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RESEARCH ARTICLE

Pharmaceutical Development and Pharmacokinetic Evaluation of Gastroretentive Floating Matrix Tablets of Ciprofloxacin

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ABSTRACT

The most common approach for achieving sustained drug release is done by the use of hydrophilic polymers into tablets. Hydrophilic polymers swell in the presence of water to form hydrogel structures from which drugs are released in a slow pattern by the mechanism of diffusion. The purpose of this study was to prepare gastroretentive drug delivery of the fluroquinolone antibiotic, ciprofloxacin utilizing the mechanism of floating drug delivery. Ciprofloxacin is highly soluble in acidic medium and precipitates in alkaline media. The fabrication was done to enhance bioavailability of ciprofloxacin by retaining them in the acidic environment of the stomach. Tablets were prepared by the direct compression technique using polymers and gas generating agents. Tablets were evaluated for their physical characteristics such as hardness, thickness, friability, weight variation, drug content and floating properties. The developed tablets were evaluated by *in-vitro* dissolution studies. Formulations showed a floating lag time of 30 seconds and a floating time above 12 hours.

KEYWORDS

Gastro Retentive Drug Delivery System, Ciprofloxacin, *In-Vitro* Studies

INTRODUCTION

Helicobacter pylorus (H.pylori) has been recognized as a major gastric pathogen with worldwide distribution. H.pylori is the causative organism of chronic active gastritis, duodenal ulcers, and gastric adenocarcinoma. The pathogen is susceptible to many antibiotics *in-vitro*, but it is difficult to eradicate from the human body. Extended resident time of the antimicrobial agents is desirable for effective eradication of H.pylori. In order to extend the gastric residence period a number of approaches have been developed such as floating drug delivery systems, swelling and expanding systems poly metric bio adhesive systems modified shape systems, high-density system and other delayed gastric emptying devices.

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The gastroretentive floating drug delivery system has a bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system. Floating drug delivery system offer important advantages. They are less prone to gastric emptying, resulting in reduced intra- and inter subject variability in plasma drug levels, effective for delivery of drugs with narrow absorption window, require reduced dosing and increases patient compliance. Reduced C_{max} and prolonged drug levels above the minimum effective concentrations provide an improved safety profile of drugs with side-effects associated with high $C_{max.}$ The various buoyant formulations include microballon granules, powders, capsules, tablets, and laminated films.

Based on the mechanism of buoyancy, non-effervescent and effervescent systems have been utilized. Non-effervescent systems are gel-forming, highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as poly carbonate, polyacrylate, poly methacrylate and polystyrene. Effervescent systems utilize matrices prepared with swellable polymers such as methocel / chitosan and effervescent compounds such as sodium bicarbonate and citric or tartaric acids or matrices containing chambers of liquid that gasify at body temperature. Ciprofloxacin is a widely used synthetic fluorinated quinolone antibiotic. It acts by inhibiting bacterial DNA gyrase enzyme that is required for DNA replication and causes bacterial lysis. It is effective for the treatment of H.Pylori. The failure of the antibiotic therapy can be avoided by providing the effective concentration of the drug at the site of action. Ciprofloxacin has a half-life of 3-5 hours and 85% oral bio availability.

MATERIALS AND METHOD

Drug and Chemicals

Ciprofloxacin was generous gift from Euro drugs (Hyderabad, India). HPMC K4M, HPMC K15M and HPMC K100M were obtained from ISP, India. Sodium bicarbonate, Citric acid, talc and Magnesium stearate were purchased from S.D. fine chemicals Ltd (Mumbai, India). All other chemicals used were of analytical grade.

Methodology

Optimization of gas-generating agent concentration and preliminary formulations were studied to optimize the drug- polymer ratio and effervescent composition. The formulations were prepared with varying proportions like 4:1, 3:1 and 1:1 (12.5% from the total weight of the tablet) of a gas generating agent composition (sodium bicarbonate) in order to determine the composition concentration on the buoyancy behaviour.

Drug–Excipients Compatibility Study

Differential scanning calorimetry (DSC): The DSC thermo grams were recorded on a DCS (model Dsc-60, Shimadzu). Samples were heated in hermetically sealed aluminium pans over a temperature range of 10°C-300°C at constant rate of 10°C/minutes under nitrogen purge.

