



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)

Platform for Pharmaceutical Researches & Innovative Ideas

www.ijprd.com

FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF CIPROFLOXACIN

Bhalchandra M. Habade^{*1},
Vidyashri Kamble¹, R. Ramesh² Milind P.Wagh³

¹Shivajirao S. Jondhale College of Pharmacy, Aasangaon-421601 Dist:-Thane, State: - Maharashtra, India.

²Dr. H.L.T. College of Pharmacy, Kengal, Channapatan, Bangalore.

³Department of Pharmaceutics, NDMVPS's College of Pharmacy, Department of Pharmaceutics, Shivajinagar, Gangapur Road, Nashik-422002, India.

ABSTRACT

Gastric retention drug delivery systems can be retained in stomach for a long time such retention systems are important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics, enzymes that should act locally in the stomach such systems are more advantageous in improving GI absorption of drug with narrow absorption windows as well as for controlling release of drugs having site specific absorption limitation. Retention of drug delivery system in the stomach prolongs overall GI transit time, there by resulting in improved bioavailability for some drug. Present investigation highlights the formulation and optimization of floating tablet of Ciprofloxacin. Ciprofloxacin is the first generation fluoroquinolone. In present investigation three different viscosity grades of Methocel namely Methocel K4M, Methocel K15M, Methocel K100M were used in different concentrations. Tablet was formulated as a floating tablet using gas-generating agent Sodium bicarbonate. Formulation was optimized on the basis of floating time and in vitro drug release. Dissolution profile were subjected various kinetic drug release equation. The tablet were subjected to evaluation for physical characteristics like weight variation, hardness, friability, drug content uniformity, floating lag time, floating time and in vitro drug release. Formulation containing Methocel K100M (M 9) showed desired duration of floating time (10hrs.) and drug release at the end of 10 hrs. Hence, it is evident from this investigation that gas powered floating tablet could be promising drug delivery system for Ciprofloxacin and improved drug availability.

Keywords: Ciprofloxacin, Floating drug delivery system, Gas generating agent, Methocel, Gastro Retentive Drug Delivery System.

Correspondence to Author



Bhalchandra M. Habade

Shivajirao S. Jondhale College of Pharmacy, Aasangaon-421601 Dist:-Thane, State: - Maharashtra, India.

Email: bmhabade@gmail.com

INTRODUCTION

Gastro Retentive Drug Delivery System^[1, 2]:

Oral route of administration is the most important and convenient route for drug delivery. The benefits of long-term delivery technology have not been fully realized for dosage forms design for oral administration. This is mainly due to the fact that the extent of drug absorption from GIT is determined by GI physiology, irrespective of the controlled release properties of the device. Although differential absorption from various regions of GI has been known for decades, only recently drug delivery systems have been designed to target drugs to differential regions of GIT. This includes gastro retentive systems, delayed release system and colon targeting.

Oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localized the drug delivery system within desired regions of GI tract and highly variable natures of gastric emptying process. It can be anticipated that, depending upon the physiological state of subject and design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hr. The relatively brief gastric emptying time in humans, which normally averages 2-3 hr. through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the drug delivery system leading to diminish efficiency of the administered dose. Thus control of placement of a drug delivery system in a specific region of GI tract offer numerous advantages, especially for drug with stability problem. Overall, the intimate contact of the drug delivery system with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to development of oral controlled release dosage forms possessing gastric retention capabilities.

The real issue in the development of oral controlled release dosage form is not just prolonging the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in small intestine. For instance, these will significantly extend the period of time over which drug may be released, and thus prolonged dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage form.

GRDF will also greatly improve the pharmacotherapy of stomach itself through local drug release leading to high drug concentration at the gastric mucosa, which is sustained over long period of time. For example, eradication of *Helicobacter Pylori*, which requires the administration of various medications several times a day according to complicated regimen and which frequently fails as a result of insufficient patient compliance, could perhaps be achieved more reliably using GRDF to administered smaller drug doses for fewer times.

