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RESEARCH ARTICLE

Formulation & evaluation of Ofloxacin sustained release matrix tablet

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ABSTRACT

The present study aimed to formulate and evaluate sustained release matrix tablets of Ofloxacin to achieve sustained drug release. Sustained release matrix tablets of Ofloxacin were prepared by wet granulation method using HPMC K4M as polymer, Avicel PH 102 (MCC) as filler and starch as binder. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity. It was found that the results comply with official standards. The *in vitro* release was studied using pH 1.2 acidic buffer and pH 6.8 phosphate buffer. The *in vitro* release study revealed that the prepared tablets were able to sustain the drug release. The release kinetics studies showed that the release was diffusion controlled and the n values obtained from the Korsmeyer-Peppas model showed that the release mechanism was non-Fickian type. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at 40°C (RH = 75%) for a period of 3 months.

Key words: HPMC K4M, Avicel PH 102 (MCC), Ofloxacin, *In vitro* drug release.

INTRODUCTION:

Fluoroquinolones are one of the most widely used categories of antimicrobial agents. The first fluoroquinolone, nalidixic acid, was introduced in 1962[(1)]. Since then, many quinolones are introduced for treating various gram positive and gram negative infections [(2)]. Ofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class considered to be a second-generation fluoroquinolone. It is a broad-spectrum antibiotic that is active against both Gram-positive and Gram negative bacteria [(3-4)]. Following oral administration, the bioavailability of Ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved one to two hours after an oral dose. It was also found to show linear and predictable pharmacokinetics after single and multiple doses. Approximately 32% of the drug in plasma is protein bound [(5)].

Designing a sustained release formulation for the drug Ofloxacin may prolong therapeutic concentration of drug in the blood and decrease the frequency of dosing and also improve the efficacy of drug and patient compliance. Hence, an attempt was made to formulate sustained release matrix tablets for the broad spectrum antibacterial agent Ofloxacin.

Hydrophilic polymer used for the present study was HPMC K4M. HPMC is most widely used hydrophilic polymer because of its easy availability & low toxicity. HPMC in water forms a viscous colloidal solution and act as a rate controlling polymer. The matrix tablets formulated by using HPMC can easily cross along the GIT and release active ingredient for prolong period of time [(6)]. In this study HPMC was used as a hydrophilic release retarding polymer in different concentrations (F-1=0%, F-2=10%, F-3=20%, F-4=30%) and the Avicel PH 102 (MCC) as filler and starch paste (10%) as binding agent.

Thus the objective of the present research work was to study the effect of HPMC K4M in different drug polymer ratio to sustain the release of Ofloxacin from the formulated matrix tablets.

MATERIALS & METHODS: Ofloxacin was obtained as a gift sample from Loba, Pharmaceuticals and Chemicals Ltd, Mumbai. Hydroxy propyl methyl cellulose (k4M). Hydrochloric acid was obtained as a gift sample from S.D. Fine chem. Ltd., Bombay. Talc and Magnesium stearate was obtained as a gift sample from Arvind Laboratories,

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Chennai. All other excipients and solvent used are of analytical grade.

MATERIALS:

Formulation of Ofloxacin tablets:

The different formulations for Ofloxacin SR matrix tablet were made as per table no.1.

Preparation of Ofloxacin granules:

Ofloxacin granules were prepared by wet granulation method [7]. Specified quantity of Ofloxacin, HPMC K4M, MCC (Avicel PH 102) were weighed and transferred in a mortar and pestle and mixed thoroughly. The composition of different batches for the preparation of the tablets using different binders with a fixed amount of the drug is shown in Table 1.

Characterization of Ofloxacin granules.

The different Pre-compression parameters such as angle of repose [8], bulk density [9], tapped density [10], Carr's index etc. were studied to check the flow ability & compressibility of the powered granules.

Preparation of tablets:

After characterization, the granules were added with the desired amount of Magnesium stearate & Talc and mixed thoroughly. Then the mixture was directly punched by single tablet punching machine. The different batches of Ofloxacin SR matrix tablets were collected and stored in air tight & light resistant containers.

