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FORMULATION AND IN VITRO EVALUATION OF GASTRO RETENTIVE NON EFFERVESCENT TABLETS OF BALOFLOXACIN

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ABSTRACT

The purpose of present investigation was to develop and evaluate gastroretentive drug delivery system of fluoroquinolone antibiotics (Balofloxacin). These floating tablets were prepared with the objective to obtain site-specific drug delivery and to extend its duration of action. More over the non effervescent system of balofloxacin will provide increased local and systemic action in stomach. Floating non-effervescent tablets were formulated by various materials like hydroxypropyl methylcellulose HPMC (K 15M, E50), Xanthum gum, Guar gum, Carbopol 976P, polypropylene foam powder were used. All the formulations were evaluated for floating properties, swelling characteristics and drug release studies. In vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow zero order release and super case 2 transport diffusion mechanism. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. After the dissolution study of prepared balofloxacin non-effervescent floating tablet was concluded that the formulation NF9 with HPMC K15 and carbopol 976P show best controlled release effect (98.24%). The release kinetic data implies that the release mechanism of all the formulations was Zero order kinetics and super case 2 transport mechanism. The developed floating tablets of balofloxacin may be used to prolong drug release for at least 12h, thereby improving the bioavaibility and patient compliance.

KEY WORDS: Balofloxacin, gastroretentive, non effervescent floating drug delivery, HPMC (K 15M, E50), Xanthan gum, Sodium alginate, carbopol 976p, talc, lactose.

INTRODUCTION

There has been considerable research over the last decade on the possibility of controlled and site specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastro retentive drug delivery system (GRDDS). Such GRDDS possess the ability of retaining the dosage forms in gastrointestinal tract (GIT) particularly, in the stomach for long period the transit time in GIT i.e., from the mouth to the anus, varies from one person to another. It also depends upon the physical properties of the object ingested and the physiological conditions of the alimentary canal. Several drugs are absorbed to the most extent in the upper part of the small intestine. Many drugs show poor bioavailability (BA) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes waste with negligible or no absorption. This phenomenon considerably decreases the time available for drug absorption after its release and expose the success of the delivery system.The GRDDS can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the

drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability. After oral administration, Balofloxacin is well-absorbed and distributed. The Vss of Balofloxacin is about 38 L. The drug is not primarily metabolized by hepatic enzymes. The terminal half-life of Balofloxacin is about 7-8 hours. The objective of this study was to developed Gastric floating drug delivery system containing Balofloxacin and having a bulk density lower than that of gastric fluid and remaining buoyant on the stomach contents. To achieve the objective low density polymers such as hydroxypropyl methylcellulose HPMC (K 15M, E50), Xanthan gum, Sodium alginate.

MATERIALS AND METHODS

Materials: Balofloxacin was obtained as a gift sample from Hetero drugs, Hydroxy propyl methyl cellulose K15M, HPMC E50 were obtained from Narmada chemicals, Xanthan gum, Mg-Stearate, Talc, guar gum were obtained from Shreeji chemicals, Mumbai, Sodium alginate, Lactose, Carbopol 976p were obtained from S.D fine chemicals, Mumbai.

Preparation of Floating tablets of Balofloxacin: Floating hydrophilic matrix tablets of Balofloxacin were prepared by direct compression technique using drug and variable concentration of polymers (HPMC K15M, HPMC E 50, Xanthan gum, Carbopol 976p, Guar gum, Sodium alginate, Lactose, Mg-stearate and Talc).

The respective powders & optional additives (composition listed in table-3) were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine.

Pre-compression evaluation

Angle of Repose: Angle of repose was determined by using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula.

$$\emptyset = \tan^{-1}\frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Bulk Density: Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) was determined. The bulk density was calculated using the formula.

$$\rho b = \frac{m}{Vd}$$

Tapped Density: The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (m) of the blend was measured. The tapped density (ρb) was calculated using the following formula

$$pt = \frac{m}{Vt}$$

Carr's compressibility index: The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules was determined by Carr's compressibility index, which is calculated by using the following formula

$$I = \frac{Vo - Vt}{Vo} \times 100$$

Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Haunser ratio} = \frac{pt}{pd}$$

Where ρt is tapped density and ρd is bulk density. Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (>1.25).

Post-Compression Evaluation Parameters for Formulated Tablets

Weight variation : Twenty tablets from each formulation were selected at random and average weight was determined. Then the individual tablets were weighed and were compared with average weight.

Hardness : The hardness of the tablet from each formulation was determined using Pfizer hardness tester.