The main objective of developing these systems is to increase the safety of product to extend its duration of action. Floating tablet of quinolone antibacterial agent like Ciprofloxacin was prepared with the aim to reduce bacterial colony by delivery of the drug in the upper gastrointestinal tract. Current therapy involves administration of proton pump inhibitor or surgery, in either case any bacterial colony might not reduce therefore there is strong need to deliver broad spectrum antibiotics like Ciprofloxacin, which can deliver the drug to the stomach and has long resident time in the gastric pouch. Buoyant tablet are one such a dosage form, which floats in gastric fluid for a longer time and delivery the drug in to the upper Gastrointestinal Tract (GIT), hence this work, is planned to deliver antibiotics like Ciprofloxacin as a floatable tablet. Selection of the best formulation based on using evaluation parameters like floating lag time, total floating time and release profile.

METHODOLOGY

MATERIALS

Ciprofloxacin received as a gift sample from Cipla pharmaceuticals Ltd., Verna estate Goa. The polymers Methocel K4M, Methocel K15M, Methocel K100M were received as a gift sample from Colourcon Asia pvt. Ltd. Goa, India. Magnesium stearate, Sodium bicarbonate and citric acid anhydrous were purchased from S.D. fine chemicals Ltd. Ahmedabad, India, Lactose and purified talc were purchased from E. Merk (India) Ltd. Mumbai.

Preparation of Ciprofloxacin floating tablets:

The composition of different formulations of floating tablets is shown in Table 1. The tablet contains uniform mixture of drug, polymer and other excipients including gas-generating agent. The tablets were prepared by direct compression technique.

Weighed quantity of drug, polymer, diluents and Sodium bicarbonate as given in Table no.1 were mixed properly in mortar. Then powder were passed through # 60 and blended thoroughly in PVC bags for 10 min. The well-mixed powder equivalent to 500 mg was compressed using a ten-station rotary tablet compression machine (Rimek Minipress).

Flow properties of Powder were characterized in term of angle of repose, Carr's index. For determination of angle of repose (θ)

The powders were poured through the wall of funnel, which was fixed at a position such that its lower tip was at height of exactly 2.0 cm above hard surface. The granules were poured till the time when upper tip of pile surface touched the lower tip of the funnel. The \tan^{-1} of the (height of the pile /radius of its base) gave the angle of repose.

Powders were poured gently through a glass funnel in to a graduated cylinder cut exactly 10 ml mark. Excess powders were removed using spatula and the weight of cylinder with powder require for filling the cylinder volume was calculated. The cylinder was then tapped from a

height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρ_b) and tapped density (ρ_t) were calculated. Carr's index calculated according to the equation given below.

$$\% \text{ Compressibility} = (\rho_t - \rho_b) / (\rho_t) \times 100$$

Evaluation of floating tablet

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets^[3], Hardness (Monsanto tester)^[4], friability using 10 tablets (Roach type friablator)^[4] drug content, *In vitro* buoyancy^[5] and in vitro dissolution studies. The result are expressed as mean \pm S.D. (n=3). The *In vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et. al.*^[5] The tablets were placed in a 100 ml beaker containing 0.1 N Hydrochloric acid. The tablet required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

The drug content in each formulation was determined by triturating 10 tablets. A quantity of triturate equal to 100 mg of Ciprofloxacin was dissolved in 0.1 N HCL in 100ml volumetric flask. The so formed sample was diluted and the absorbance was measured at 276 nm using 0.1 N HCL as blank.

The release rate of Ciprofloxacin from floating tablet was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900ml of 0.1N HCL, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 9 hrs, and samples were replace with fresh dissolution medium. The samples were filtered through Whatman filter paper no.41. Absorbance of this solution was measured at 276 nm. Cumulative percent drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Table no.1 Formulation of floating tablet. (All ingredients were taken in percentage milligrams of tablet weight 500mg.)