Evaluation of Ofloxacin SR matrix tablet:

Different quality control tests such as Hardness test [11], Friability [12], Weight variation [11] & Drug content [13] etc. for Ofloxacin SR matrix tablet were performed.

***In vitro* dissolution Studies:**

The *In vitro* dissolution studies were carried out for the formulations using USP apparatus [14] type II (Paddle). The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 hours and phosphate buffer of pH 6.8 for 12 hours. The temperature was maintained at 37°C ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 294 nm against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time.

***In vitro* Release Kinetics:**

The rate & mechanism of release of Ofloxacin from the prepared SR matrix tablets were analyzed by the dissolution data into the Zero-order equation.

Zero order equation:

$Q = Q_0 – K_0 t$

Higuchi equation:

$Q = K_2 t^{1/2}$

Korsmeyer - Peppas equation:

$Q/Q_0 = K\ t^n$

Where, K_0 to K_2 were release rate constants, Q/Q_0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), $n \leq 0.5$; for non-Fickian (anomalous/ zero order) release, 'n' value is in between 0.5 to 1.0; for zero order release, n=1.0; for super case transport II, $n > 1.040$.

Stability studies:

A study was carried out to assess the stability of the Ofloxacin tablet (F-3). Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies were adopted. The tablets were packed in High Density Polyethylene (HDPE) container. Stability studies were carried out at 40°C (RH =75%) over a period of 3 months. Samples were evaluated at 0, 1, 2 and 3 months for different parameters such as physical appearance, hardness, weight variation, drug content and dissolution.

RESULTS & DISCUSSION:

Pre compression parameters

The obtained granules were smooth and almost uniform sized. Results of bulk densities (0.45 to 0.49 gm/ml), Tapped densities (0.49 – 0.55 gm/ml), compressibility index (12.11 to 15.81) and the angle of repose (23.7 to 26.3) shows satisfactory results, signifies good flow property of the granules for all the formulations. The details of the Pre-compression parameters were given in the table 2.

Post compression parameters

In each batch, it was concluded that the tablets of all batches had desirable physical characteristics. Results of drug content of various batches of prepared formulations (185.6-198.6), Hardness (6.3 –6.5 kg / sq cm.) and Friability (0.079 – 0.25 %) indicates that the tablets having sufficient strength to withstand physical abrasion. Tablets of all batches pass the weight variation test and uniformity in content was as per the limits prescribed in IP shown in post compression parameters. The details of Post-compression parameters of Ofloxacin SR tablets were given in table 3.

***In vitro* drug release studies:**

Comparative dissolution profile of Ofloxacin SR matrix tablets of each batch for Zero-order release kinetics was shown in Fig 1. It was cleared from the figures that the polymer HPMC retarded the release of drug from the tablets depend on the drug polymer ratio. Among the formulations, Formulation-3 had showed maximum sustained release. The release pattern of Formulation-3

was compared with that of marketed product (Zanocin). Dissolution profiles of Ofloxacin SR tablets of Marketed Product (Zanocin) & Formulation-3 for Zero-order kinetics were shown individually in Fig 2 & Fig 3 respectively. Similarly the dissolution profiles of Ofloxacin SR tablets of Marketed Product (Zanocin) & Formulation-3 for Higuchi model & Peppas model were shown individually in Fig 4, Fig 5, Fig 6 & Fig 7 as well as the data were given in the table 4, 5, 6 & 7 respectively. The regression coefficients for Zero-order, Higuchi & Peppas model of both Marketed Product (Zanocin) and Formulation-3 were given in the table 8. The cumulative percentage releases of Ofloxacin from the tablets were varied from to 86.42 to 100.2 depends upon the drug polymer ratio for 12 hours. The Formulation-1 was not shown any sustained release. This can be explained by the fact that the Formulation-1 was prepared by omitting the release retarding polymer HPMC. It is cleared from the figures that the polymer HPMC retarded the release of drug from the tablets depend on the drug polymer ratio. Among the formulations, Formulation-3 had showed maximum sustained release. This indicates that the combination of drug, polymer and other excipients probably ideal in Formulation-3. It was observed that the release pattern of Formulation-3 was better as compared to other formulations and comparable with that of marketed product.