Fourier Transform Infra-Red Spectroscopy (FTIR): FTIR- 8400S (Shimadzu) studies were conducted to detect any incompatibility between drug and excipients. Samples were prepared in KBr disc. Data were collected over a spectral region from 4000 to 400cm^{-1}.

Preparation of Ciprofloxacin Floating Tablets

Preliminary studies were done to optimize the effervescent composition. The floating tablets were prepared with an optimized concentration of gas generating agent. The powder mixture containing drug, polymers and other excipients were weighed as per required quantity and thoroughly blended in mortar and pestle and passed through sieve No.40. The obtained unisized powder was directly compressed using 8mm flat punches on a rotary compression machine. The compression force was adjusted to obtain tablets with crushing strength in the range of 6 to 7 kg/cm^2. Seven batches of tablets were prepared by direct compression technique according to the formula shown in Table 1.

Evaluation of Powder Blend

The flow properties of the powder blend (before compression) were characterized in terms of angle of repose, tapped density, bulk density and the Carr's index and Hausner ratio.

Evaluation of Physicochemical Properties of Tablets

The tablets were evaluated for weight variation, thickness, crushing strength, friability, content uniformity, *in vitro* buoyancy properties, and *in vitro* release studies.

Weight Variation

20 tablets were selected in a random and the average weight was determined. The weights of individual tablets were compared with the average weight.

Table 1: Formulation Chart Ciprofloxacin floating tablets

Sl.No	Ingredients	Formulation Identity						
		F1	F2	F3	F4	F5	F6	F7
1	Ciprofloxacin	250	250	250	250	250	250	250
2	HPMC K 4 M	60	40	40	20	40	60	20
3	HPMC K 15 M	40	60	20	60	40	20	40
4	HPMC K 100 M	20	20	60	40	40	40	60
5	Sodium bicarbonate	100	100	100	100	100	100	100
6	Lactose	50	50	50	50	50	50	50
7	Magnesium stearate	5	5	5	5	5	5	5
8	Talc	5	5	5	5	5	5	5

*All the ingredients in tablets were in milli grams

Thickness

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using vernier calipers. The average thickness and standard deviation were recorded.

Crushing Strength and Friability

Crushing strength of tablet was determined by the Monsanto (Campbell Electronics, India) hardness tester. Friability test was carried out using a Roche friabilator. 10 tablets were weighed and subjected to the combined effect of attrition and shock by utilizing a plastic chamber. The friabilator was operated for 100 revolutions. The tablets were dedusted and re-weighed to calculate the percentage of friability.

Content Uniformity

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in a volumetric flask containing 0.1 N HCl, followed by stirring for 30 minutes. The solution was made up to 100 ml with 0.1 N HCl. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of the resultant solution was measured at 278 nm using UV-Visible spectrophotometer using 0.1N HCl as blank. The linearity equation obtained from calibration curve was used for estimation of the drug content in formulations.

In-Vitro Buoyancy Studies

The *in vitro* buoyancy was determined by floating lag time method. This was performed by placing the tablets in a 250 ml beaker containing 0.1 N HCl.The time required for the tablet to rise to the surface of the medium was recorded as floating lag time and time for the tablet remained to floating on the surface of medium was recorded as floating time.

***In-Vitro* Release Studies**

The release rate of ciprofloxacin from floating matrix tablets was determined using USP Dissolution Testing Apparatus II (Paddle method). The dissolution test was performed using 900 ml of 0.1N HCl maintained at 37 ± 0.5°C with a rotation speed of 50 rpm. Aliquots of 5 ml were collected at predetermined time intervals and replenished with equivalent volume of fresh medium.Samples were filtered through a 0.45 µ membrane filter and drug contents were determined by a UV-Visible double beam spectrophotometer at 278nm.

In Vitro Drug Kinetic Studies

There are several linear and non-linear kinetic models to describe release mechanisms to compare test and reference dissolution profiles.

