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RESEARCH ARTICLE

Development and Evaluation of Gastro Retentive Ciprofloxacin Floating Tablets

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ABSTRACT

Gastro retentive drug delivery system is one of the novel drug delivery system have lot of advantages. The various disadvantages of conventional oral dosage form can be successfully rectified by converting to this system. Ciprofloxacin is a broad spectrum antibiotic used commonly for the treatment of lower respiratory tract infection, H. Pylori infection and infectious diarrhea. Gastro retentive drug delivery system of ciprofloxacin fabricated to deliver the drug in a controlled manner. Fabrication done by incorporating drug with mixture of hydroxyl propyl methyl cellulose and sodium alginate as polymers and sodium bicarbonate, as gas forming agent. Various evaluation parameters were undertaken to found out the ideal formulation. The various physico chemical and *in-vitro* release studies for the system were done. Stability studies also conducted for the ideal formulation and proved for its adequate shelf-life. Pharmacokinetic studies revealed the exact mechanism of drug permeation from the dosage form. Thus, the ideal formulation may be utilized for its controlled release to improve patient compliance.

KEYWORDS

Gastro retentive drug delivery system, Ciprofloxacin, H. pylori, *In-vitro* studies, Floating tablets, HPMC K4M, Sodium alginate

INTRODUCTION

Floating dosage forms[1] are dosage forms with a bulk density lower than that of the gastric content. This allows them to remain buoyant on the surface of the gastric content for a certain period of time without affecting the intrinsic rate of emptying. They are also referred to as hydro dynamically balanced systems (HBS) as they are able to maintain their low density while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is progressively released from the swollen matrix as in the case of conventional hydrophilic matrices.

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In order to design successful floating dosage forms, three major conditions should be met: (i) they must have sufficient structure to form a cohesive gel barrier. (ii) They must have an overall specific gravity lower than that of gastric contents (reported as 1.004-1.010g/ml); (iii) they should dissolve slowly enough to serve as a reservoir for the delivery system.

The selection of potential excipients that allow the formulation of matrices having sustained delivery characteristics and a bulk density of less than 1g/ml is the key point. After extensive work on the floating and swelling characteristics of commonly used excipients that polymers with high molecular and less hydrophilic grades usually exhibit enhanced floating characteristics[2].

Floatation not only prolongs the gastrointestinal (GI) residence time, or obtains a sustained local action into the stomach, but also does so in an area of the gastrointestinal tract (GIT) that would maximize the amount of drug reaching its absorption site in solution, and hence ready for absorption. The retentive characteristics of the dosage form are most significant for drugs insoluble in intestinal fluids, for those acting locally in the upper GIT and those exhibiting site specific absorption.

Different hydrocolloids of natural and semi synthetic origin have been used for the formulations of HBS forms. Among the different hydrocolloids recommended for floating formulation, cellulose ether polymers are the first choice, especially hydroxy propyl methyl cellulose (HPMC), which is extensively used.

Ciprofloxacin[3] is a broad spectrum fluoroquinolone antibiotic. It is approved for the treatment of bone and joint infections, infectious diarrhea, lower respiratory tract infections, urinary tract infections, hospital acquired infections and *meningococcal prophylaxis.*

The drug is freely soluble in water and has a short elimination half-life of about 4h; various sustained release preparations were aiming to enhance its antibacterial activity. It has a narrow absorption window and is mainly absorbed in the proximal areas of GIT. Therefore Ciprofloxacin HCl floating systems were developed.

An infection of stomach mucosa with *H.pylori*, a gram negative bacillus that causes chronic gastritis, is now generally considered as a risk factor of gastric cancer and duodenal ulcer. Ciprofloxacin is the drug of choice for the treatment of *H.pylori* infection. The drug does not readily cross blood brain barrier (BBB).Considering the above shortcomings, decided to formulate the dosage form that will be beneficial for the patient.

