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Development and *in vitro* Evaluation of an Oral Floating Matrix Tablet Formulation of Ciprofloxacin.

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Recently many drugs are formulated as floating drug delivery systems with an objective to sustain release and restrict the region of drug release to stomach. The intensive research of recent past has resulted in the development of five commercial floating drug delivery systems. Ciprofloxacin, which is better absorbed in stomach and upper small intestine was formulated as floating matrix tablet using gas generating agent (sodium bicarbonate) and hydrophilic polymer (hydroxypropylmethycellulose). Formulation was optimized on the basis of floating time and *in vitro* drug release. Two batches of fabricated tablets containing ciprofloxacin (580 mg), sodium bicarbonate (200 mg), hydroxypropylmethylcellulose-K100M (100 mg), lactose between 9.7-12% and polyvinyl pyrrolidone 4.8% with hardness between 14-14.6 kg/cm² showed desired duration of floating (8 h or more). *In vitro* drug release study of these tablets indicated controlled sustained release for ciprofloxacin and 80-89% release at the end of 8 h. Hence, it is evident from this investigation that gas powered floating matrix tablet could be promising delivery system for ciprofloxacin with sustained release action and improved drug availability.

The most convenient method of controlled delivery of drug is undoubtedly oral, but oral controlled release for extended period of time of drug, that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. In an attempt to develop sustained release forms of drugs that are either absorbed in stomach and upper small intestine or poorly soluble or and unstable in intestine, research has been made during recent years to use only stomach as a depot due to difficulty to place oral dose at the selected sites in small intestine. Consequently, most research efforts have been focused on platforms to extend gastric residence time (GRT) of these drugs. The underlying principle of gastric retentive system (GRS) is simple. The aim is to prolong release and restrict the region of delivery to stomach. The floating drug delivery approach is one of the currently utilized methods in the prolongation of GRT. All floating dosage forms have the common property of possessing density lower than that of gastric fluids so that they can float in the stomach for a prolonged period of time. Emptying is not completed until the level of gastric fluid approaches the base of the stomach.

However, by the very physiological nature, gastric emptying rate imposes constrains on the presence of food and fluid in the stomach. A number of research works have shown that the GRT of floated dosage form significantly increases under fed state[1-3]. Nonetheless overcoming physiological adversities, such as shorter GRT and unpredictable gastric emptying time is possible utilizing gas generating component in the formulation to achieve the desired low density. It has been reported that gas generation can be used in multiple unit floating dosage form for GRS with an added advantage of retaining longer period in stomach[4,5]. In the present study, gas powered system has been selected to control the delivery of ciprofloxacin hydrochloride for longer period in the stomach from floating drug delivery system.

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Ciprofloxacin hydrochloride, a fluoroquinolone antibacterial, is widely absorbed from the stomach and upper part of the small intestine. Oral bioavailability is approximately 70% and a peak concentration of about 2.5 μg/ml is achieved 1 to 2 h after a dose of 500 mg by mouth[6]. Absorption becomes less as the drug passes beyond this. The bioavailability of the drug can be improved by making the drug completely absorbed in the stomach and upper small intestine. The objective of this present investigation was to formulate floating matrix tablet of ciprofloxacin hydrochloride using gas generating component with set limits of dissolution profile and minimum floating ability for 8 h. We attempted to formulate to retain the matrix tablet substantially monolithic form in the stomach and subsequently to provide delivery of the drug over the period of time of GRT.

MATERIALS AND METHODS

Ciprofloxacin hydrochloride was obtained from Dr. Reddy's Laboratories Ltd., Hyderabad. Methocel K100M, a grade of hydroxypropylmethylcellulose was purchased from Colorcon Asia Pvt. Ltd., Mumbai, PVP K30 (polyvinyl pyrrolidone K-30) was procured from Coverlal Company, Chennai. Materials and excipients used in preparing matrix tablets were IP grades. All other ingredients were of analytical grades and were used as procured.

Formulation of ciprofloxacin hydrochloride floating tablets:

Floating tablets of ciprofloxacin hydrochloride were prepared by wet granulation method using sodium bicarbonate as gas generating agent and a water soluble polymer (suitable grade of HPMC) as hydrophilic matrix in each formulation. The composition of formulation is given in Table 1 and 2. The composition with respect to polymer was selected based on trial preparation of tablets (with HPMC K4M), that did not float more than 2 to 3 h. Hence higher viscous variety of HPMC (Methocel K100M) was chosen. The concentration of gas generating agent (sodium bicarbonate) was developed as optimal concentration under experimental formula and conditions of preparation. The formulation in each formula code, specified in Table 1 and 2, was developed to optimize drug release as per predetermined limits with minimum required duration of floating (8 h). The ingredients except glidant and lubricant were thoroughly mixed in a poly bag and passed through sieve No. 60. Granulation was done with a solution of calculated quantity of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through sieve No. 12 and dried at 45-55º for 2 h. The dried granules were sized by sieve No. 18 and mixed with magnesium stearate and talc. Granules thus obtained were compressed into tablets on a 16-station single rotary Cadmach machine using 19.2 mm standard punches.