Zero-Order Kinetics: This model can be used to describe the drug dissolution of several types of modified /matrix tablets with low soluble drugs, coated forms etc**.** It describes the system in which the drug release rate is independent of its concentration. Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$$Q_t = Q_0 + K_0 t$$

Q_t = amount of drug dissolved in time t

Q_0 = initial amount of drug in the solution

K_0 = zero order release constant

First Order Kinetics

This type of drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. It describes the drug release from the system in which the release rate is concentration dependent. The following relation can be used to express first-order kinetics:

$$\log Qt = \log Q_0 - K.\ t / 2.303$$

K = first order release constant

Higuchi Model

This was the most widely used model to describe release of drug from pharmaceutical matrices. This model helps to study the release mechanism of water soluble and low water soluble drugs incorporated in semi-solid and solid matrices. The mathematical expression for drug release is:

$$Q_t = K_H\ t^{1/2}$$

K_H = Higuchi dissolution constant

A linear relationship between the square root of time versus the cumulative percentage of drug released indicates that the drug release follows Fickian diffusion. The linearity of the plots can be checked by carrying out linear regression analysis and determination of regression coefficient of plot.

Korsmeyer Peppas Model

Korsmeyer developed a simple semi empirical model relating exponentially the drug release to the elapsed time (t). To verify the fact that whether the diffusion follows Fick's law or not, the drug release data can be plotted according to Peppas equation, in which log percentage cumulative release was plotted against log time. According to Peppas equation, the rate of drug release can be expressed as,

$$Q = K\ t^n$$

$$\log Q = \log K + n \log t$$

Q = fraction of drug released in time t

n = slope of log Q v/s log time

K = constant, obtained from the intercept of graphical relation between log Q v/s log t

RESULTS AND DISCUSSION

The floating tablets of Ciprofloxacin with different grades of polymers (HPMC K 4 M, HPMC K15 M, HPMC K 100 M) were prepared and evaluated. Drug and polymer compatibility studies were performed by FTIR spectroscopy. The results obtained were shown in Fig.no: 1 to 3. After interpretation of all the spectra it was confirmed that there was no shifting or disappearances of peak between the spectra of drug, polymer and drug – polymer mixture.