MATERIALS AND METHOD

Ciprofloxacin hydrochloride was obtained as a gift sample from Fourrts India Ltd, hydroxy propyl methyl cellulose (K 15M) and (HPMC K4M) were obtained from colorcorn Asia Ltd, Goa, India. Low viscosity sodium alginate, Magnesium stearate were purchased from SD fine chemicals Ltd, Mumbai, Lactose and Microcrystalline cellulose were obtained from E.merk (India) Ltd., Mumbai. All other reagents were of analytical grade.

Methodology

Fabrication of Floating Tablet

Floating tablets were fabricated by using direct compression [4] techniques. All the polymers and the active ingredient were passed through a fine sieve. Accurately weighed quantity of ciprofloxacin powder, polymer, effervescent agent and excipient were thoroughly mixed in a glass mortar-pestle. Compression of the mixture was done by an automatic punching machine using 12mm flat punch at 3.5 to 4.5 Kg/Cm^2.

Drug Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopic Analysis[5]

In order to evaluate the integrity and compatibility of the drug in the formulation, drug and Excipients in 1:1 ratio were mixed and analyzed by FT-IR (shimadzu 8400s) spectrometer using KBr pellet method.

Pre Compression Parameters[6]

Angle of Repose

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was studied.

$$\tan\theta = \frac{h}{r} \quad , \quad \theta = \tan^{-1}\frac{h}{r}$$

Where, θ =Angle of repose, h=height, r=radius

Bulk Density and Tapped Density of Powders

Accurately weighed powder blend was taken in a graduated vessel. Initial volume was recorded and tapped on a wooden surface until the volume of bulk remains constant. Final volume of the powdered blend was recorded and tabulated for bulk and tapped density.

Table1: Formulation chart for HPMC K 4M and K 15M

S.No	Formu[n] Identity	Ciproflox acin (mg)	HPMC K4M (mg)	HPMC K15M (mg)	$NaCO_3$ (mg)	Na alginate (mg)	MCC (mg)	Lactose (mg)	Mg. Sterate (mg)
1	A1	250	-	100	50	50	125	65	10
2	A2	250	10	90	50	50	125	65	10
3	A3	250	20	80	50	50	125	65	10
4	A4	250	30	70	50	50	125	65	10
5	A5	250	40	60	50	50	125	65	10
6	A6	250	50	50	50	50	125	65	10
7	A7	250	60	40	50	50	125	65	10
8	A8	250	70	30	50	50	125	65	10
9	A9	250	80	20	50	50	125	65	10
10	A10	250	90	10	50	50	125	65	10
11	A11	250	100	_	50	50	125	65	10

$$Bulkdensity = \frac{\text{weight of granules}}{\text{apparent volume}}$$

$$Tappeddensity = \frac{\text{weight of granules}}{\text{Tapped volume}}$$

Compressibility Index

The values obtained from the bulk and tapped density, taken for calculating compressibility index and Hausner's ratio.

$$carr's..index = \frac{tappeddensity - bulkdensity}{tappeddensity} \times 100$$

$$hausnerratio = \frac{tappeddensity}{bulkdensity}$$

Post Compression Parameters[7, 8]

Tablet Dimension

Thickness and diameter were measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly selected and hardness of the tablets was determined.

Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$)

and transferred into friabilator. The friabilator was operated 25rpm for 4minutes or run upto 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by

$$\%F = \frac{W - W_0}{W_0} \times 100$$

Uniformity in Weight[9]

Twenty tablets were selected randomly from each batch and weighed. Weight of each tablet was recorded with the help of digital balance. The readings were recorded and tabulated.

Swelling Index[10]

The swelling property of floating tablet was done by putting the tablet in a graduated glass vessel which contains 250ml of 0.1N HCl acid maintained at 37±0.5° C. At regular time intervals, the tablet was collected and the liquid present on the surface of tablet was carefully removed. The swollen tablet was then reweighed and calculated swelling index.

$$\%Swelling = \frac{W_2 - W_1}{W_1} \times 100$$

In vitro Buoyancy Studies[11]

The time between introduction of dosage forms and its buoyancy in the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called total lag time (TLT) or buoyancy lag time (BLT) and the total duration of time by which dosage form remain buoyant is called total floating time.

