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Enhancement of bioavailability and gastric residence time of cephalexin by hydrodynamically balanced system

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Abstract

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. More than 50% of the drug delivery systems available are to be administered through oral route. During the last decade, many studies have been performed concerning the sustained release dosage forms of the drug, which have aimed at the prolongation of gastric emptying time (GET). Oral sustained release gastro retentive dosageforms (GRDFs) offer many advantages for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery System is one amongst the GRDFs used to achieve prolonged gastric retention time. Cephalexin is in a group of antibiotics and is used to fight against gram positive infections in the body. In this present study to enhance the gastric retention of the Cephalexin, it is formulated as effervescent floating dosage form by direct compression method. The polymers like HPMC K4M, HPMC K15M, HPMC K100M and Sodium bicarbonate are used. From the results of dissolution profile it was conformed that the antimicrobial action of Cephalexin may be increased in the stomach due to increase retention time and absorption by using HPMC K100M (F9 formulation) than other formulations. Drug release of F9 was found to follow first order kinetic model and the mechanism of the drug release was found to be diffusion controlled process.

Key-Words: Cephalexin, Gastric Emptying Time (GET), Floating Drug Delivery System, HPMC K4M, HPMC K15M, HPMC K100M, First order

Introduction

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed[1]. More than 50% of the drug delivery systems available are to be administered through oral route[2]. In oral delivery conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level[3]. And oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today[4].

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During the last decade, many studies have been performed concerning the sustained release dosage forms of the drug, which have aimed at the prolongation of gastric emptying time (GET): swelling and expanding systems, alter dosage forms, low density or floating drug delivery systems, bioadhesive systems, high density non-floating drug delivery systems, modified shaped systems. Floating drug delivery system is also called as hydrodynamically balanced system. Depending on the mechanism of buoyancy, two distinctly different methods i.e. effervescent and non-effervescent system have been used in the development of floating drug delivery system.[5]

Cephalexin is in a group of drugs called cephalosporin antibiotics and is used to fight bacteria in the body. It works by interfering with the bacteria's cell wall formation, causing it to rupture, and killing the bacteria.[6,7,8] It's have good absorption in GIT, low pKa, which remained unionized in the stomach for better absorption and it's have half life 0.5-1-2 hours. Cephalexin is used to treat infections caused by bacteria, including upper respiratory infections, ear

infections, skin infections, and urinary tract infections.[9,10,11]

The aim of the present study was not only preparing a cephalexin floating system but also to release the drug in the controller manner, therefore the maximum drug release is maintained at desired site. The effect of different polymers and the effect of amount of polymers was investigated in the formulation to monitor the sustained release effect respectively.

Material and Methods

Materials

Cephalexin was obtained as gift sample from orchid chemicals & pharmaceutics ltd., Chennai. HPMC all grades and other excipients are obtained from yarrow chem. Products.

Method of preparation

Preparation of floating tablets of Cephalexin[12,13,14]

Floating effervescent tablets of cephalexin were prepared by direct compression method. The powder mixture contains drug, controlled release polymers as for the formulae and MCC was used as the diluent, sodium bicarbonate added as effervescent agent. The blend was lubricated with magnesium stearate for 3-5 mins and talc was added as glidant. Then the mixed blend was then compressed into tablets by direct compression method using 12.5 mm punches on a ten station rotary tablet punching machine.

Formulation

Method[15,16]

The composition of different formulations of cephalexin floating tablets is shown in the table no.1. Different tablet formulations were prepared by direct compression method. All the powders passed through 40/60 mesh sieve. The required quantity of drug, various polymers and other ingredients were mixed thoroughly. Talc and magnesium striate were finally added as a glidant and lubricant respectively. The blend was compressed into tablets by direct compression method using 12 mm diameter punches on a 10 station rotary tablet punching machine.

Characterization of Cephalexin[7,10,15,16]

Description

The pure drug cephalexin was analyzed for colour, odour and taste.