Ingredients	Formulation code.								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Drug	40	40	40	40	40	40	40	40	40
Methocel K4M (%)	15	20	30	-	-	-	-	-	-
Methocel K15M (%)	-	-	-	15	20	30	-	-	-
Methocel K100M (%)	-	-	-	-	-	-	15	20	30
Microcrystalline cellulose (%)	29	24	14	29	24	14	29	24	14
Sodium bicarbonate	15	15	15	15	15	15	15	15	15
Magnesium stearate	1	1	1	1	1	1	1	1	1

Flow Properties of powder

The powder for compression of floating tablets was evaluated for their flow properties. Powder of floating tablet showed angle of repose from 22.76 ± 3.05 to 26.14 ± 2.57 , Carr's index from $11.53 \pm$

0.26 to 23.09 ± 0.60 Data given in the Table No. 2 indicates that as concentration of Methocel increases in tablets, angle of repose and Carr's index were increases.

Table No.2 Evaluation of powder of floating tablet. *Each sample was analyzed in triplicate (n=3)

Sr. No.	Formulation Code.	*Angle of Repose (θ) S.D. \pm	*Bulk Density (gm/cm^3) S.D. \pm	*Tapped Density (gm/cm^3) S.D. \pm	* % Carr's Index S.D. \pm
1	M 1	23.43 ± 1.26	0.928 ± 0.015	1.049 ± 0.016	11.53 ± 0.26
2	M 2	24.35 ± 0.68	0.920 ± 0.023	1.056 ± 0.024	12.87 ± 0.35
3	M 3	25.15 ± 2.69	0.914 ± 0.058	1.085 ± 0.032	15.76 ± 0.24
4	M 4	22.76 ± 3.05	0.915 ± 0.018	1.047 ± 0.025	12.60 ± 0.67
5	M 5	23.30 ± 1.84	0.899 ± 0.044	1.055 ± 0.015	14.76 ± 0.84
6	M 6	24.67 ± 1.9	0.924 ± 0.010	1.088 ± 0.023	15.07 ± 0.79
7	M 7	23.65 ± 2.10	0.795 ± 0.024	0.978 ± 0.045	18.71 ± 0.56
8	M 8	24.80 ± 2.35	0.764 ± 0.032	0.985 ± 0.038	22.43 ± 0.36
9	M 9	26.14 ± 2.57	0.789 ± 0.018	1.026 ± 0.020	23.09 ± 0.60

Evaluation of floating tablet

Tablet Thickness and Diameter (Table No.3)

Diameter and Thickness of formulations M 1 to M 9 varying from 11.0 to 10.7 mm and 4.1 to 4.6 mm, respectively.

Tablet Hardness (Table No.3)

Hardness of tablets of each formulation was measured and found in the range of 4.75 to $5.10 \text{kg}/\text{cm}^2$.

Friability (Table No.3)

Percentage weight loss of the tablets (Table No.3) of each formulation was measured and found in the range of 0.1805 ± 0.0042 to 0.5023 ± 0.0182 %

Table No.3 Evaluation of floating tablet. *each sample was analyzed in triplicate (n=3)

Sr. No.	Formulation Code.	Thickness mm	Diameter mm	Hardness Kg/cm ²	*Friability(%)S.D.±
1	M 1	4.4	11.0	4.85	0.2415 ± 0.0121
2	M 2	4.1	11.0	4.80	0.3205 ± 0.0201
3	M 3	4.5	10.8	5.10	0.4665 ± 0.0154
4	M 4	4.3	10.7	4.75	0.3210 ± 0.0142
5	M 5	4.2	10.9	5.10	0.2801 ± 0.0098
6	M 6	4.3	11.0	4.80	0.3315 ± 0.0210
7	M 7	4.4	11.0	4.95	0.4085 ± 0.0101
8	M 8	4.6	11.0	5.00	0.1825 ± 0.0042
9	M 9	4.5	11.0	4.80	0.5013 ± 0.0182

- Uniformity of weight (Table No.4)

Tablet from each batch showed uniformity of weight as per IP limits.

- Uniformity of content (Table No.4)

Tablet from each batch showed uniformity of content as per IP limits.

