CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1027975

Available online at: http://www.iajps.com Research Article

DEVELOPMENT AND *IN VITRO* EVALUATION OF CONTROLLED RELEASE ORAL FLOATING CAPSULES OF CIPROFLOXACIN HYDROCHLORIDE

Muqtader Mohammad*[1,5]. Farhat Fatima [1], Saad Abdullah Alharbi[1], Fahad I Al-Saikha [2], Saad Maria Alshahrani. [1], Ahmed Alalaiwe. [1], Abdullah Saud Alshetaili [1], Bader B. Alsulays. [1], Abdel-Kader MS.[3] Mohammad Javed Ansari. [1], Mohammad Khalid Anwer. [1], Mohamed Hassan Fayed. [1,] Prakash Katakam[4]

[1] Department of Pharmaceutics, College of Pharmacy Prince Sattam Bin Abdulaziz University P.O.Box 173, Al-Kharj-11942, KSA

[2]Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O.Box 173, Al-Kharj-11942, KSA.

[3]Department of Pharmacognosy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia / Department of Pharmacognosy, College of Pharmacy, Alexandria University, Alexandria, Egypt

[4] Department of Pharmaceutics, Sahyog Sewabhavi Sanstha's Indira College of Pharmacy, Nanded Maharashtra India

[5]Carbon consultants, Zaheerabad, Telangana, India, 502220

Abstract:

The aim of the present investigation was to develop the ciprofloxacin gastroretentive floating capsules by using hydrophilic rate retarding and swellable polymers. The different concentration and combination of Hydroxy Propyl Methyl Cellulose (HPMC) and carbopol 947P polymers influenced the release of the drug, the swellable matrix retained in the stomach by imbibing the CO_2 gas released. The effervescence of CO_2 generated by the sodium bicarbonate and citric acid added in 2.70 - 6.0 and 2.70 - 4.0 % w/w respectively except for formulation F4&F8. Formulation F1-F8 were prepared by adding 27 – 43.86% w/w of HPMC (F1-F4) and same % weight for carbopol swellable polymer (F5-F8). The combination of these polymers was used to prepare F9 & F10 formulation contained with 20.83% w/w of HPMC and carbopol polymers. 2.08 % w/w Sodium carbonate and 4.17% w/w of citric acid for F9 whereas F10 formulation composed of with 30.00% w/w of HPMC and 10.00 % w/w carbopol polymers, 04% w/w Sodium carbonate and 06% w/w of citric acid. The floating capsules evaluated for weight variation, content uniformity showed the acceptable results as per standards. In vitro gastric buoyancy was acceptable for the selected formulations, the order of drug released was as follows for the selected formulations F4>F10 >F9>F3>F8>F7. The optimized F9 formulation showed (70.85% drug release within 12 hours) with non –Fickian diffusion release pattern as per the applied release kinetic models. Further XRD studies revealed compatibility for the drug and polymers used in the optimized formulation F9. Thus F9 floating capsules could be a model for sustained release of the ciprofloxacin from the narrow absorption window in the stomach thereby achieving the maximum antibacterial activity and patient compliance.

Keywords: *Swellable, Floating, Ciprofloxacin, Buoyancy study, Release Kinetics.*

Corresponding author:

DR. Mohammad Muqtader Ahmed,

Associate Professor
Department of Pharmaceutics, College of Pharmacy
Prince Sattam Bin Abdulaziz University
Al-Kharj, Kingdom of Saudi Arabia
Contact No: - 00966-0506735642
Office: 0115886076
E-mail: mo.ahmed@psau.edu.sa, drmuqtaderx@gmail.com

QR code

*Please cite this article in press as Muqtader Mohammad et al , **Development and In Vitro Evaluation of Controlled Release Oral Floating Capsules of Ciprofloxacin Hydrochloride**, Indo Am. J. P. Sci, 2017; 4(10).*

INTRODUCTION:

Oral route is the robust and extensively accepted, add up to 60 % of formulation marketed are from this category [1].The retention of the dosage unit in the stomach is desirable to achieve the pharmacodynamics and pharmacokinetics benefits. Prolonged gastric retention can be achieved by high density, low density, and mucoadhesive and swelling systems [2].

Ciprofloxacin HCl is a broad spectrum, fluroquinolone antibiotics used in bone infection, respiratory tract, and urinary tract infections [3]. It has the absorption window in the stomach and proximal part at the pylorus region [4]. The matrix tablets have the drawback of lower absorption for tablet passes down to GIT [5].