In-vitro Drug Release Studies[12]

Six tablets of each formulation were used in the release experiment. *In-vitro* drug release of tablets was studied using USP type II apparatus at 37±0.5°C in 900ml 0.1N HCl solution (pH; 1.2) with a speed of 100rpm. At appropriate time intervals 0, 0.5, 1, 2, 4, 6, 8, 10,12h, 5ml of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed spectrophotometically at 278nm. The dissolution data obtained were plotted as percent cumulative drug release versus time.

Analysis of Release Data[13, 14, 15]

Different kinetic models (zero- order, first order, Higuchi, and Hixson-Crowell) were applied to interpret the release from matrices and Korsmayer-Peppas kinetics model was used to describe the release mechanism.

$$\frac{M_t}{M_\alpha} = kt^n$$

Where, Mt= drug released at time t,

Mα=drug released at infinite time

k= kinetic constant,

n=release exponent

Mean dissolution time (MDT) and dissolution efficacy (DE) were used to compare the release rates amongst formulations. MDT was calculated by the following equation.

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{i=1}^{n} \Delta M_j}$$

Where, j=sample number,

n=number of dissolution sample time

$\hat{t}$=time at midpoint between t_j and t_{j-1},

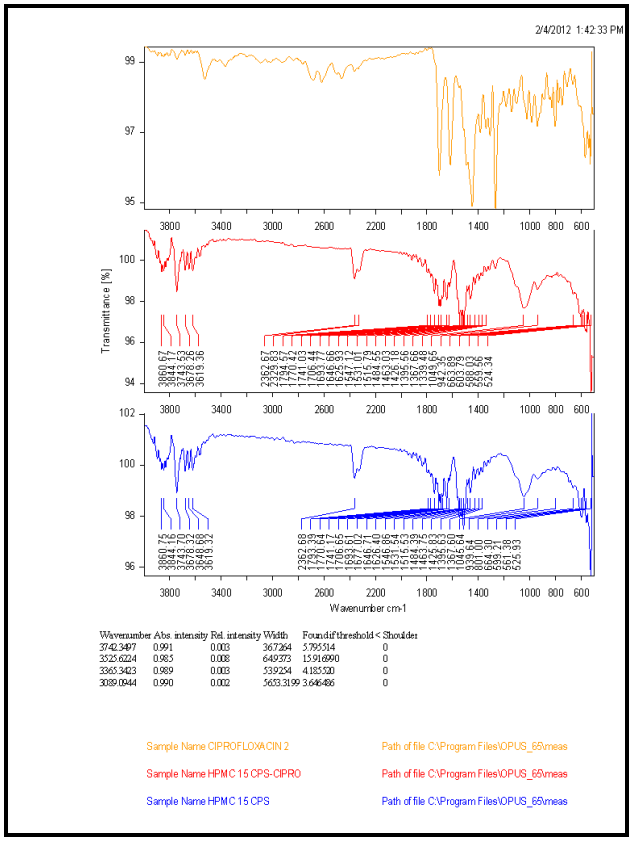
ΔM_j =additional amount of drug dissolved between t_j and t_{j-1}