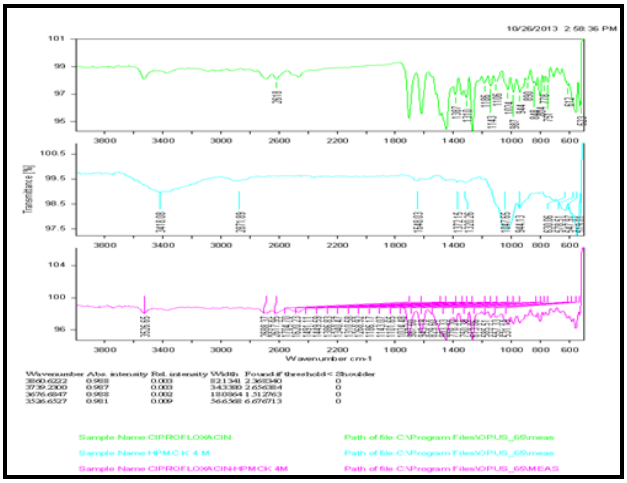

Figure 1: FTIR spectra of Ciprofloxacin with HPMC K 4 M

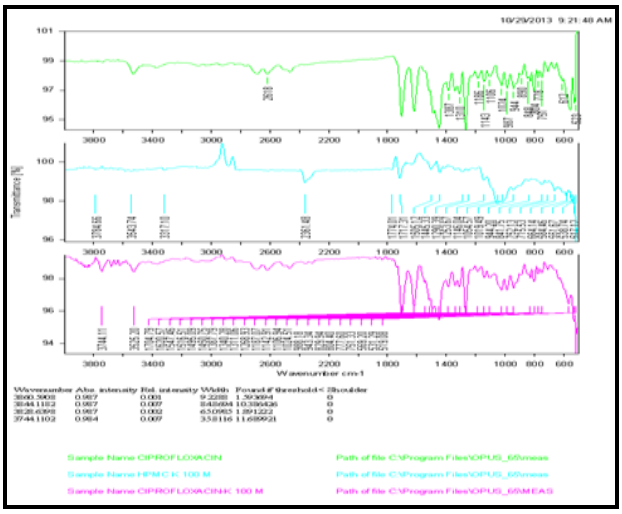

Figure 2: FTIR spectra of Ciprofloxacin with HPMC K 100 M

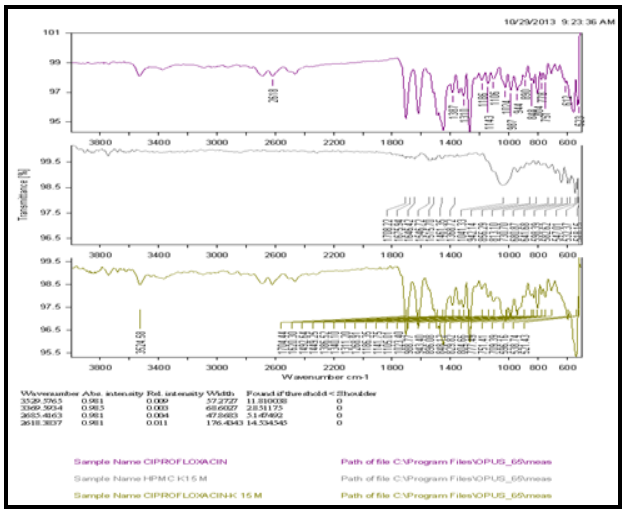

Figure 3: FTIR spectra of Ciprofloxacin with HPMC K 15 M

Table: 2 Micromeritics of powder blend

Formulation	Angle of Repose (Θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio (H_R)
F 1	26°38'	0.920	1.041	12.62	1.13
F 2	29°42'	0.916	1.110	17.47	1.21
F 3	25°08'	0.896	1.029	12.92	1.14
F 4	27°93'	0.884	1.067	13.15	1.20
F 5	25°14'	0.904	1.102	14.96	1.21
F 6	30°06'	0.857	1.015	16.56	1.18
F 7	28°98'	0.832	.998	15.63	1.1995

Table: 3 Evaluation of Physico-Chemical parameters of Ciprofloxacin floating tablets

Form[n]	Thickness (cm)	Diameter (cm)	Hardness (Kg/cm^2)	Wt. Variation (g)	Friability (%)	Density (g/cm^3)	Drug content (%)	Floating lag Time (sec)	Total floating Time (hr)	Swelling index (%)
F 1	0.56	0.92	4.5	0.527	0.75	0.9201	98.46	90	>12	17.35
F 2	0.50	0.92	4.0	0.531	0.35	0.8432	99.34	65	>12	23.83
F 3	0.52	0.93	5.0	0.526	0.38	1.002	101.09	58	>12	28.04
F 4	0.57	0.93	5.5	0.529	0.54	0.8584	98.67	110	>12	34.62
F 5	0.54	0.92	4.5	0.532	0.48	0.8864	101.25	62	>12	42.16
F 6	0.58	0.93	5.5	0.528	0.62	0.9102	98.89	74	>12	41.86
F 7	0.60	0.92	6.0	0.533	0.49	0.8996	99.63	50	>12	38.05

The angle of repose of the powder blend was carried out and the results were shown in the table no: 3. It indicates that all the batches was found to be in the range 25 °08' – 30 °0 'which indicate good flow property. Carr's index was found between 12.62 – 16.56 % indicating the powder blends have the required flow property for compression. Hausner's ratio was found to be in the range 1.13 – 1.21. It indicates good flow.

Microscopic examination of tablets was found to be circular in shape. The thickness and diameter were found to be 0.52 -0.60, 0.92 -0.93 respectively. The measured hardness of tablets of each batch ranged between 4.0 – 5.5kg/cm^2. This ensures good mechanical strength of all the batches.

The percentage friability of the tablets were found to be less than 1% in all the formulation ensuring that the tablets were mechanically stable. All the formulated tablets passed weight variation as the percentage weight variation was within the Pharmacopoeial limits of ± 5 % .The weights of all the tablets were found to be uniform with low standard deviation values .

To provide good floating behavior in the stomach, the density of the tablet should be less than that of the gastric fluid (1.004 gm/cm^3). The percentage drug content of the seven formulations was found to be between 98.46% to 101.25%, which is within acceptable limits indicating dose uniformity in each formulation. The results of floating lag time of the seven formulations were found to be between 50 – 110 sec. The total floating time of F1 and F6 formulation are more than 8 hours. Total floating time of F2, F3, F4, F5 and F7 formulations are more than 12 hours. But the F7 formulation show decrease in floating lag time and increases in total floating time.