Melting point

The melting point of drug was determined by open capillary method.

Standard curve

Standard curve of cephalexin was estimated by UV spectrophotometric method.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed on drug, excipient and the optimized formulation using FTIR.The sample were analysed between wave numbers 4000 and 400 cm-1.

Evaluation [9,10,17,18,19,20]

Evaluation of granules

Angle of repose

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

$\Theta = \tan^{-1} (h/r)$

Bulk density

Apparent bulk density (p_b) were determined by pouring the blend in to a graduated cylinder.The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.

$p_b = M/ V_b$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. Theminimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. Thetapped density (ρ_t) was calculated using formula.

$\rho_t = M/ V_t$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, a indication ofthe ease with which a material can be induced to flow is given by compressibility index (I) was calculated as follows.

$I = V0 - V_t /V_0 100$

Where, V_0 is the bulk volume and V_t is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by thefollowing method

Hausner ratio = ρ_t /ρ_d

Where, ρ_t tapped density and ρ_d bulk density lower hausner ratio.

Evaluation Of Tablets

Characterization of tablets for physiochemical parameters

The prepared Cephalexin floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

In vitro floating lag time

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at

37ºC. The time required for the tablet to rise to the surface and float was determined as floating lag time.

***In vitro* floating duration time**

The floating capacity of the tablets was determined using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of the tablet in to the dissolution medium and its buoyancy to the dissolution medium was taken as buoyancy lag time and for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration.

***In vitro* drug release [21]**

The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5ºC temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbancevalue of the diluted sample was measured at 257nm for Cephalexin by using UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve.

Characterization of drug in Floating tablets

FTIR studies were conducted for characterization of drug in tablets. The floating tablets were compressed and powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectra of pure Cephalexin and pelletized powder of tablets were taken, interpreted and compared with each other.

Results and Discussion

The sample of drug Cephalexin was off white or almost, white, crystalline powder and have characteristicodour. The melting point value was observed in the range of 326^{0}C. The absorption maximum was found to be 257 nm when scannedbetween 200 to 400 nm in 0.1 N HCl by the UV-Visible spectrophotometer. FTIR spectra revealed that there was no interaction between the drug and the polymers.

The Preformulation studies were performed and the results were shown in the following table 2. Bulk density was found in the range of 0.64-0.66 g/cm^3 and the tapped density between 0.77-0.80 g/cm^3. Using these two density data compressibility index was calculated. The compressibility index was found between 15.38 and 22.02 and the compressibility-flowability correlation data indicated a fairly good flowability of the blend. The good flowability of blend was also evidenced with angle of repose (range of 27.15^0 – 29.62º), which is below 40º indicating good flowability.

The mean thickness values were found in the range from 2.72±0.06 to 2.86±0.12 mm, the hardness of formulated tablets was found to be 4.52 to 5.80 kg/cm^3. The loss in friability was ranged from 0.28±0.06 to 0.41±0.03.These values were represented in Table 3. The disintegration time was ranged from 22□8.26 to 39□2.32 sec. All the formulations showed good floating buoyancy time i.e. >12 hrs so the formulations remained in the stomach for long time thus the bioavailability of the dosage form was increased.

The FTIR spectrum of formulated blend showed characteristic peaks of drug which indicated that the compatibility of the drug with the excipients used. The spectrum was shown in Figure 1.

The release of Cephalexin from floating tablets was determined by using Dissolution type II test apparatus. And the dissolution profile was represented in the below figures 2-4.

From the results of %drug release of the tablet dosage form it was observed that all the formulations shows the drug release in the controlled manner and the formulation F9 showed 59.064% drug release at the end of 12 hrs. Thus the biological half life of the drug was increased.

Data obtained from the *in vitro* release studies were fitted to various kinetic models such as zero order, first order, Higuchi and korsmeyer-peppas model and the results are shown in the table 4 and the figure 5 below.