Evaluation of floating tablets:

The prepared floating tablets were evaluated for hardness, weight variation, thickness, buoyancy, and *in vitro* drug release characteristics. Two selected batches of tablets were subjected to detailed dissolution study. The hardness of the tablets was determined using a Schleuniger tablet hardness tester. The thickness of the tablets was measured using a Vernier calipers.

Buoyancy determination:

Floating time was determined using USP 24 dissolu-

TABLE 1: FORMULATION OF CIPROFLOXACIN FLOATING TABLETS WITH VARYING QUANTITIES OF CITRIC ACID

Ingredients mg/tab.	Formulae of Ciprofloxacin floating tablets				
	CFT I	CFT II	CFT III	CFT IV	CFT V
Ciprofloxacin HCl	580	580	580	580	580
Sodium bicarbonate	200	200	200	200	200
Methocel K100M	100	100	100	100	90
Citric acid	30	25	20	15	10
PVP K30	75	75	75	75	75
Magnesium stearate	15	15	15	15	15
Talc	10	10	10	10	10

Each matrix tablet of ciprofloxacin with citric acid 30 mg (CFT I), 25 mg (CFT II), 20 mg (CFT III), 15 mg (CFT IV) and 10 mg (CFT V).

TABLE 2: FORMULATION OF CIPROFLOXACIN FLOATING TABLETS WITH VARYING QUANTITIES OF LACTOSE

Ingredients mg/tab.	Formulae of Ciprofloxacin floating tablets				
	CFT VI	CFT VII	CFT VIII*	CFT IX*	CFT X*
Ciprofloxacin HCl	580	580	580	580	580
Sodium bicarbonate	200	200	200	200	200
Methocel K100M	100	100	100	100	90
Lactose	100	75	75	100	125
PVP K30	75	75	75	50	50
Magnesium stearate	15	15	15	15	15
Talc	10	10	10	10	10

* compressed with higher compression force (to reduce tablet thickness). Each compressed matrix tablet of hardness 9.1-9.2 kg/cm2 with lactose 100 mg (CFT VI) and 75 mg (CFT VII). Each tablet of hardness 14.0-14.6 kg/cm2 with lactose 75 mg (CFT VIII), 50 mg (CFT IX) and 50 mg (CFT X).

tion apparatus 2[7] at 100 rpm using 900 ml of 0.1N HCl and temperature was maintained at 37±0.5º throughout the study. The duration of floating (floating time) is the time the tablet floats in the dissolution medium (including buoyancy lag time).

***In vitro* drug release studies:**

Drug release was studied using USP 24 paddle dissolution apparatus[7], in 900 ml of 0.1N HCl at 37±0.5º and at 100 rpm. Ten millilitres of the sample was withdrawn at regular intervals and the same volume of pre-warmed (37±0.5º) fresh dissolution medium was replaced. The samples withdrawn were filtered and drug content in each sample was analyzed after suitable dilution by Shimadzu 1201 UV/Vis spectrophotometer at 276 nm. The actual content in samples was read from a calibration curve, prepared with USP ciprofloxacin hydrochloride RS[8]. The predetermined drug release requirements chosen were, 30-50% at 1 h, 45-65% at 3 h, 60-85% at 6 h and not less than 80% at 8 h.

RESULTS AND DISCUSSION

Table 3 depicts the physical parameters (hardness and thickness) and floating time of all the fabricated tablets. Table 3 also reflects the *in vitro* release of the drug from these tablets. In the trial study to determine the optimum concentration of the gas generating agent and hydrophilic matrix to entrap gas, 200 mg sodium bicarbonate and 100 mg HPMC K100M per tablet showed good constancy, with desired floating ability and sustained release, hence the same was selected for prototype formula for further study. The thickness of the tablets prepared was in the range of 8.7 to 9.2 mm, when hardness was in the range of 8.8 to 9.8 kg/cm² (except in CFT VIII, CFT IX and CFT X). Decrease in citric acid concentration in formulae CFT I to CFT V showed decrease in drug release. This is due to citric acid's reaction with sodium bicarbonate resulting generation of carbon dioxide gas at a faster rate, increasing rate of drug release. Even though a good release rate was observed when citric acid concentration was increased, the floating time was reduced, probably due to presence of excess carbon dioxide, disturbing the monolithic tablet. As can be seen, in CFT I (citric acid 30 mg/tablet) and CFT II (citric acid 25 mg/tablet), floating time was less than 6 h, whereas 10 mg citric acid per tablet provided 7.9 h floating time.