Therefore the aim of this study will be retaining the drug unit at the stomach region to enhance the absorption from sustained release floating capsule with prolonged duration of antibiotic action. The plasma fluctuation could be decreased by the controlled release of drug with the use of hydrophilic rate retarding polymer (HPMC).

Controlled release of the ciprofloxacin HCl could be achieved by formulating the floating capsules with hydrophilic rate retarding and swellable (HPMC & Carbopol) polymers. The effervescence of CO_2 will be generated by the citric acid and sodium bicarbonate added in the formulation, this gas helps the dosage form to float in the stomach by imbibing in the swelling matrix. The prepared capsule will be evaluated for gastric retention (Buoyancy study), dissolution and release kinetics.

Globally there are about 375 identified generic infectious diseases of which 215 are proliferating to Saudi Arabia [6]. Therefore the floating capsules of ciprofloxacin HCl could be an efficient drug delivery for the effective treatment of drug, thereby reducing the cost of therapy and increase the patient compliance.

METHODOLOGY

Preparation of oral floating capsules

Weighted amount of ciprofloxacin HCl (250mg) is blended with hydrophilic rate retarding and swellable (HPMC & Carbopol) polymers in the different % weight ratios and combinations to get 10 formulations in three different concentrations of each polymers and its blend as showed in table -01. This blend was then mixed with gas generating effervescent agents; anhydrous citric acid and sodium bicarbonate to get the homogeneous mixture of all the ingredients. The powder material was filled in the hard gelatin capsule of # 00 size [7].

Evaluation of floating capsules

After filling the capsules with the above mentioned ingredients they were evaluated for the following parameters.

Appearance and capsules locking

The general appearance detected *viz* morphological features; size shape, colour. As the content of the capsule was filled with hand therefore after filling the capsules were evaluated for to ensure the cap is fixed with the base of the capsule and locked in the ring.

Uniformity of weight

Uniformity of dosage units' weight was performed as per USP the United States Pharmacopeial Convention report. Capsules were randomly selected from the batch and weighed on electronic balance the result was correlated with the theoretical weight of individual capsule [8]. The results showed in the table no 2.

Uniformity of content

Accurately weight about 100 mg of the formulation content and dissolved in 0.1 N HCl and volume was made up to 100 ml. The solution was filtered by Whattman filter paper # 41. The concentration was tested in UV Spectrophotometer (Jasco-V-750 UV-Visible/NIR) at 277 nm against the blank of 0.1 N HCl [9,10]. The results showed in the table no 2.

In-vitro Buoyancy study

Formulated capsules were subjected to floating study by placing the capsule in the USP Dissolution test apparatus II method with a paddle rotation of 50 Rpm and 0.1N HCl used as medium. The duration of time was assessed for all the formulation and based on the maximum floating time they were selected for further evaluated for release & kinetics studies [11]. The results showed in the table no 3 and figured in Fig 01.

In-vitro dissolution studies

In-vitro dissolution studies were performed in dissolution test apparatus II (Paddle). The dissolution medium was 900 ml 0.1 N HCl the test was performed at 37°C the rotation of paddle was 75 Rpm as per the USP specifications. The samples were withdrawn at predetermined time intervals of 0.0, 0.5, 01, 02, 03, 04 and 12 hours. 5 ml sample was withdrawn and same amount is replaced with dissolution medium to maintain the sink conditions [12]. The aliquots were then assessed for concentration of ciprofloxacin, diluted when required with 0.1 N HCl and analysed in UV Spectrophotometer at 277 nm λ max. The dissolution time profiles graphs for all formulations are figured in Fig 02.

Table 1: Formulation of Ciprofloxacin floating capsule

INGRIDIENT (mg)	FORMULATIONS CODE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ciprofloxacin HCL	250	250	250	250	250	250	250	250	250	250
HPMC K4M	100	150	200	250	-	-	-	-	100	150
Carbopol	-	-	-	-	100	150	200	250	100	50
Sodium Carbonate	10	20	30	-	10	20	30	-	10	20
Citric Acid	10	15	20	-	10	15	20	-	20	30

***In-vitro* drug release kinetics**

The release profiles of all the 6 formulations were exploited in the kinetics models viz; Zero order, First order, Higuchi and Korsmeyer-Peppas models by using MS-Excel software integrated with the respective equations of these models [13].

The mechanism of release was determined by R^2 value from each of the model for all the 6 formulations. The results showed in the table no 4.

Drug-polymer compatibility studies

XRD Studies was done by taking the diffractograms of the ciprofloxacin, polymers individually and for the optimized formulation F9. Diffractograms are pictured in Fig 03.