It was found that all the formulations were shown Peppas as te best fit model except F9 and it was fitted into first order model. When the release data's were analyzed as per peppas equation, the release exponent 'n' was found to be in the range of 0.5413 to 0.8544 indicating non-fickian diffusion mechanism.

Conclusion

In conclusion, in the present research, the floating tablets of Cephalexin were successfully prepared by using different viscosity grades of HPMC to increase the gastric residence time and hence bioavaibility of Cephalexin. From the above results, it was observed that as the concentration of the polymers are increased and there is a decrease in the drug release rates. Formulations containing higher HPMC viscosity grades have slower drug release rates when compared to formulations with lower HPMC viscosity grades. By observing the dissolution profile of the formulation it can be concluded that the anti

microbial activity of the Cephalexin may be increased in the stomach due to increase in the retention time and absorption by using HPMC K100M than the other polymers. Drug release of F9 was found to follow first order kinetic model and the mechanism of the drug release was found to be diffusion controlled process.

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Table: 1: Composition of floating tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	250	250	250	250	250	250	250	250	250
HPMC K 4M	80	140	190	-	-	-	-	-	
HPMC K 15M	-	-	-	80	140	190	-	-	-
HPMC K 100M	-	-	-	-	-	-	110	165	220
$NaHCo_3$	55	55	55	55	55	55	55	55	55
MCC	140	80	30	140	80	30	140	80	30
Talc	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Mg. stearate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Total weight	550	550	550	550	550	550	550	550	550

Note: All ingredients are mentioned the above table is in mg/tab

Table: 2: Flow properties of Cephalexin powder blend:

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
F1	29.13 ± 0.04	0.64 ± 0.02	0.80±0.02	20.02 ±0.04	1.25 ± 0.02
F2	27.31 ± 0.03	0.65 ± 0.02	0.78±0.03	16.66 ±0.02	1.20 ± 0.01
F3	28.26 ± 0.01	0.64 ± 0.01	0.78±0.02	17.94 ±0.04	1.21 ± 0.04
F4	28.46 ± 0.02	0.65 ± 0.04	0.78±0.04	16.58 ±0.03	1.20 ± 0.02
F5	29.62 ± 0.04	0.65 ± 0.02	0.79±0.01	17.72 ±0.01	1.21 ± 0.05
F6	28.14 ± 0.03	0.66 ± 0.03	0.78±0.01	15.38 ±0.02	1.18 ± 0.01
F7	28.22 ± 0.03	0.65 ± 0.01	0.77±0.04	15.58 ±0.01	1.18 ± 0.04
F8	27.15 ± 0.02	0.64 ± 0.04	0.78±0.01	17.64 ± 0.04	1.21 ± 0.08
F9	27.18 ± 0.01	0.64 ± 0.03	0.77±0.02	17.56 ± 0.02	1.20 ± 0.03

All values are expressed as mean ± SD, n=3

Table: 3: Evaluation of physical parameters of Cephalexin floating tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Average weight (mg)	Friability (%)	Drug content (%)	Floating lag time (sec)	Total floating time (h)
F1	2.86±0.12	4.52	552	0.41±0.05	99.81 ± 1.4	18	>24
F2	2.82± 0.16	5.20	550	0.31±0.08	99.67 ± 1.7	13	>24
F3	2.85± 0.14	4.55	549	0.36±0.03	98.75 ± 0.5	20	>24
F4	2.81± 0.08	4.95	553	0.37±0.01	99.47 ± 1.3	21	>24
F5	2.79± 0.12	5.25	554	0.36±0.08	100.07 ± 0.4	24	>24
F6	2.79± 0.10	5.30	551	0.28±0.06	100.38 ±0.6	17	>24
F7	2.75± 0.12	5.45	548	0.41±0.03	100.01 ±1.5	36	>24
F8	2.72± 0.06	5.80	552	0.36±0.12	98.24 ±0.6	32	>24
F9	2.73± 0.14	5.68	554	0.34±0.10	99.39 ±0.2	38	>24