Friability : Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed

in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$F(\%) = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

Thickness and diameter : The thickness and diameter of tablet was carried out using Digital caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

Drug content : Powder one tablets extraction was carried out using 0.1 N HCL. The concentration was determined spectrophotometrically against appropriate blank. Calculate the content of Balofloxacin specific absorbance at 293 nm. As given in IP.

In-vitro dissolution studies : The release rate of Balofloxacin from floating tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The dissolution test was performed using 900ml of 0.1 N HCL, at 37 ± 0.50C and 50 rpm. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution medium.

Stability studies : In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

RESULTS AND DISCUSSION

Pre-compression parameters

Balofloxacin along with other excipients were evaluated for bulk density, tap density, angle of repose, compressibility and Hausner ratio, before proceeding to direct-compression. The physical parameters are recorded in Table 4.

Angle of repose: 23.57 ±0.01 to 28.94 ± 0.12 indicating good.

Compressibility index: 10.04 ± 0.10 to 29.07 ± 0.12 indicating good

Hausner ratio: 1.11 ± 0.06 to 1.63 ± 0.01 indicating good.

Post compression parameters

The important parameters in the production of tablets were evaluated and reported in Table 5 The thickness varied from 4.18 mm to 4.29 mm. The hardness varied from 4.1 kg\cm2 to 4.6 kg\cm2 found satisfactory. The friability test, Weight variation tests were passed.

Dissolution Studies

Based on the objectives of the present investigation, the tablets were evaluated for release of Balofloxacin. Dissolution studies were attempted. Since the delivery system was Gastroretentive non effervescent tablets, stimulated gastric acid fluid pH 1.2 solutions was used as dissolution medium. The results are shown in Table.

In-vitro non-effervescent dissolution studies were performed for all the batches of tablets containing Balofloxacin using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. Formulations NF1 containing drug and polymers like HPMC K15M, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 96.12% of drug `release in 5 hours, NF2 containing drug and polymers like HPMC K15M, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 91.65 % of drug `release in 6 hours, NF3 containing drug and polymers like HPMC K15M, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 85.65% of drug `release in 7 hours, NF4 containing drug and polymers like HPMC E50, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 92.78% of drug `release in 7 hours, NF5 containing drug and polymers like Carbolol, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 93.13% of drug `release in 11 hours, NF6 containing drug and polymers like Xanthane gum, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 91.21% of drug `release in 8 hours, NF7 containing drug and polymers like Guar gum, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 43.15% of drug `release in 8, NF8 containing drug and polymers like HPMC K15M, Guar gum, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 46.32% of drug `release in 8, NF9 containing drug and polymers like HPMC K15M, Carbopol, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 98.24% of drug `release in 12 hours, NF10 containing drug and polymers like HPMC K15M, Sodium alginate, polypropylene foam powder, megnisium stearate, talc, lactose exhibited 92.45% of drug `release in 7 hours and the data is given in table 6.

The *in-vitro* dissolution data as log cum percent drug release versus log time were fitted to Zero order kinetics, values of the exponent 'r^2' was found to be

in the range of 0.885(NF9), indicating that the drug release is by zero order case 2 mechanism.

CONCLUSION

From the compatibility studies, it is concluded that, HPMC K15M, HPMC E 50, Xanthan gum, Carbopol 976P, Guar gum, Sodium alginate, talc, lactose were compatible with drug Balofloxacin and thus suitable for the formulation of Balofloxacin non effervescent tablets. Balofloxacin tablets were fabricated by direct compression method. *In-Vitro* drug release study is performed for 12 hrs. Optimized formula containing HPMC K15M, Carbopol 976P(NF9) showed better release compare to other formulations and it followed zero order kinetics. The zero order case 2 diffusion for NF9 is confirmed as the drug release mechanism from this formulation. From this study, it was concluded that HPMC K15M and Crbopol 976 p can be used in formulation of Balofloxacin gastro retentive non effervescent drug delivery system by using direct compression method.

Table-1: angle of repose limits

Angle of Repose (ɵ)	Flow
25-30	Excellent
30-40	Good
<40	Very poor

Table-2: compressibility index limits

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

Table-3 : Formulation of floating tablet

Ingredients(mg)	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9	NF10
Drug	100	100	100	100	100	100	100	100	100	100
HPMC K15M	70	80	90	-	-	35	35	35	35	35
HPMC E50	-	-	-	70	-	-	-	35	-	-
Carbopol 976p	-	-	-	-	70		-	-	35	
Xanthan gum	-	-	-	-	-	35		-	-	-
Guar gum	-	-	-	-	-	-	35	-	-	-
Sodium alginate	-	-	-	-	-	-	-	-		35
Polypropylene foam powder	-	40	40	40	40	40	40	40	40	40
Mg Stearate	8	8	8	8	8	8	8	8	8	8
Talc	7	7	7	7	7	7	7	7	7	7
Lactose	165	115	105	125	125	125	125	125	125	125
Total	350	350	350	350	350	350	350	350	350	350