Table No.4 Weight variation of tablet. *each sample was analyzed in triplicate (n=3)

Sr. No.	Formulation Code.	Weight of the tablet (%Deviation±)	*Drug Content
1	M 1	495 ± 0.4542	98.14 ± 3.01
2	M 2	494 ± 0.3212	97.26 ± 2.22
3	M 3	501 ± 0.1021	98.41 ± 1.77
4	M 4	497 ± 0.5201	97.37 ± 2.01
5	M 5	495 ± 0.3257	98.91 ± 2.15
6	M 6	486 ± 0.6544	97.51 ± 2.26
7	M 7	492 ± 0.7782	97.74 ± 1.89
8	M 8	510 ± 0.1323	97.63 ± 2.48
9	M 9	499 ± 0.1432	97.82 ± 2.41

- Floating Lag Time (Table No.5)

The values of buoyancy lag time for different batches were given in Table No. 5. The buoyancy lag time of tablets depends on amount of sodium bicarbonate involved in CO₂ formation. For the floating system the ideal matrix or coating material should be highly permeable to dissolution media in order to initiate rapid generation of CO₂ and should be permeable for CO₂ to promote floating.^[6]

Formulation M1 to M9 showed buoyancy lag time ranges from 120 to 154 sec.

Results indicate that FLT was found to be decrease with increase in the concentration of Methocel with in all tablet formulations.

- Floating time^[7] (Table No.5)

Floating time was found to be dependent on Methocel content. Methocel was swelling polymer and degree of gelling and gel strength determines its buoyancy. Tablets showed floating time over 12 hrs. This finding was in good agreement by study of Li and co-workers^[8] who reported that Methocel of higher viscosity grade generally exhibited greater floating capability.

Table No.5 Floating Lag Time and Floating time of Formulation

Sr. No.	Formulation Code.	Floating Lag Time (Sec.)	Floating Time (Min.)
1	M 1	140	365
2	M 2	151	424
3	M 3	165	475
4	M 4	120	378
5	M 5	144	440
6	M 6	150	460
7	M 7	134	380
8	M 8	146	485
9	M 9	154	475

- Swelling Characteristics (Table No. 6)

The percentage water uptake of the formulations M1 to M9 ranges 113.55 to 198.00 %. The percentage water uptake was found to be improved by increasing concentration of Methocel Table No.6 Swelling Characteristics of Floating Tablet

in the formulation. Thickness and diameter was found to be increased in swelling characteristics study. Table No. 6 showed swelling characteristic value of Floating tablets.

Batch	Initial Weight	Initial Thickness	Initial Diameter	Final Weight	Final Thickness	Final Diameter	Swelling Index
M1	501.63 ± 2.00	4.4	11.08	787.36 ± 3.24	6.53	14.43	113.55
M2	502.53 ± 1.33	4.1	11.04	845.46 ± 4.36	6.2	14.44	135.80
M3	501.06 ± 2.45	4.5	11.05	883.58 ± 2.76	6.57	14.48	152.36
M4	501.66 ± 1.89	4.3	11.10	792.2 ± 0.46	6.17	14.49	115.44
M5	502.56 ± 2.11	4.2	11.06	815.1 ± 4.25	6.19	14.62	123.74
M6	503.13 ± 1.24	4.3	11.14	847.66 ± 2.94	6.47	14.71	136.11
M7	502.5 ± 1.34	4.4	11.04	925.06 ± 4.16	7.43	14.74	167.35
M8	502.26 ± 1.50	4.6	11.04	947.6 ± 5.64	7.69	14.84	176.54
M9	502.03 ± 1.68	4.5	11.04	1001.06 ± 4.96	7.54	15.11	198.00

Dissolution Profile (Table No.7)