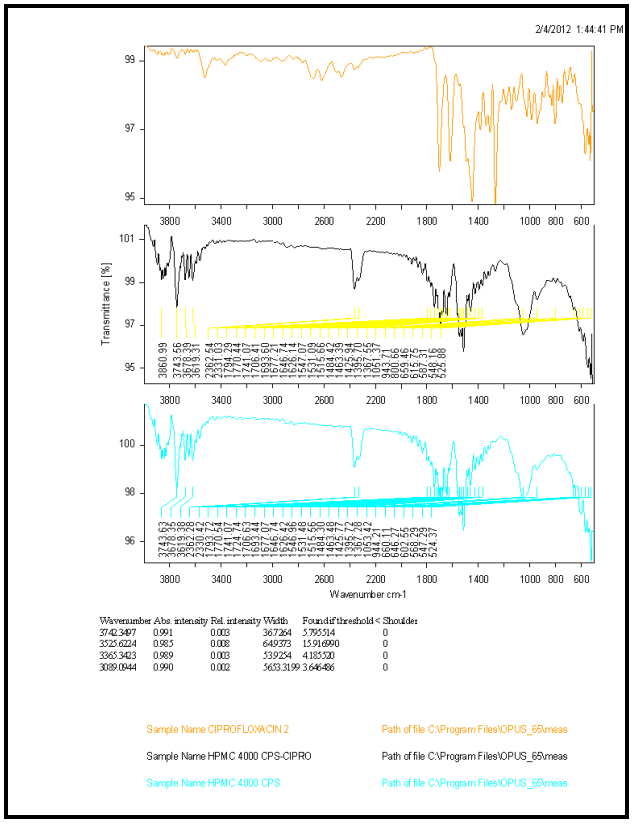
RESULTS AND DISCUSSION

Physico-Chemical Characteristics of Tablets

Controlled release Ciprofloxacin HCl effervescent floating tablets were developed using release retarding gel-forming polymers like HPMCK15M, K4M and sodium alginate and gas forming agent sodium bicarbonate. The incorporation of microcrystalline cellulose in the designed system was suggest to impart superior flow and enhance powder compaction in direct compression and that MCC is capable of swelling in contact with aqueous fluid as

simulated gastric fluid leading to an increase in the water uptake capacity.

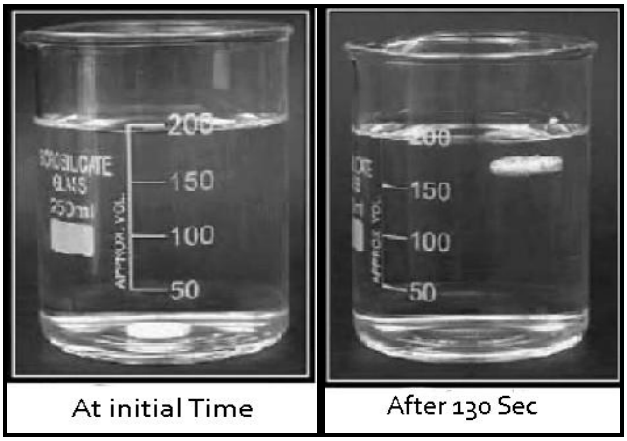




Increasing the hardness would possibly lead to prolongation of the floating lag time by affecting the rate of the tablet penetration by the dissolution medium. Based on these conclusions the hardness of the floating tablets was adjusted in the current work to 4.5 to 5 Kg/Cm^2 .The thickness of the tablet batches ranged from 3.92±0.10 to 4.12 ± 0.06mm.All the formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, Drug content, Friability.

Floating Lag Time and Duration

From the lag time measurement study, it was evident that for all the formulations, the lag time was between 2 and 3min. The investigated gastric floating systems employed sodium bicarbonate as a gas forming agent dispersed in a hydro gel matrix (HPMC and Na-alginate). The in vitro testing revealed the ability of most formulae to maintain the buoyancy lag time ranging from 30 sec to 120 sec.