Release kinetics:

The *In vitro* release data obtained from Formulations-3 was fitted to kinetic models. In case of zero order ($Q = Q_0 - K_0t$) the graph was plotted in cumulative percent of drug released Vs time, for Higuchi model kinetics ($Q = K_2 t^{1/2}$) the graph was plotted in cumulative percent of drug released Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = K t^n$) the graph was plotted in log cumulative percent of drug released Vs log time. The release of Ofloxacin from the tablets was diffusion controlled as indicated by higher r^2 values in Higuchi model. The n values (n =0.670) obtained from the Korsmeyer-Peppas model showed that the fabricated tablets followed by non-Fickian diffusion mechanism, which indicates the drug release through diffusion followed by polymer relaxation.

Stability studies:

The table no.9 shows the stability studies results of prepared tablet formulation (F-3) was no significant changes in their physical appearance, hardness, weight variation and drug release profile. It was observed that the initial drug content and the drug contents of the samples analyzed after 1, 2 and 3 months of storage were similar. The release profile also not showed any significant changes indicating that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed tablets were stable and retain their pharmaceutical properties over a period of 3 months. The data regarding different parameters after stability study were given in table 9.

CONCLUSSION:

From the present study it was found that SR matrix tablet of Ofloxacin prepared with polymer HPMC K4M can sustain the release for 12hrs. The effect of polymer concentration was also studied by using four different drug polymer ratios. It was found that that the physicochemical parameters of the prepared tablets as well as the marketed tablets (Zanocin) were comply with the standards. The *In vitro* release data of the selected formulation was fitted to kinetic models. The release of Ofloxacin from the tablets was diffusion controlled and the release mechanism was non-Fickian.

A stability study was carried out to assess the stability of the selected Ofloxacin tablets at 40°C (RH = 75%) over a period of 3 months. The results revealed that the developed tablets were stable and retain their pharmaceutical properties over a period of 3 months.

The best batch was selected from the formulations based on their physicochemical and release characteristics. Formulation-3 was selected as the best batch and subjected to further studies like release kinetics, stability studies.

Table 1: Formulation for Ofloxacin SR Matrix Tablet

Ingredient	F1	F2	F3	F4
Ofloxacin (mg)	200	200	200	200
HPMC K4M (mg)	0	50	100	150
Avicel PH 102 (MCC) (mg)	285	235	185	135
Starch paste 10%	Qs	Qs	Qs	Qs
Talc (mg)	10	10	10	10
Megnesium stearate (mg)	5	5	5	5

Table 2: Pre-compression parameters of Ofloxacin Granules

Parameters	F1	F2	F3	F4
Angle of Repose(degree)	24.5	26.3	23.7	25.3
Bulk density(gm/ml)	0.45	0.45	0.49	0.46
Tapped density(gm/ml)	0.52	0.51	0.55	0.49
Carr's Index (%)	12.11	12.35	15.81	13.42

Table 3: Post compression parameter

Parameter	F1	F2	F3	F4
Avg. Wt.(mg)	501.29	503.87	499.87	496.12
Drug content(mg)	195.0	198.6	193.3	185.6
Hardness(kg/cm^2)	6.3	6.4	6.3	6.5
Friability (%)	0.25	0.17	0.099	0.079

Table 4: Data for Higuchi Model of Marketed Product (Zanocin)

SQRT	%CDR
0	0
0.707	8.02
1.00	15.16
1.414	29.13
2.00	45.44
2.449	58.86
3.16	73.67
3.464	78.05

Table 5: Data for Higuchi Model of Ofloxacin SR tablet of Formulation-3

SQRT	%CDR
0	0
0.707	9.05
1.00	18.17
1.414	35.71
2.00	50.42
2.449	63.92
3.16	80.67
3.464	86.42

Table 6: Data for Peppas Model of Marketed Product (Zanocin)

Log T	Log% CDR
-0.3010	0.9041
0	1.180
0.3010	1.464
0.6020	1.657
0.7781	1.769
1.00	1.867
1.0791	1.892