Available online on www.ijprd.com

Floating tablets were prepared by using three viscosity grades of Methocel. Almost 9 formulations were prepared by using three different concentration of each viscosity grade of Methocel. In all formulation it was observed that the release rate of drug was a function of Methocel K4M, Methocel K15M and Methocel K100M content. An increased in polymer concentration, induce a decrease in the release rate. High concentration of Methocel resulting in the more gel formation and forms a gelatinous barrier, which may retard drug release in the formulation M3, M6 and M9 (i.e.30% Methocel Conc.) Ratio of Methocel in the matrix was the key factor in the controlling the drug release in all formulations. As

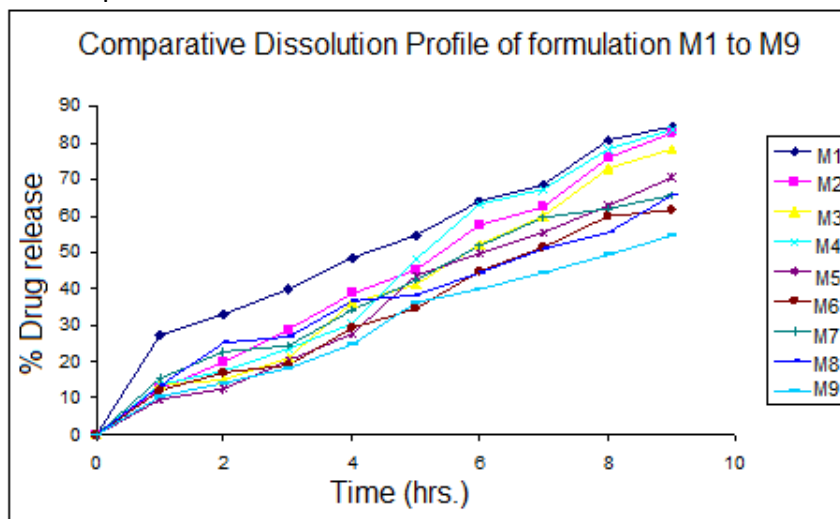
seen from figure no.1 the higher the ratio of Methocel, slower the drug release was observed.

As expected the drug release was dependent on the concentration of Methocel in all formulation. In the batches M1 to M3, formulation M1 showed all 84.157 % release and formulation M3 showed 78.094% release in 9 hrs. The t_{50} % and t_{70} % values were given in the Table No.7 In the batches of Methocel K15 M, formulation M4, M5 to M6 showed 83.281%, 70.583%, and 61.47% respectively. The t_{50} % and t_{70} % values were given in Table No.7. Formulation containing Methocel K100M (M9) showed desired duration of floating time (10hrs.) and drug release at the end of 10 hrs.

Table No.7 Dissolution Profile and T_{50} %, T_{70} % for Floating Tablet *each sample was analyzed in triplicate (n=3)