RESULTS:

Table 2: Uniformity of weight and content for Ciprofloxacin floating capsule

Formulation code	Calculated total weight (mg)	Accepted variation standards as per USP % weight range*	Uniformity of content %
F1	370	3.21	98.99
F2	435	1.25	99.26
F3	500	2.33	99.15
F4	570	4.25	99.48
F5	370	3.45	98.47
F6	435	2.54	99.77
F7	500	2.14	99.74
F8	570	2.24	101.0
F9	480	4.25	99.92
F10	500	3.45	99.66

*All formulation showed less than 5% weight variation

Table 3: *In-vitro* Buoyancy study

Formulation code	Total floating time (Hours)	Integrity of polymer matrix
F1	≤24	-
F2	<24	-
F3	≥24	-
F4	≥24	-
F5	≤1	-
F6	<1	-
F7	≥3.1	-
F8	≥4.9	-
F9	≥12	+
F10	>24	+

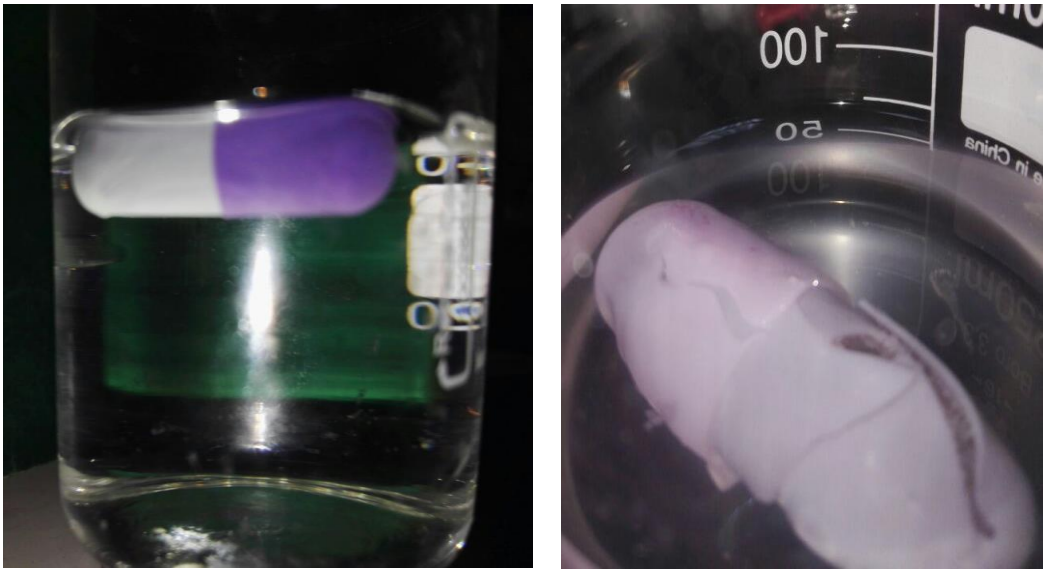


Fig 01: *In-vitro* Buoyancy study of floating capsules

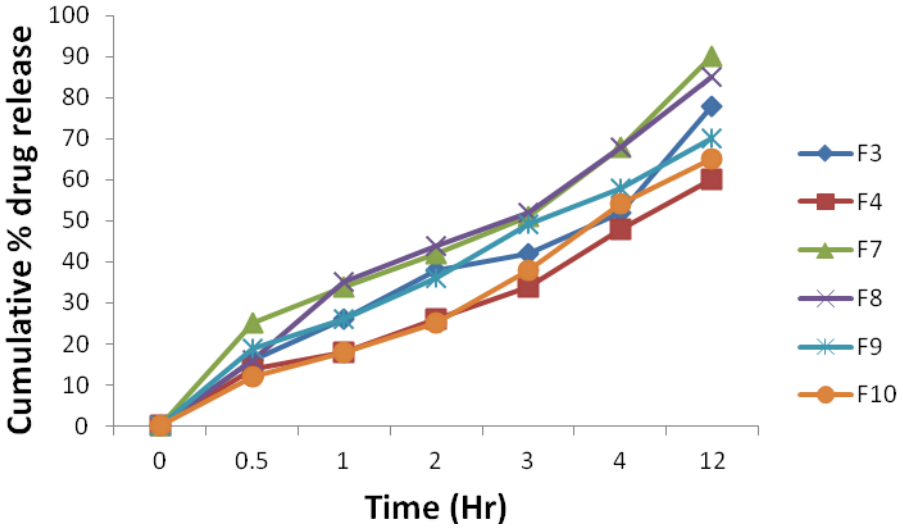
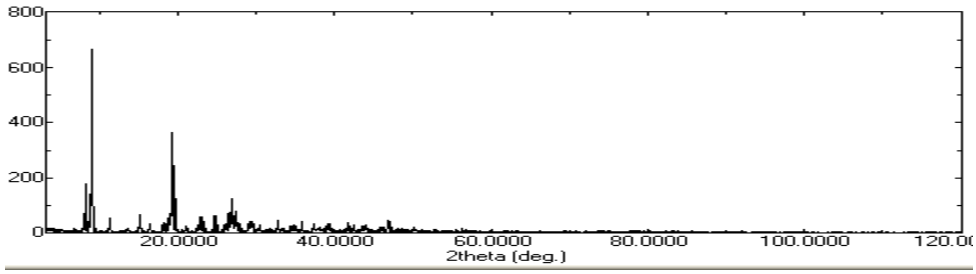


