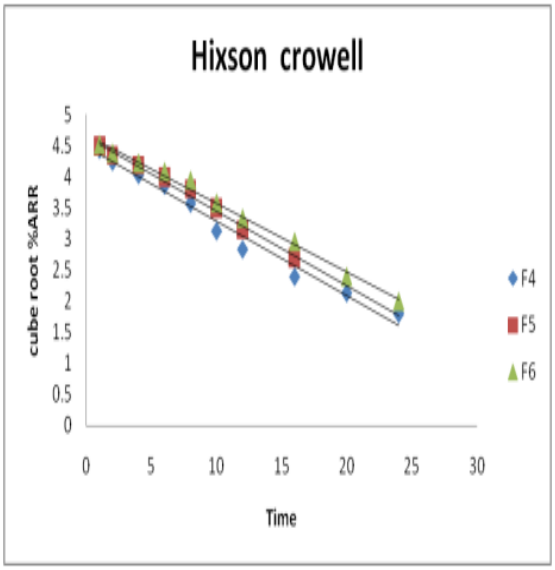

Fig17: Hixson Crowell plots of F4-F6

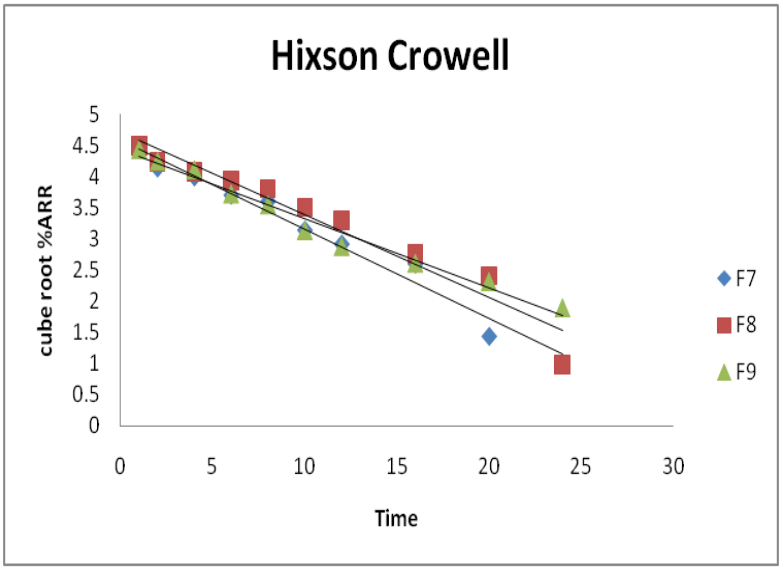

Fig 18: Hixson Crowell plots of formulations F7-F9

Higuchi Plots

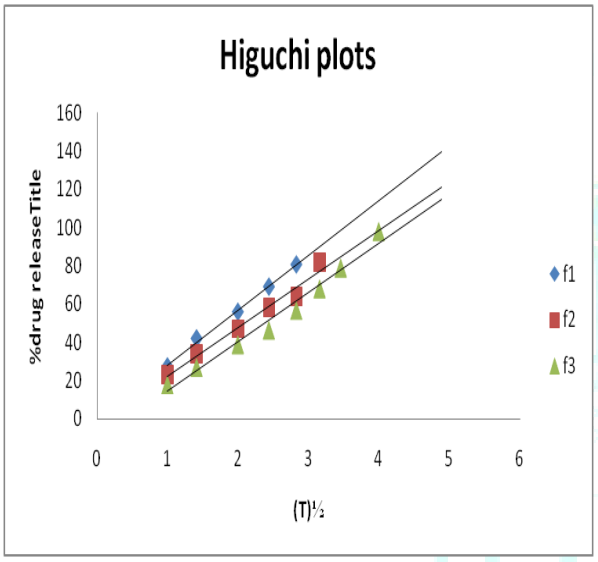

Fig19: Higuchi plots of F1-F4

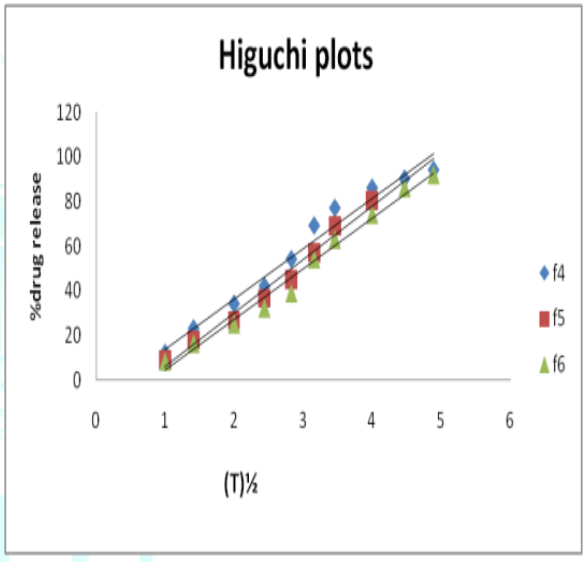

Fig 20: Higuchi plots of F4-F6

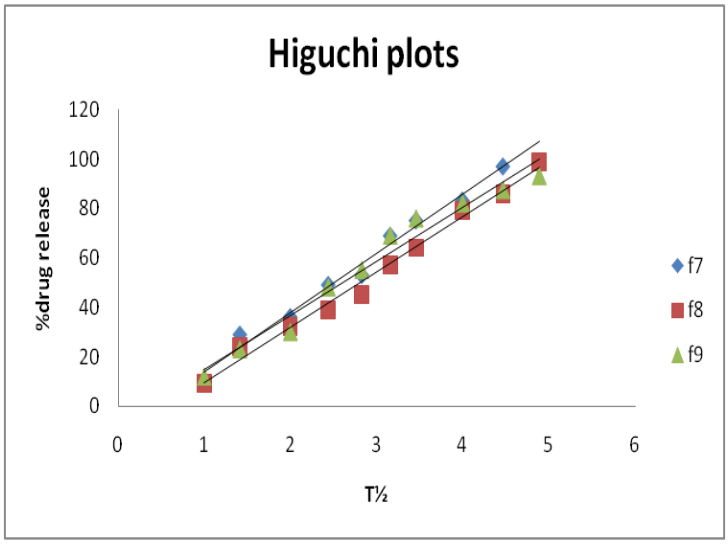

Fig 21: Higuchi plots of F7-F9

Korsmeyer Peppas Plots

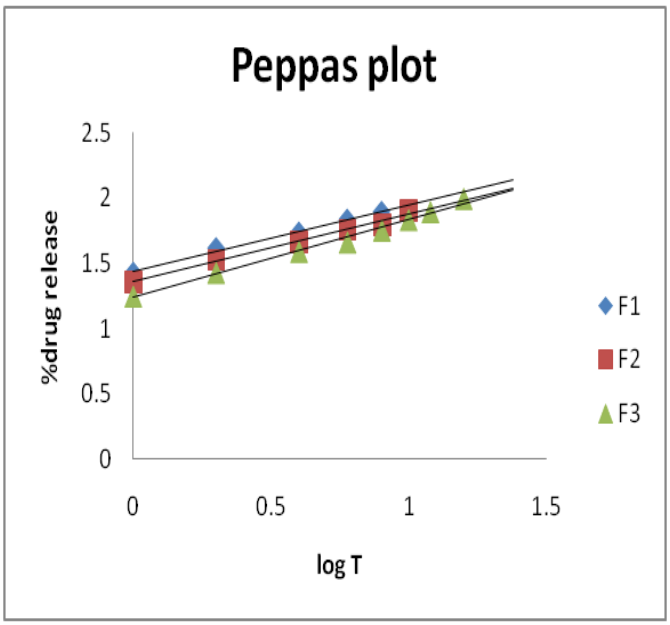

Fig22: Korsmeyer Peppas plots of F1-F3

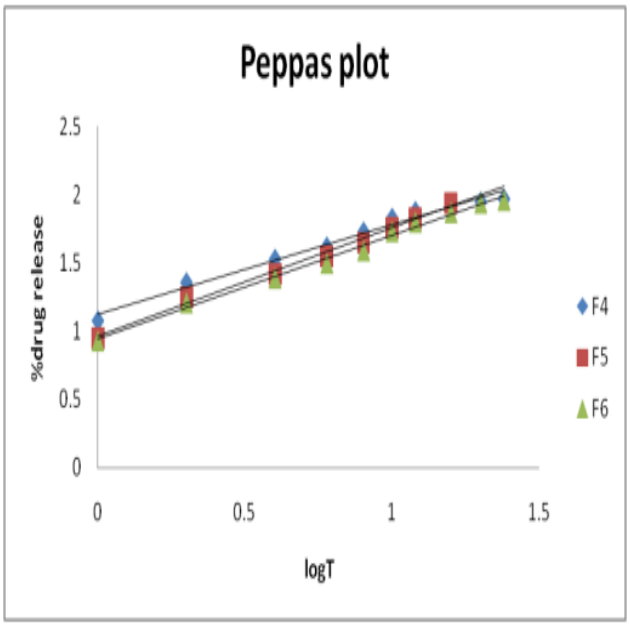

Fig 23: Korsmeyer Peppas plots of F4-F6

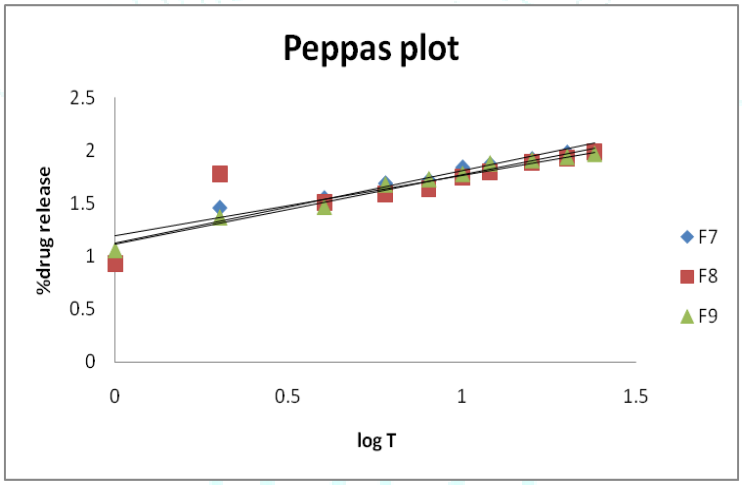

Fig 24: Korsmeyer Peppas plots of formulations F7-F9

Table 6: Release Kinetics Studies for different strengths of final optimized formulation

Formulation Code	R^2 Values				n values
	Zero order	First order	Hixson Crowell	Higuchi	Peppas
F1	0.914	0.079	0.995	0.997	0.509
F2	0.934	0.146	0.961	0.979	0.517