Table: 4: Regression coefficient fits to different drug release kinetics models

Formulation code	r^2					Best fit model
	Zero order	First order	Higuchi's model	Korsmeyer Peppas	n	
F1	0.9757	0.8900	0.9803	0.9991	0.7073	Peppas
F2	0.9323	0.9021	0.9935	0.9975	0.5782	Peppas
F3	0.935	0.9783	0.9892	0.9892	0.5413	Peppas
F4	0.9423	0.9451	0.9868	0.9929	0.6140	Peppas
F5	0.8035	0.9771	0.9951	0.9958	0.4609	Peppas
F6	0.9281	0.9915	0.9905	0.9942	0.5987	Peppas
F7	0.9622	0.9949	0.9803	0.9953	0.6679	Peppas
F8	0.9866	0.9895	0.9579	0.9952	0.8544	Peppas
F9	0.9819	0.9956	0.9672	0.9953	0.7248	1st order

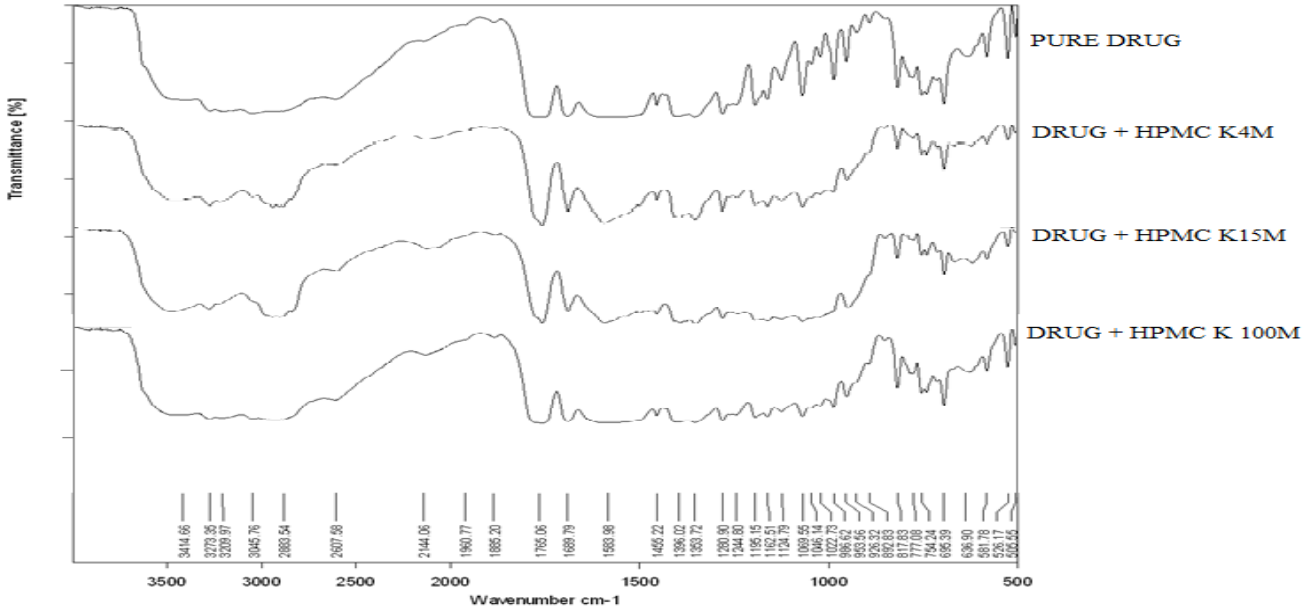

Fig. 1: FTIR Spectra of Cephalexin by Polymers

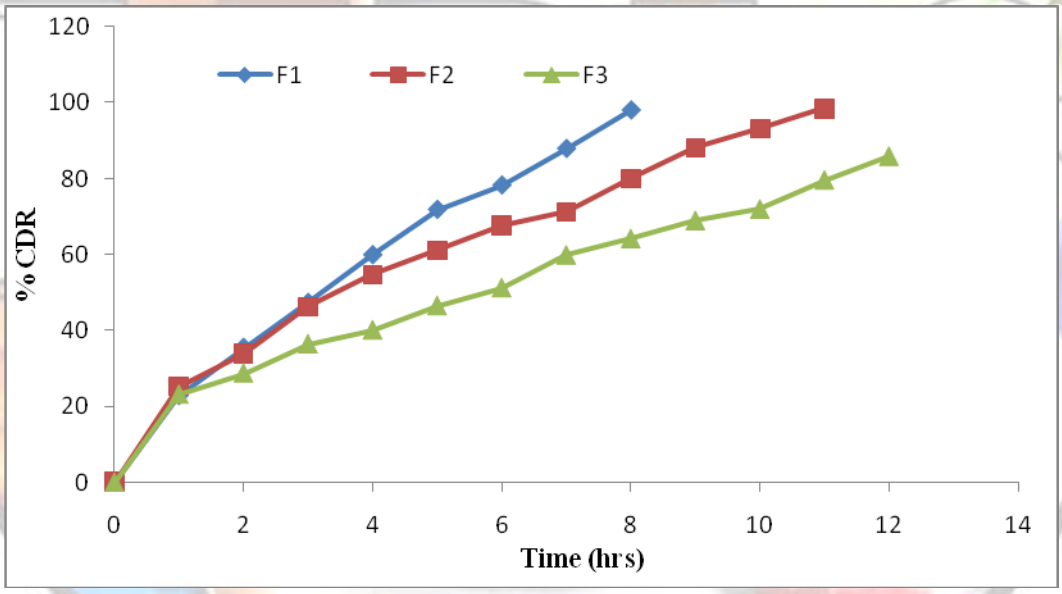