Table 7: Data for Peppas Model of Ofloxacin SR tablet of Formulation-3

Log T	Log %CDR
-0.3010	0.9566
0	1.2593
0.3010	1.552
0.6020	1.702
0.7781	1.805
1.00	1.906
1.0791	1.936

Table 8: Regression coefficient values (r^2)

Formulations	Zero Order	Higuchi	Pepaas
F3	0.922	0.988	0.971
MP	0.928	0.986	0.980

Table 9: Stability studies of the Formulation-3 stored at 40°C (RH=75%)

Parameters	0 month	1 month	2 month	3 month
Physical Appearance	Whitish Yellow	No change	No change	No change
Average Wt.(gm)	0.499	0.503	0.501	0.499
Hardness(kg/cm^3)	6.3	6.5	6.2	6.4
Drug Content(mg)	193.3	192.5	192.76	191.42
%CDR	86.42	85.79	84.98	82.70

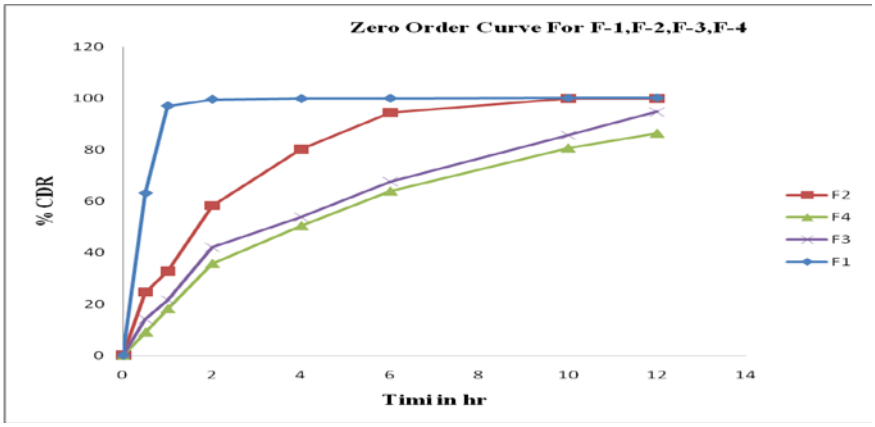

Figure 1: Zero Order release kinetics of SR Formulations, F-1, F-2, F-3 & F-4

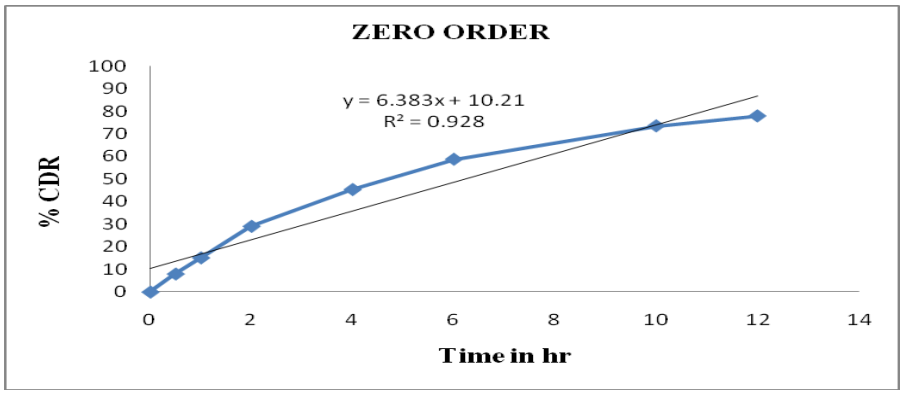

Figure 2: Zero Order release kinetics of Marketed Product (Zanocin)