Time (Hrs.)	% Release (\pm S D)								
	Formulation Code.								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
1	27.10 \pm 1.93	12.54 \pm 2.27	13.96 \pm 3.30	13.85 \pm 1.53	9.73 \pm 3.36	12.42 \pm 2.10	15.29 \pm 1.1	13.25 \pm 3.65	10.54 \pm 1.85
2	33.17 \pm 2.96	19.979 \pm 3.07	15.015 \pm 2.82	17.382 \pm 1.99	12.643 \pm 2.45	17.243 \pm 1.60	22.646 \pm 3.98	25.339 \pm 1.14	14.325 \pm 2.47
3	39.80 \pm 1.2	28.96 \pm 1.1	21.023 \pm 2.89	23.64 \pm 2.5	20.48 \pm 1.26	18.985 \pm 1.23	24.51 \pm 2.14	26.89 \pm 0.66	18.26 \pm 1.02
4	48.53 \pm 2.11	38.525 \pm 2.19	36.049 \pm 2.99	30.447 \pm 2.54	27.844 \pm 2.90	29.49 \pm 1.84	34.197 \pm 2.67	36.801 \pm 2.34	24.711 \pm 1.45
5	54.40 \pm 1.7	45.23 \pm 3.12	41.33 \pm 1.33	48.23 \pm 2.32	43.48 \pm 1.47	34.47 \pm 1.36	42.21 \pm 2.56	38.45 \pm 3.2	36.25 \pm 1.24
6	63.816 \pm 3.0	57.34 \pm 1.32	52.189 \pm 3.02	63.259 \pm 3.34	49.792 \pm 1.21	44.912 \pm 1.15	51.76 \pm 1.14	44.323 \pm 2.71	39.905 \pm 1.85
7	68.233 \pm 2.13	62.35 \pm 2.35	59.89 \pm 1.63	67.38 \pm 3.0	55.32 \pm 1.85	51.22 \pm 1.65	59.38 \pm 2.54	50.74 \pm 3.56	44.32 \pm 2.33
8	80.555 \pm 2.16	75.688 \pm 2.10	72.781 \pm 3.97	78.321 \pm 2.55	62.631 \pm 2.78	59.938 \pm 1.72	61.709 \pm 2.24	55.55 \pm 3.83	49.461 \pm 1.18
9	84.157 \pm 3.05	82.817 \pm 2.62	78.094 \pm 2.28	83.281 \pm 2.67	70.583 \pm 1.12	61.47 \pm 2.64	65.387 \pm 1.07	65.618 \pm 4.40	54.523 \pm 1.59
T_{50} %	4.1149	5.4072	5.1247	4.4758	6.1595	7.1458	5.5127	7.3931	7.7147
T_{70} %	6.2706	7.3027	7.1399	6.1251	8.4398	>9	>9	>9	>9

Fig No.1 Comparative Release profile of formulation M1 to M9



CONCLUSION

The present investigation carried out to develop a Gastro retentive drug delivery dosage form for Ciprofloxacin. Several approaches are currently utilized in the prolongation of the Gastric residence time, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, high density systems, modified shape systems, and other delayed gastric emptying devices. In this present work attempt to prepare Floating drug delivery with prolong gastric residence time. Various Gastric retention systems are useful for drugs that have local effect in the stomach. The release of Ciprofloxacin from the formulations is proportional to the concentration of polymers. As the concentration of polymers increases, the drug release rate decreases. Result of the study based on in vitro performance clearly suggests that sustain release floating tablet can be prepared by incorporating sodium bicarbonate as a gas generating agent in Methocel polymer with different grade. Higher the bicarbonate concentration, faster is the drug release and shorter is the floating lag time and floating duration. On increasing the hardness of tablets resulted in significant increased in floating lag time.

Available online on www.ijprd.com

REFERENCES

1. Singh B N, Kim K H. Floating Drug Delivery System: An approach to oral controlled Drug Delivery via Gastric Retention .J. Control. Rel, 63,2000,235-259
2. Vyas S P, Khar R K, In; Controlled drug delivery concepts and advances. 1st Edn. Vallabh Prakashan, Delhi 2002. 196
3. Indian Pharmacopoeia, The Controller of Publications: Delhi, Vol. II, 1996, 734-736.
4. Banker, G.S.; Anderson, N.R. In The Theory and Practice of Industrial Pharmacy, Lachmann, L., Liberman, H.A.; Kaing, J.L. Eds. Varghese Publishing House: Bombay, 1987, 297-99.
5. Rosa, M.; Zia, H.; Rhodes, T. Int. J. Pharm., 105, 1994 65-70,
6. Gerogiannis V S, Rekkas D M, Dallas P P, Choulies N H Drug Dev. Ind. Pharm.,19(9): 1993, 1061-108.
7. Zhenping Y, Dianzhou B, Zhanfeng Y. Design and evaluation of a two layer floating tablet for gastric retention using Cisapride as a model drug. *Drug Dev Ind Pharm.* 27(5): 2001, 469-474
8. 7. Li. s., Lin, S., Chien Y. W., Daggy B.P., and Michandani H.L., Pharm. Sci. Tech., 2,2001,1

9. De Carli C, Murphy DG, Tranh M, Grady CL, Haxby JV, Gillette JA. J Neurology 1995; 45: 2077.