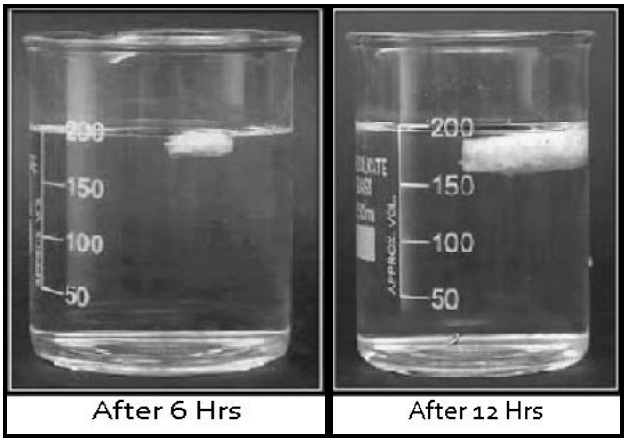


Table 2: Physico Chemical Evaluation Results of Ciprofloxacin Floating Tablets

Formulation Identity	Tablet thickness (mm)*	Tablet weight (mg)*	Hardness (kg/cm^2) *	Tablet friability (%)*	Floating lag time (s)	Total floating duration
A1	3.92±0.10	648.18±2.34	3.8±0.21	0.52±0.07	85	>12h
A2	3.98±0.05	651.19±3.92	3.7±0.22	0.54±0.10	97	>12h
A3	4.03±0.05	657.33±1.30	4.0±0.01	0.28±0.05	54	>12h
A4	3.97±0.05	647.04±2.56	4.2±0.21	0.21±0.07	42	>12h
A5	3.93±0.10	648.43±2.70	3.9±0.31	0.31±0.15	52	>12h
A6	3.98±0.05	652.16±2.33	4.3±0.03	0.38±0.14	73	>12h
A7	4.02±0.10	656.39±1.14	4.5±0.05	0.26±0.04	31	>12h
A8	4.06±0.05	647.04±2.70	3.7±0.02	0.34±0.12	43	>12h
A9	4.01±0.05	653.16±2.38	3.9±0.04	0.43±0.08	116	>12h
A10	3.97±0.05	646.13±3.10	4.6±0.06	0.32±0.18	96	>12h
A11	4.09±0.05	657.14±2.75	4.2±0.02	0.48±0.04	76	>12h

*n=3observations±SD

In vitro Buoyancy Time Measurement

Buoyancy time was defined as the time period for which tablets kept floating on the surface of media before sinking completely to the bottom.

From the buoyancy studies it was evident that all the formulations showed similar buoyancy time (over 12h). Hence the differentiating factor to choose the optimal formulation was taken as the drug release criterion 12 h buoyancy period where shown in Table No 2.

***In-vitro* Drug Release Studies**

A rigorous study of dissolution profile for all the formulations gave an insight into the effect of polymeric filters and gas generating agent on release profile of the formulations. Depending on the types and concentration of the Investigated polymers in the current study, variable drug release profiles were successfully tailored. The influence of HPMC/Na alginate ratio on the release of ciprofloxacin from the floating tablets in 0.1N HCl (pH 1.2) at 37±0.5°C was shown in fig 1a, 1b, it is clear that all batches succeeded in controlling the rate of drug release for 12 h.

From the release profiles it was observed that the variation in grade of polymer and its concentration, combination from A1 to A11 had variable effect on drug release. The effect of HPMC K4M and K 15M could be observed at constant sodium bicarbonate level. The combination of HPMC K4M, and K15M increased the release rate. Similar profiles are observed through to a much smaller extent (due to closeness of the formulations) in case of the

optimized formulations. A7and A8 fig 1(b).These findings can be explained in the light of difference in molecular weight of three varieties of HPMC.HPMC K15M with higher molecular weight forms gel of higher viscosity (15,000cps) compared to HPMC K4M (nominal viscosity 4000cps). However due to higher molecular weight, the polymer chains are bulkier in K15M leading to less flexibility and hence more time for polymer-solvent interaction and polymer chain relaxation and polymer chain relaxation. Consequently, the polymer chain unwinding is delayed in case of HPMC K15M compared to HPMC K4M, there by leading to reduce gelling rate for the former variety.