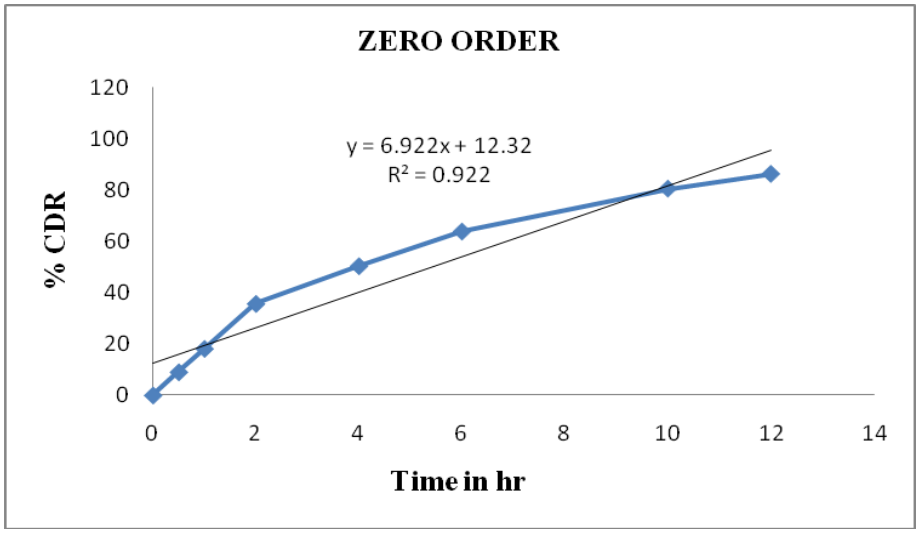

Figure 3: Zero Order release kinetics of SR Ofloxacin Formulation-3

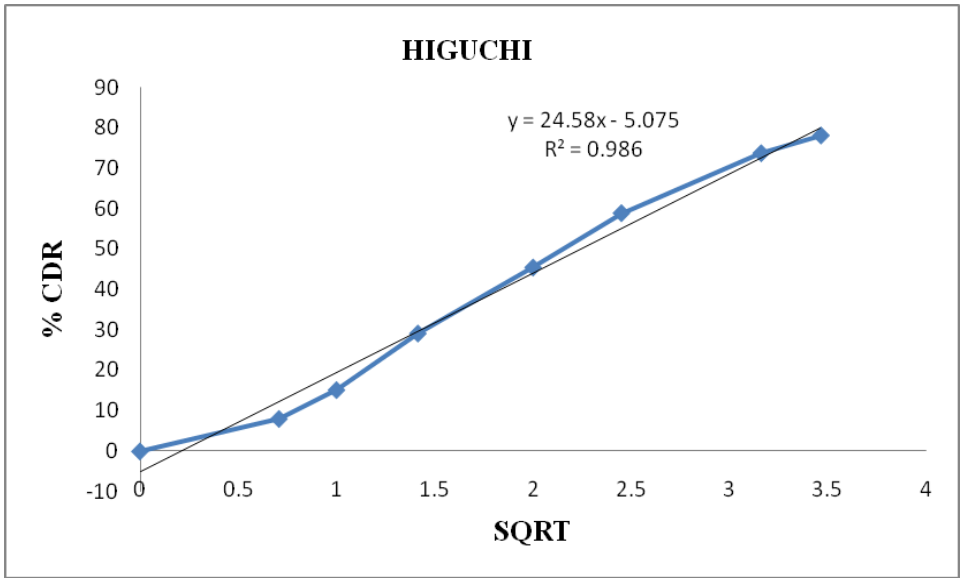

Figure 4: Higuchi model for Marketed Product (Zanocin)