Table-4 : Pre-compression parameters of balofloxacin Non-effervescent tablets

F.code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
NF1	0.237±0.001	0.317±0.003	24^0.51±0.10	25.23±0.21	1.33±0.05
NF2	0.231±0.004	0.314±0.002	26^0.12±0.14	26.43±0.17	1.35±0.02
NF3	0.229±0.012	0.313±0.008	25^0.82±0.09	26.83±0.12	1.36±0.10
NF4	0.321±0.006	0.371±0.004	25^0.26±0.07	13.4±0.09	1.15±0.04
NF5	0.213±0.001	0.241±0.010	24^0.85±0.21	11.61±0.04	1.63±0.01
NF6	0.307±0.002	0.343±0.014	28^0.94±0.12	10.4±0.10	1.11±0.06
NF7	0.244±0.005	0.344±0.007	23^0.57±0.01	29.06±0.09	1.40±0.07
NF8	0.307±0.010	0.389±0.006	25^0.95±0.06	21.07±0.15	1.26±0.09
NF9	0.222±0.003	0.313±0.002	25^0.78±0.08	29.07±0.12	1.40±0.12
NF10	0.228±0.002	0.321±0.003	24^0.65±0.01	28.97±0.10	1.40±0.09

Table-5; Post-compression evaluation of balofloxacin non-effervescent tablets

F.code	Thickness (mm)	Hardness (kg/cm2)	Weight (mg)	Friability (%)	Drug content (%)
NF1	4.29±0.01	4.2±0.3	349.6±4.6	0.44±0.03	98.0±0.3
NF2	4.18±0.06	4.0±0.2	350.8±3.4	0.48±0.08	98.7±0.2
NF3	4.2±0.04	4.1±0.8	349.3±2.8	0.54±0.02	98.5±0.2
NF4	4.25±0.11	4.8±0.2	348.3±1.3	0.47±0.03	94.6±0.1
NF5	4.2±0.06	4.3±0.1	349.9±2.8	0.42±0.01	98.1±0.5
NF6	4.3±0.07	4.6±0.5	350.5±3.2	0.39±0.05	96.2±0.2
NF7	4.2±0.07	4.2±0.4	349.2±2.3	0.39±0.01	95.7±0.1
NF8	4.18±0.04	4.2±0.1	350.1±1.7	0.57±0.01	97.4±0.6
NF9	4.22±0.03	4.3±0.6	349.4±4.5	0.42±0.03	98.1±0.3
NF10	4.24±0.01	4.5±0.1	350.4±4.2	0.42±0.01	96.3±0.5

Table-6; *In-vitro* drug release data of balofloxacin Non-effervescent tablets of Batch F1 to F10

Time (hrs)	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9	NF10
0	0	0	0	0	0	0	0	0	0	0
1	56.51±0.2	44.21±0.1	38.36±0.1	31.14±1.0	11.22±0.7	22.13±0.6	16.34±0.8	15.16±0.3	37.14±0.8	27.48±0.1
2	74.16±0.5	62.54±0.5	47.23±0.1	45.56±0.8	19.13±0.9	38.01±0.2	21.13±0.4	22.06±0.1	42.56±0.9	39.34±0.5
3	89.31±0.1	77.26±0.9	52.78±0.3	63.41±0.7	26.52±0.1	56.11±0.2	27.47±0.6	29.63±0.3	55.41±0.4	50.13±0.6
4	94.06±0.7	80.97±0.2	58.34±0.1	74.16±1.2	32.64±1.0	69.35±0.3	29.79±0.1	34.56±0.1	59.16±0.6	63.54±0.8
5	96.12±0.3	83.42±0.1	69.05±0.3	82.41±0.7	40.85±0.5	74.65v0.1	31.16±0.2	38.44±0.5	66.21±0.4	74.12±0.4
6	--	91.65±0.3	81.69±0.2	89.32±0.2	49.79±0.8	83.14±0.5	38.42±0.1	41.64±0.7	70.02±0.1	86.15±0.2
7	--	--	85.65±0.5	92.78±0.9	56.41v1.2	89.19±0.4	40.64±0.1	44.87±0.1	75.98±0.2	92.45±0.3
8	--	--	--	--	67.26±0.1	91.21±0.1	43.15±0.4	46.32±0.3	78.64±0.6	--
9	--	--	--	--	76.52±0.5	--	--	--	84.44±0.5	--
10	--	--	--	--	84.54±0.8	--	--	--	89.32±0.8	--
11	--	--	--	--	93.13±0.05	--	--	--	93.62±0.7	--
12	--	--	--	--		--	--	--	98.24±0.1	--