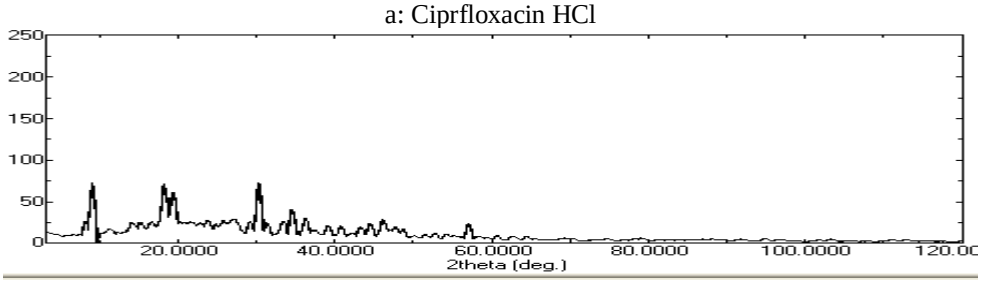
Fig 02: *In-vitro* dissolution profiles of floating capsules

Table 4: Release kinetics models of ciprofloxacin floating capsules

Kinetics Models	FORMULATION CODE					
	F3	F4	F7	F8	F9	F10
Zero Order	0.966	0.979	0.966	0.987	0.990	0.980
First Order	0.845	0.939	0.812	0.904	0.972	0.932
Higuchi matrix	0.960	0.979	0.966	0.987	0.990	0.980
Korseneyer - Peppas	0.961	0.996	0.995	0.913	0.982	0.990



a: Ciprfloxacin HCl



b: Optimized formulation F9

Fig 03:XRD diffractograms of pure drug (a) and formulation (b)

DISCUSSION:

Appearance and capsules locking

The formulation were prepared as per the standard procedure by following the cGMP and passed this test.

Uniformity of weight

The weight variation was found to be within the USP limits of < 25 % weight for the formulated capsules.

Uniformity of content

All the formulation showed the % content uniformity as per the USP standards and the % drug was found to be within the permissible limits of +/- 5%.

***In-vitro* Buoyancy study**

The total floating time was from 1 to 24 hours. It was observed that the concentration of gas generating agents plays an important role in the floating time formulation F3 & F10 contains sodium bicarbonate and citric acid in 30:20 % w/w ratios has total floating time ≥24. Formulation F4 & F8 without gas generating agents has ≥24hr and ≥4.9 hr respectively the reason could be F4 contained 43.86% HPMC K4M and F8 composed of same % of carbopol but float only ≥4.9 hours. HPMC K4M in aqueous environment lower the density of capsule units and float for prolong time.

The gas generating agents integrated with polymer matrix once reached the gastric pH starts releasing the effervescent due to CO2 generations which could forms bubbles in the matrix and helps to float the dosage unit.

***In-vitro* dissolution studies**

From the Figure -2 it was observed that the Ciprfloxacin floating capsules released 20% of the drug within 1 hour except for the formulation F4 & F10.

After 4 hours all formulation released 50% of the drug except F4 formulation consisting of 43.86: 43.86 % w/w Drug: HPMC K4M polymer ratio. The dissolution time profile plot revealed that the F3& F4 formulation consisting of 50:40 ; 43.86: 43.86 % w/w Drug: HPMC K4M polymer ratio released the drug sustained manner for more than 12 hours. Whereas F7 & F8 formulation prepared by carbopol in the same ratio released the more than 85% of drug within 12 hours.

The formulation F9& F10 prepared with combination of Drug : HPMC K4M : Carbopol in 52.08:20:20 & 50:30:10 % w/w ratios released the drug in sustained manner with integrity of polymeric matrix.

The order of drug released was as follows for the selected formulations F4>F10 >F9>F3>F8>F7.

Thus formulation F9 was considered to be the optimized one based upon its sustained release (70.85% within 12 hours) along with maximum floating by possessing its integrity.