Hence we concluded that citric acid may not be suitable to increase the drug release from the matrix. Consequently we made CFT V to CFT X with lactose, a hydrophilic agent, with an assumption that capillary action of lactose may facilitate higher drug release without affecting the matrix (thereby floating ability). All the five formulations floated beyond 8 h. Drug release pattern of CFT VI and CFT VII showed satisfactory and sustained release. Tablet thickness was reduced from 9.2 mm to around 8.1 mm by increasing compression force in CFT VIII to improve consumer acceptance. This resulted in a reduction of drug release failure to meet the preset release limits. The incorporation of lactose in higher concentration and reduction of PVP K30 concentration in CFT IX and CFT X showed appropriate release and floating time, at higher compression force. Based on this study tablets compressed with higher compression force resulting hardness of 14.0 to 14.6 kg/cm² by using 100-125

TABLE 3: EVALUATION DATA OF FLOATING TABLETS OF CIPROFLOXACIN

Formula	Physical parameters			% drug released			
	Hardness kg/cm2 ± SD (n=3)	Thickness mm ± SD (n=5)	Floating time h ± SD (n=3)	1 h	3 h	6 h	8 h
CFT I	9.4±0.06	8.9±0.12	5.2±0.03	46.1	71.9	86.2	97.2
CFT II	9.8±0.17	8.7±0.15	6.0±0.07	41.0	62.2	82.1	94.2
CFT III	8.8±0.15	9.0±0.06	6.4±0.07	21.2	34.1	67.9	93.5
CFT IV	8.9±0.05	9.0±0.11	7.9±0.03	22.3	37.1	55.2	75.5
CFT V	9.5±0.07	9.1±0.11	8.1±0.08	19.5	35.4	56.3	74.9
CFT VI	9.1±0.13	9.2±0.06	8.0±0.03	37.9	74.7	93.5	96.2
CFTVII	9.2±0.09	9.1±0.06	8.3±0.07	30.1	51.2	71.2	92.2
CFT VIII	14.4±0.10	8.2±0.05	8.2±0.05	20.2	36.6	45.2	75.9
CFT IX	14.0±0.12	8.1±0.08	8.3±0.05	30.5	47.2	65.2	79.2
CFT X	14.6±0.11	8.2±0.07	8.5±0.04	32.5	56.7	75.6	89.2

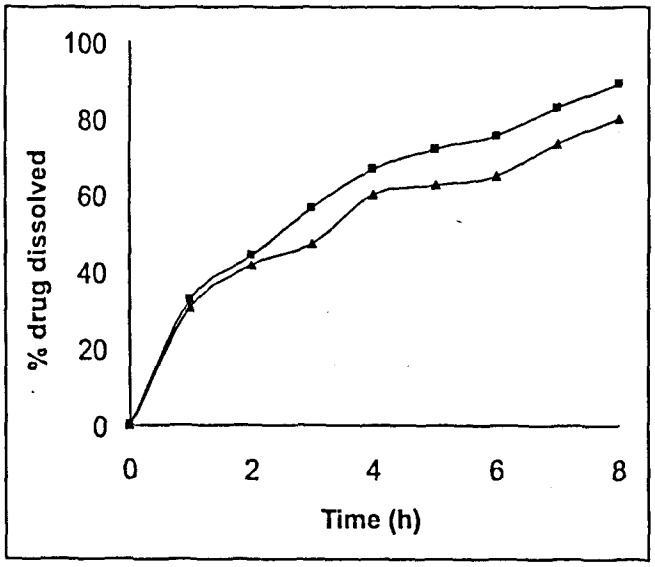

Fig. 1: Dissolution profile of ciprofloxacin from formulated floating tablets.

***In vitro* cumulative release of ciprofloxacin from formulation CFT IX (-▲-) and CFTX (-■-).**

mg lactose per tablet with 50 mg PVP K30 per tablet (in CFT IX and CFT X) were found to be more suitable to give a good floating ability having better drug release characteristics and consistency. The *in vitro* release observed for CFT IX and CFT X show well controlled and sustained release (fig.1). On conclusion the results of the study based on *in vitro* performance clearly suggest that sustained release floating matrix tablets can be prepared by incorporating sodium bicarbonate as gas generating agent in HPMC K100M.

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