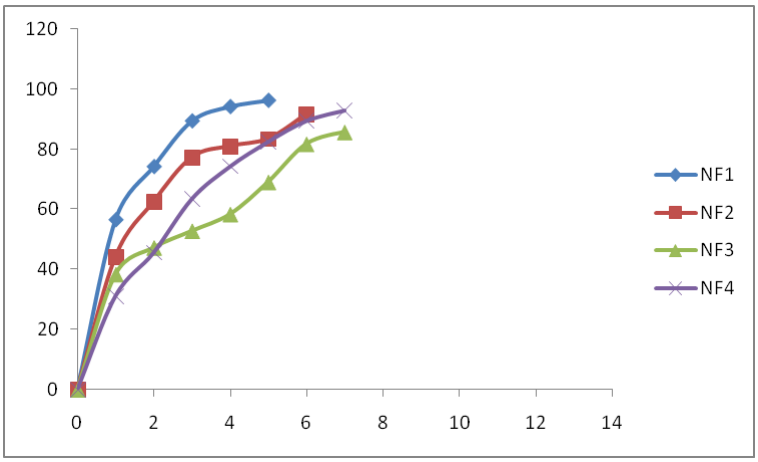

Figure-1: *In-vitro* drug release profile of Balofloxacin non-effervescent tablets of batches NF1 to NF4.

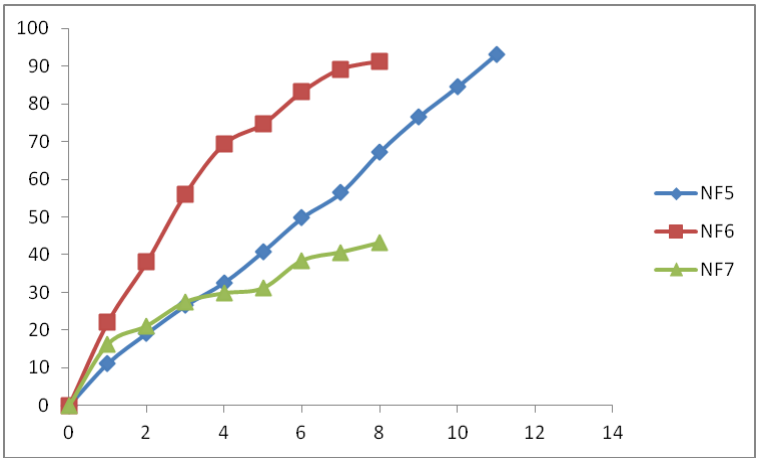

Figure-2: *In-vitro* drug release profile of Balofloxacin non-effervescent tablets of batches NF5 to NF7

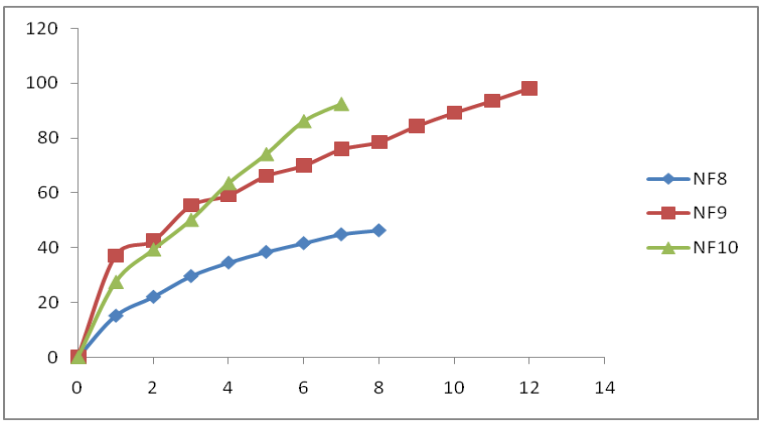

Figure-3: *In-vitro* drug release profile of Balofloxacin non-effervescent tablets of batches NF8 to NF10