Fig. 2: Dissolution profile of Cephalexin with HPMC K4 M

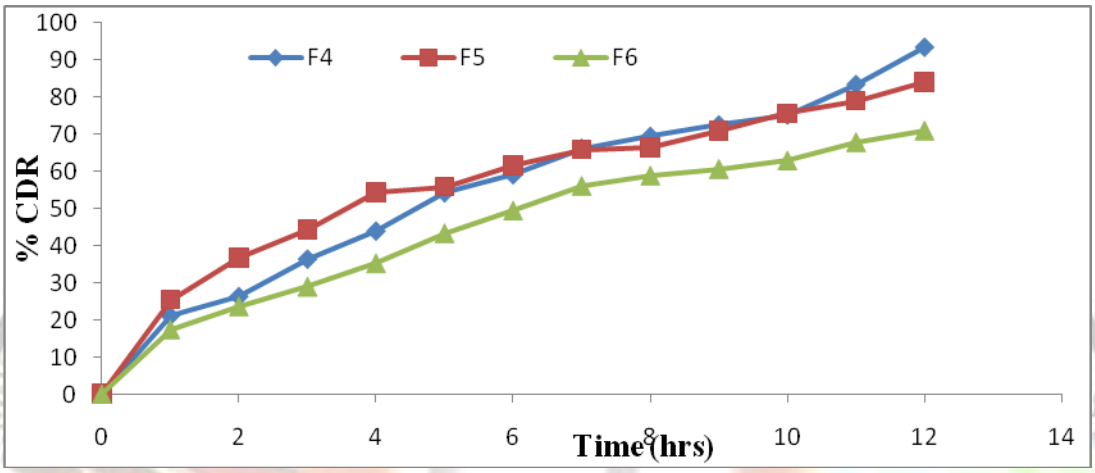

Fig. 3: Dissolution profile of Cephalexin with HPMC K15 M

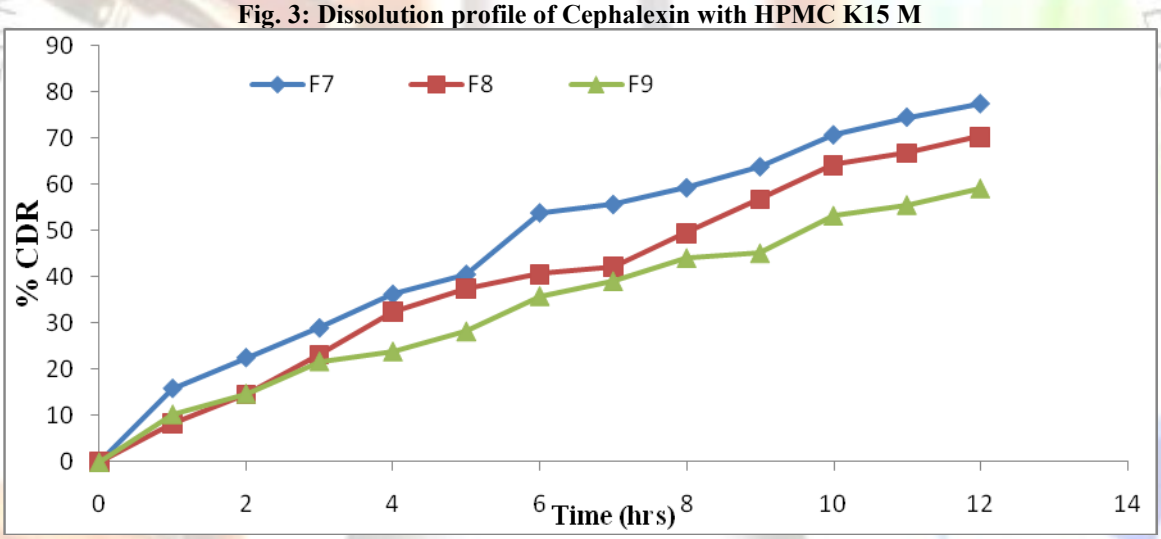

Figure:4: Dissolution profile of Cephalexin with HPMC K100

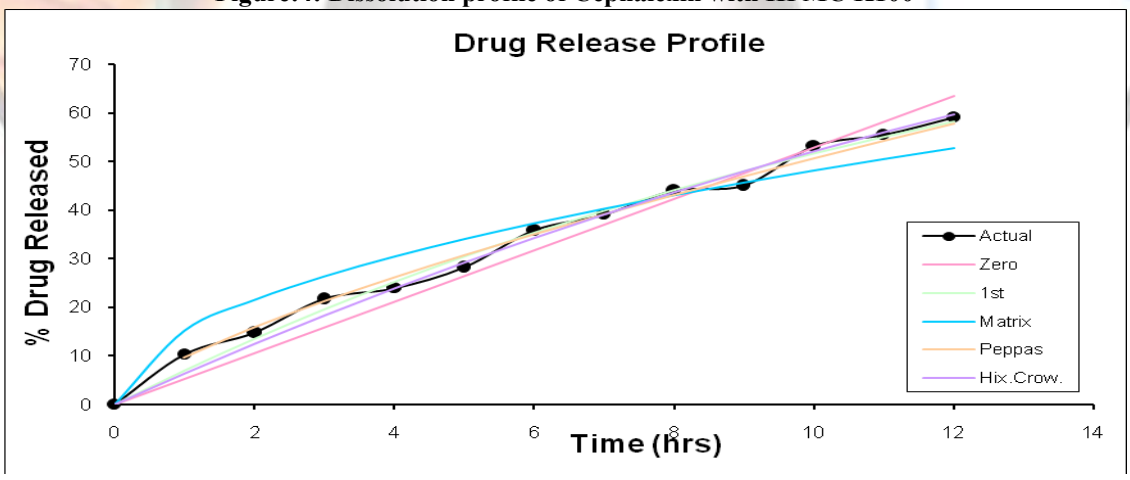

Fig. 5: Graphical representation of *in vitro* drug release kinetics for F9