As a result of this the effective diffusion rate of drug through matrices containing higher percentage of HPMC K4M is more leading to higher dissolution rates from these tablets. Formulation A8 was chosen as optimal based on their ability to sustain drug release up to 12 h periods as evident from Fig 1a and 1b.By comparing different grades of HPMC (K4M, K100M, K50M, and K15M) it may be concluded that low viscosity grade HPMC K4M provided better release characteristics and showed good *in vitro* buoyancy and with the increase in molecular weight of HPMC, the drug release could be retarded greatly.

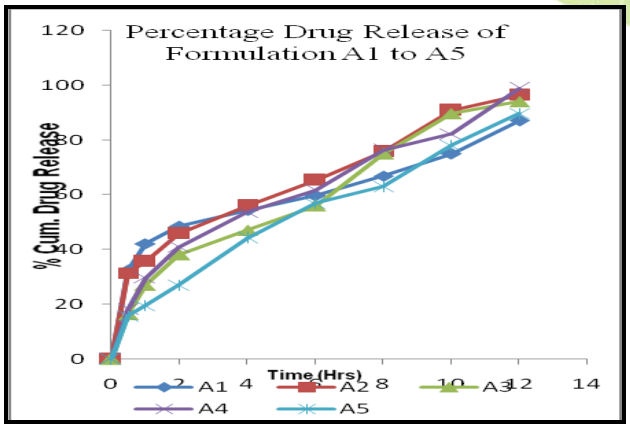


Figure: 1(a) Percentage Drug Release from the Formulation A1 to A5

Drug Release Kinetics

The mechanism of release for the above formulations was determined by finding the R^2 value for each kinetic model viz. Zero order, first order, Higuchi, and Korsemeyer-Peppas corresponding to the release data of each formulation.

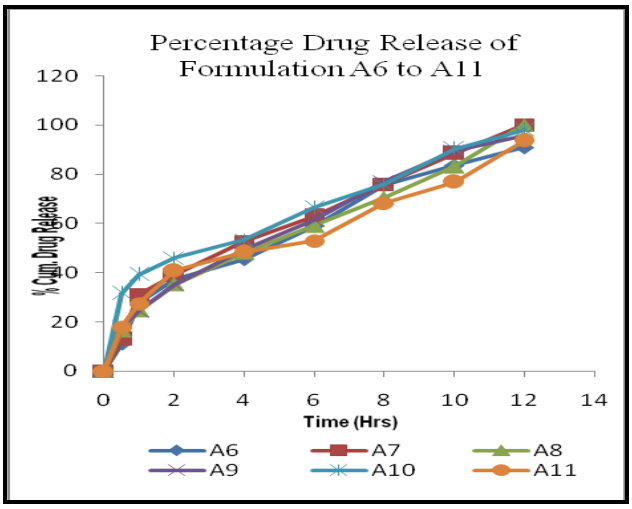


Figure: 1(b) Percentage Drug Release from the Formulation A6 to A11

For most of the formulations the R^2 value of Korsemeyer-Peppas and Zero order models is very near to one than the R^2 value of other kinetic models. Thus it can be said that the drug release follows Korsemeyer-Peppas and Zero order model mechanism.

The 'n' values of Korsemeyer-Peppas model for the best formulations were in the range of 0.45-0.85. Therefore the most probable mechanism of release was non-Fickian diffusion or anomalous diffusion. All the values are shown in Table No.3 and the corresponding graphs are represented in Fig No 2a to 2c.