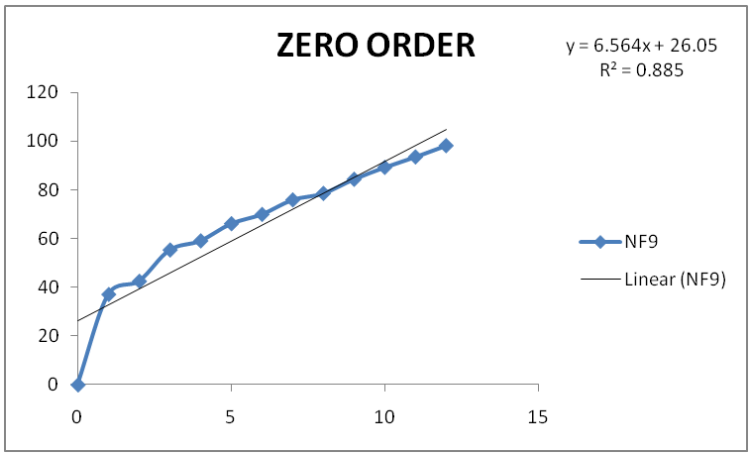

Figure-4: Zero order release profile of Balofloxacin floating tablets of NF9

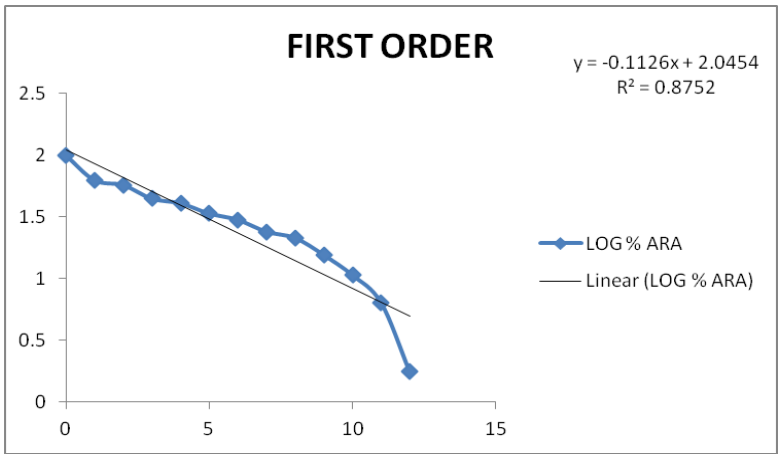

Figure-5: First order release profile of Balofloxacin floating tablets of NF9

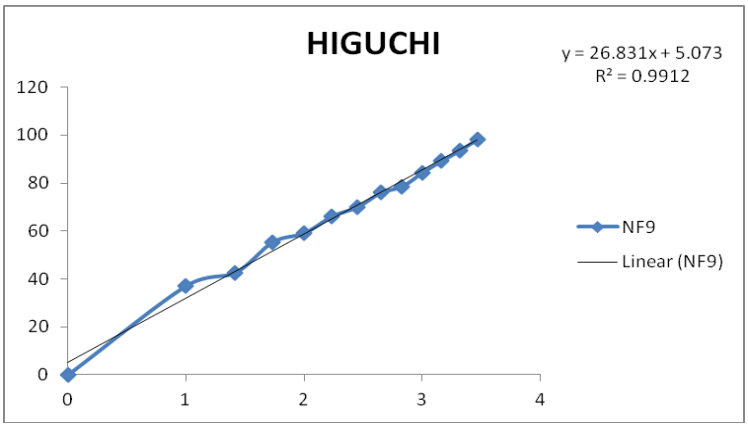

Figure-6: Higuchi release kinetics profile of Balofloxacin floating tablets of NF9

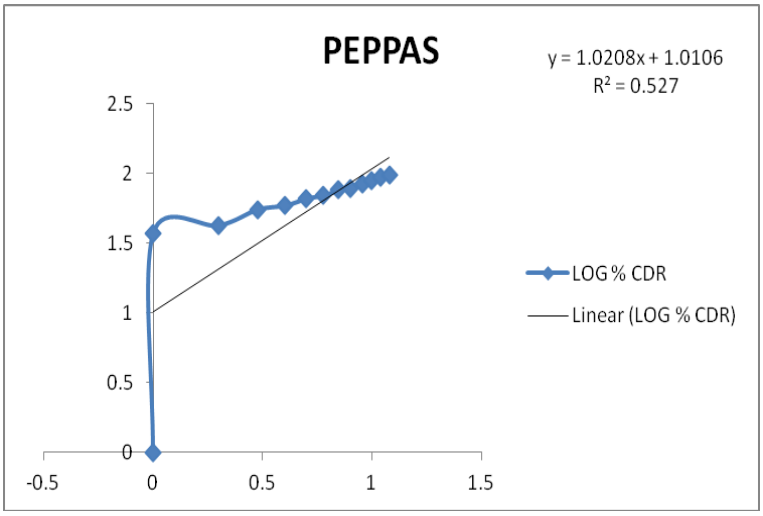

Figure-7: Peppas release kinetics profile of Balofloxacin floating tablets of NF9

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