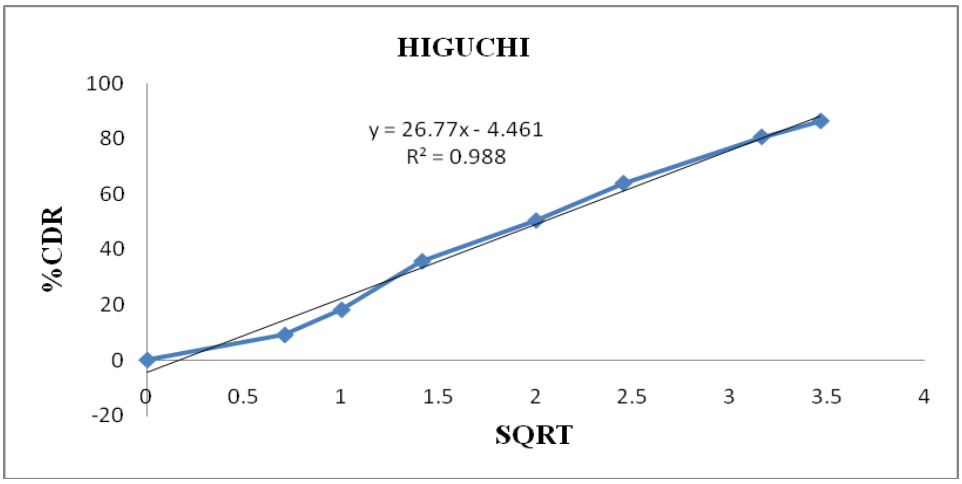

Figure 5: Higuchi model for SR Ofloxacin Formulation-3

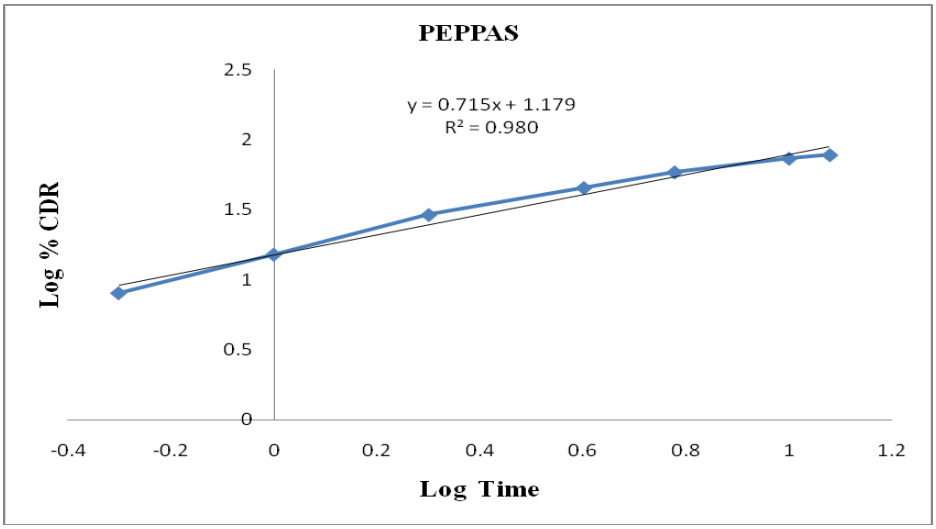

Figure 6: Peppas model for Marketed Product (Zanocin)

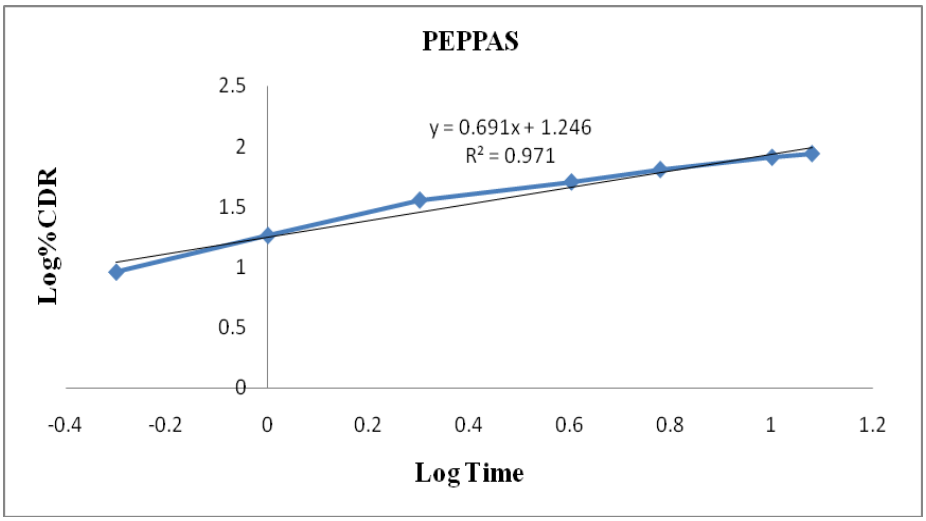

Figure 7: Peppas model for SR Ofloxacin Formulation-3

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