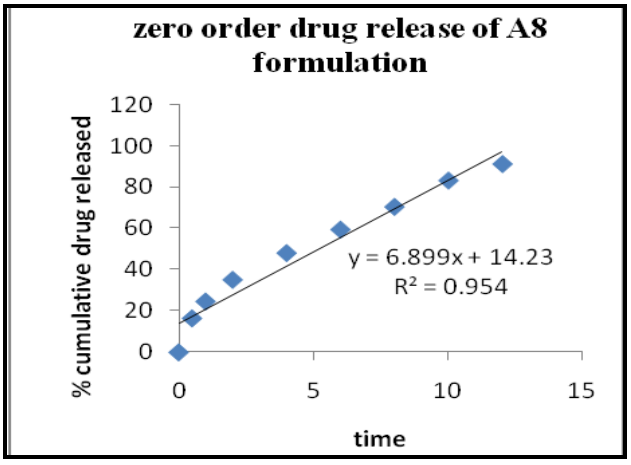


Figure: 2(a) Zero Order Release Plot for A8

Table 3: Release Kinetics of Ciprofloxacin Floating Tablets

Form Code	Zero-order	First order	Korsemeyer model		Higuchi
	r^2	r^2	N	r^2	r^2
A1	0.803	0.912	0.272	0.960	0.931
A2	0.827	0.922	0.356	0.973	0.98
A3	0.951	0.941	0.524	0.982	0.982
A4	0.934	0.774	0.491	0.989	0.991
A5	0.971	0.946	0.558	0.985	0.984
A6	0.942	0.974	0.592	0.954	0.986
A7	0.944	0.642	0.570	0.959	0.989
A8	0.954	0.865	0.527	0.997	0.996
A9	0.953	0.940	0.532	0.993	0.992
A10	0.826	0.870	0.345	0.962	0.973
A11	0.931	0.874	0.472	0.976	0.976

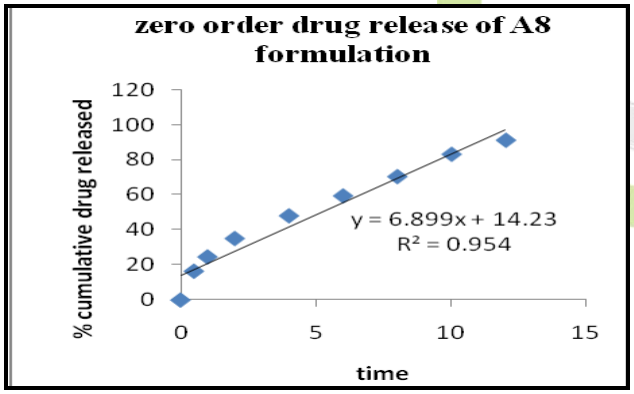


Figure: 2(b) Higuchi's Plot for A8

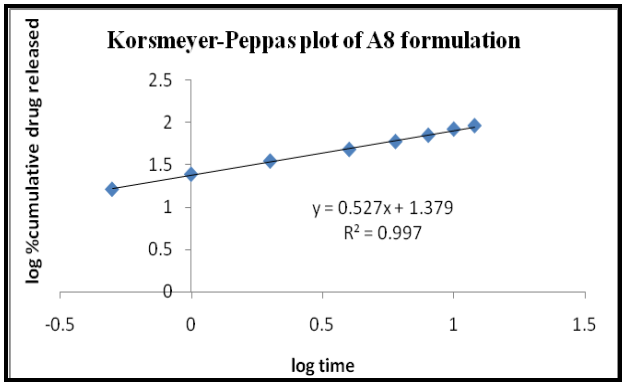


Figure: 2(c) Korsmeyer-Peppas Plot of A8

CONCLUSION

Systematic studies were conducted using different polymers in different polymers in different concentrations to manufacture Ciprofloxacin floating tablets. Controlled-release tablets of Ciprofloxacin were successfully formulated by effervescent technique. Tablet containing HPMC K4M and K15M, sodium alginate and Sodium bicarbonate (formula A7 and A8) showed satisfactory results with respect to floating lag time, total floating duration, swelling index and sustained drug release rates. The Formulation A8 was found to have maximum release profile. Higher R^2 values were obtained for zero order, Korsemeyer, Peppas (Non-Fickian release) was found to be the best fit kinetic model. Formula A8 showed better physical stability when stored at 40°C under 75% RH for 3 months. From the studies performed it was concluded that the gastro retentive floating tablets of Ciprofloxacin hydrochloride showed excellent buoyancy and sustained drug release more than 12hr and thus enhanced the bioavailability.

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