***In-vitro* drug release kinetics**

From the table- 3 it was noted that all formulations were exhibiting Zero order sustained release due to drug –polymer integrations. Formulations F4, F7 and F10 were seen to followed the Korsmeyer-Peppas model whereas formulation F9 demonstration Zero Order & Higuchi matrix kinetic model.

Based on the above results it can be evident that formulation F9 could be considered as the optimized formulation from this study which was further confirmed for its probable mechanism of release by 'n' values of Korsmeyer–Peppas mode which was found to be 0.85. The 'n' values within the range of 0.45-0.85 indicated that F9 formulation release mechanism was non –Fickian diffusion or anomalous diffusion.

Drug polymer compatibility studies

The XRD pattern of pure drug showed in the figure also appeared on the same location in the

formulations indicating there is no crystalline interaction and ciprofloxacin and polymers diffractograms showed the amorphous pattern.

CONCLUSION:

Controlled release floating capsules released the drug in sustained manner due to HPMC K4M the rate retarding polymer and could float at the target site (Stomach) for more than 24 hours by carbopol swelling polymer. Gas generating agent further supports the prolong floating with short lag time by CO_2 gas generation resulting the dosage unit to retain in the stomach. Thus this could be beneficial in enhancing the bioavailability of the drug due to its absorption window at the target site. Henceforth the effectiveness of treatment and patient compliance could be improved with the proposed F9 ciprofloxacin floating capsule.

ACKNOWLEDGMENT

Investigators of this study are thankful to Dr. Ramadan Al-Shdefat for providing the drug gift sample, empty capsules and other necessary accessories used to carry out this research.

REFERENCES:

1.Sirisolla, J., & Ramanamurthy, K. Formulation and evaluation of cefixime trihydrate matrix tablets using HPMC, sodium CMC, ethyl cellulose. Indian Journal Of Pharmaceutical Sciences,2015; 77(3): 321.

2.Pawar, V., Kansal, S., Garg, G., Awasthi, R., Singodia, D., & Kulkarni, G. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug Delivery, 2010;18(2): 97-110.

3. National Center for Biotechnology Information. PubChem Compound Database; CID=2764, https://pubchem.ncbi.nlm.nih.gov/compound/2764 (accessed Apr. 17, 2017).

4.Mandal, U., Chatterjee, B., & Senjoti, F. Gastro-retentive drug delivery systems and their in vivo success: A recent update. Asian Journal Of Pharmaceutical Sciences,2016; 11(5): 575-584.

5.Arza, R., Gonugunta, C., & Veerareddy, P. Formulation and Evaluation of Swellable and Floating Gastroretentive Ciprofloxacin Hydrochloride Tablets. AAPS Pharmscitech, 2009;10(1): 220-226.

6. Infectious Diseases of Saudi Arabia - GIDEON - Global Infectious Diseases and Epidemiology Online Network. (2017). GIDEON - Global Infectious Diseases and Epidemiology Online Network. Retrieved 17 April 2017, from https://www.gideononline.com/ebooks/country/infectious-diseases-of-saudi-arabia/

7.Smriti Khatri, Farhan Jalees Ahmed, Pallavi Rai. Formulation and evaluation of floating gastroretentive capsules of acyclovir with piperine as a bioenhancer. The Pharma Innovation Journal; 2015;3(11): 78-81

8.Banker GS, Anderson NR; Tablets: Lachman L,Lieberman HA, Kanig JL; The Theory and Practice of Industrial Pharmacy. 3rd edi, Varghese Publication House, Bombay, 1987; 296-303.

9.Shakya, R., Thapa, P., & Saha, R. In vitro and in vivo evaluation of gastroretentive floating drug delivery system of ofloxacin. Asian Journal Of Pharmaceutical Sciences,2013; 8(3), 191-198

10.Indian Pharmacopoeia. Publications and information directorate (CSIR). New Delhi, 1996, Vol II, 179-183, 662-663.

11.Zeenath S, Ramesh Gannu, Suresh Bandari and Madhusudan Rao Y;Development of gastroretentive systems for famotidine: in vitro Characterization. Acta Pharmaceutica Sciencia ;2010;52: 495-504

12.Aulton ME, Wells TI. “Pharmaceutics: The Science of Dosage Form Design”, London,England: Churchill Livingstone; 1988.

13.MM Ahmed et al. Equivalent Assessment of Ciprofloxacin Tablets Available in KSA : A Post Market Surveillance Study for Cost Effective Treatment J. Pharm. Sci. & Res. Vol.2016; 8(1):13-18.