The results of *in vitro* drug release profile of formulation F5 slow at the drug release for 12 hours. Formulation F1 ratio is 1:2:3 and F6 ratio is 2:1:3 have faster drug release of 98.98% and 99.34% respectively within 8 hours. Formulations F2, F3, F4, and F7 have their drug release of 92.78%, 93.90%, 91.44% and 96.84% within 12 hours respectively. The formulation F7 showed a reasonable drug release when compared with other formulations. Also all other parameters like weight variation, thickness, hardness, friability and drug content for these formulation was within the range. So formulation F7 was selected as the optimized formulation.

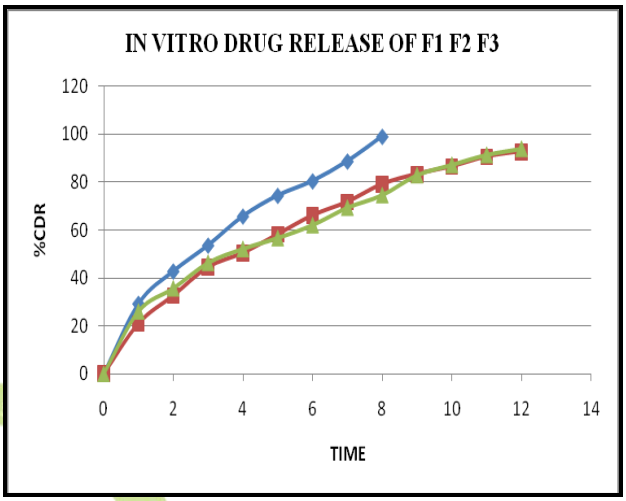

Figure 4: *In vitro* drug release of F1, F2, F3

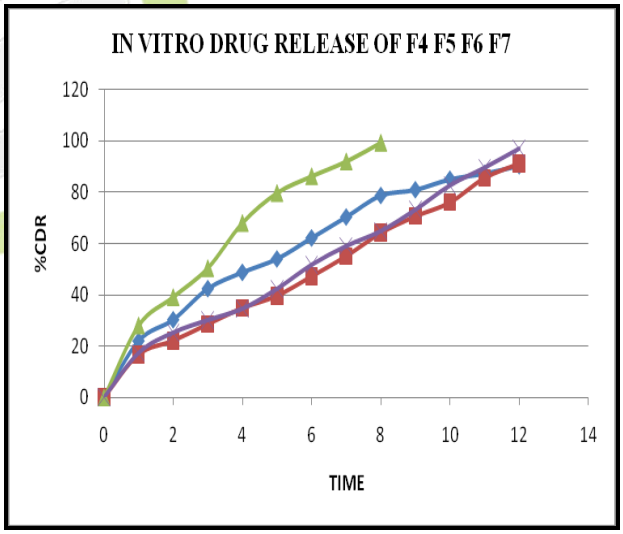

Figure 5: *In vitro* drug release of F4, F5, F6, F7

The result of kinetic drug release of formulation F7 follows zero order kinetics. The mechanism of drug release was confirmed by Higuchi and Korsmeyer peppas model. The R^2 value was highest for Korsmeyer peppas model. The value obtained was 0.973 and the n value is 0.712 hence it follows non Fickian diffusion .The R^2 value of Higuchi model obtained is 0.957 hence it follows simple diffusion process.

Table 4: Kinetic study of F7 formulation

Formulation No.	Zero order		First order		Higuchi		Korsmeyer	
F7	R^2	n	R^2	n	R^2	n	R^2	n
	0.992	7.565	0.819	0.098	0.957	33.04	0.973	33.04