F3	0.975	0.053	0.916	0.978	0.595
F4	0.899	0.088	0.98	0.972	0.582
F5	0.986	0.002	0.989	0.98	0.794
F6	0.969	0.04	0.993	0.984	0.758
F7	0.934	0.073	0.966	0.985	0.691
F8	0.961	0.155	0.942	0.989	0.573
F9	0.888	0.061	0.978	0.97	0.655

DISCUSSION OF RESULTS:

In the present study first characterization of API was done followed by its compatibility studies with various excipients and API was found to be compatible with all the excipients. Then various Pre-compression parameters like bulk density, tapped density, Hausner's ratio, Carr's consolidation index and angle of repose were determined and found to be within the limits and post compression parameters like weight variation, hardness, friability were determined and found to be within limits and I*n-vitro* dissolution of all the formulations were analyzed and Among all the nine formulations F8 shown maximum drug release of 99.08% after 24 hours and all the data were fitted into various kinetic models like Zero order, First order, *Hixson Crowell, Higuchi, Korsmeyer peppas* and based on the results obtained

from these studies the release was found diffusion controlled and followed Zero order kinetics.

CONCLUSION

So in this present work an attempt is made to formulate sustained release matrix tablet which shown prolonged drug release for 24 hours. Prior to the development of dosage form, all the fundamental Pre-formulation and Post-formulation Parameters of drug molecule are evaluated and the results were found satisfactory. The formulation was characterized for various properties of the dosage forms like assay, dissolution and other physical properties. Drug release was extended up to 24 hours with diffusion controlled and followed Zero order kinetics. Further the scope of the work need to be extended to carry out stability studies.

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