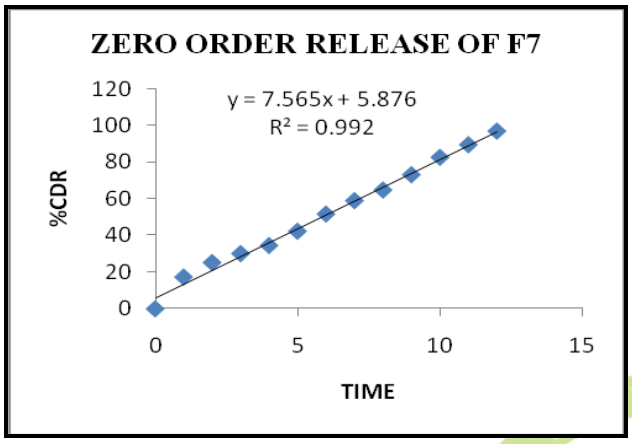

Figure 6: Zero order release of F7

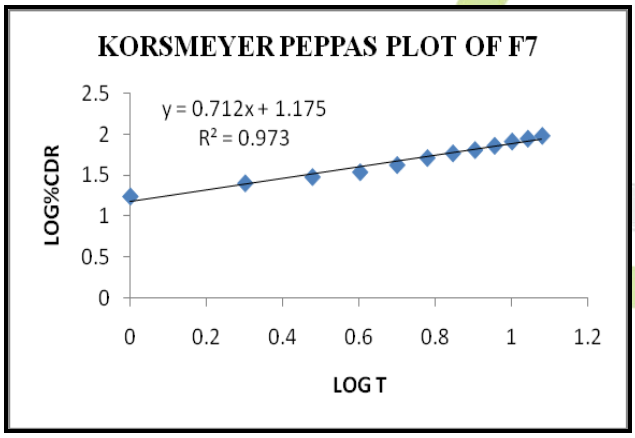

Figure 7: Korsmeyer Peppas plot of F7

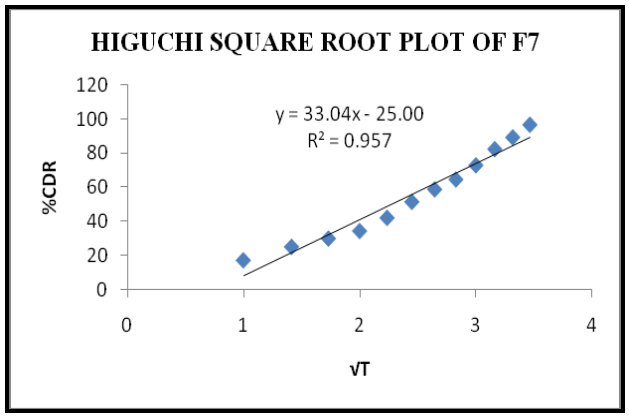

Figure 8: Higuchi Square Root plot of F7

CONCLUSION

The present study was attempted for the formulation of ciprofloxacin floating tablet with polymer HPMC of different grades. The formulations showed different flow properties and floating behavior. All the formulations of floating tablet remained buoyant for 8 to 12 hrs. Drug release kinetic performed for identifying ideal formulation and this formulation fitted best with zero order and Korsmeyer-peppas equation based on the highest R^2 value. The F7 formulation might be used for reducing the dosing frequency thereby improving the effectiveness of the drug. Based on the observation it could be concluded that the formulated floating tablet of ciprofloxacin using HPMC polymers of different grades were capable of exhibiting controlled release properties over period of 12 hours. Thus reducing frequency of dosing, thereby minimizing the occurrence of side effects, increasing residence time in stomach and increasing the effectiveness of the drug.

Hydrodynamically balanced tablets of Ciprofloxacin can be formulated with an approach to increase gastric residence and thereby improve bioavailability. An attempt to develop floating tablets of a Ciprofloxacin using sodium bicarbonate as gas generating agent and HPMC (HPMC K 4 M, HPMC K 15 M, HPMC K 100 M) as hydrophilic polymer by direct compression technique was achieved. The formulated tablets showed compliances for various physicochemical parameters like, such as weight variation, thickness, hardness, friability, drug content and tablet density .The formulation F_7 was selected as the optimized formulation indicated the floating test, swelling index and *in vitro* drug release study. Data

obtained from kinetic treatment revealed F7 formulation follows Korsmeyer – peppas model. The n value is 0.712 indicating the non Fickian diffusion. Based on the observation it could be concluded that the formulated floating tablet of ciprofloxacin using HPMC polymers of different grades (K4, K15, K100) were capable of exhibiting controlled release properties over period of 12 hours and they might reduce frequency of dosing, thereby minimizing the occurrence of side effects, increase residence time in stomach and increase the effectiveness of the drug.

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