ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-6 | JUNE-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

Formulation and In-vitro Evaluation of Floating Matrix Tablets of Cefditoren pivoxil: Effect of Effervescent agent on properties

Pharmacy

Naga Raju Kandukoori Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

M. Spruha Shanthi Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

J. Sushma Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

G. Madhu Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

Ch. Ramya Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

M. Swapna Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

B. Deepika Department of Pharmaceutics, Nalanda College of Pharmacy, Cherlapally, Nalgonda Dist., T. S- 508001

ABSTRACT

The main purpose of this study was to check the effect of concentration of effervescent agent on floating and dissolution properties of tablets. In this study floating matrix tablets of Cefditoren pivoxil were prepared by using three different polymers like HPMC K4M, Xanthan gum and Guar gum with drug : polymer ratio of 1 : 1. Each polymer was used with two different concentrations (15% w/w and 20% w/w) of effervescent agent. Total six formulations were developed and evaluated for their floating and drug release properties. In this study it was confirmed that the concentration of effervescent agent has greatly affected the buoyant behavior of tablets and drug release rate controlling power of the polymer.

KEYWORDS:

Floating matrix tablets, Cefditoren pivoxil, HPMC K4M, Xanthan Gum, Guar gum, Gastric retention.

Introduction:

The bioavailability of drugs can be greatly increased by allowing them to retain in their favored pH environment. Some drugs show high bioavailability in gastric pH environment because of their physicochemical properties like pKa and log p values. Gastroretentive drug delivery systems are the one which allow the drugs to retain in gastric region for longer times. Floating drug delivery systems (FDDS) are one type of gastroretentive systems which remain buoyant in the stomach and act as promising options for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract 1.

The best suitable drugs to formulate as FDDS are the drugs that show action in upper gastro intestinal tract (GIT) or drugs that can be degraded in intestine or drugs that are less absorbed from intestinal mucosa or drugs that are having narrow absorption window in the gastric region. Acid sensitive drugs and other drugs that show gastric irritation are not suitable to formulate as FDDS. The buoyancy of the dosage form in the gastric region depends upon various factors like pH, size of the dosage form, formulative ingredients of the dosage form, diet, and biological factors which include age, body mass index, gender, posture, and diseased states. Among all available gastro retentive systems floating tablets, floating beads, floating granules, and floating microspheres have gained major importance in the formulation development more recently 2.

Cefditoren pivoxil is a semi-synthetic, third generation cephalosporin, which kills bacteria by inhibiting cell wall synthesis. Chemically, cefditoren pivoxil is (6R, 7R) [(2Z)-(2-amino-thiazolyl) (methoxyimino) acetylamino]-3-[(1Z)-2-(4-methyl-5-thiazolyl) ethenyl] 8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid. This prodrug is converted to its active form cefditoren because of hydrolysis by esterase during absorption and is distribured in the blood circulation. Cefditoren pivoxil is best suitable for the treatment of mild-to-moderate pharyngitis, tonsillitis, uncomplicated skin infections, skin structure infections and acute exacerbations of chronic bronchitis. This drug has biological half life of 1.6 hours and it has narrow absorption window in gastric region3.

In the present study, an attempt has been made to increase the absorption of drug through gastric mucosa and to decrease the dose frequency by formulating Cefditoren pivoxil as floating matrix tablets. The prepared tablets were evaluated for their floating properties and in-vitro drug release. In this research mainly effect of concentration of effervescent agent on buoyant and drug release properties of prepared tablets, was studied.

Materials and methods:

The materials used in this research were Cefditoren pivoxil (API) (Sura labs pvt. Ltd.) and polymers like HPMC K4M, Xanthan gum and Guar gum (Accord labs) and effervescent agent like Sodium carbonate and other excipients like Micro crystalline cellulose, Magnesium stearate (Himedia labs).

1. Preformulation study

To confirm the compatibility of drug with polymers and other excipients, preformulation studies were conducted. FTIR method was used to perform the compatibility studies. In this method, the sample along with KBr was used to get the IR spectrum. The IR spectra of pure drug and physical mixture containing drug, polymers and other excipients were produced and analyzed.

After confirmation of compatibility of drug with other ingredients, the formulation blends were prepared and their flow properties were checked by estimating the angle of repose, Carr's index and Haussner ratio.

2. Preparation of floating matrix

tabletsFormulationF1F2F3F4F5F6Cefditoren pivoxil200 mg200 mg200 mg200 mg200 mg200 mgHPMC K4M200 mg2020200 mgMCC56.5 mg29 mg56.5 mg29 mg56.5 mg29 mgNaHCO382.5 mg110 mg82.5 mg110 mg82.5 mg110 mgMg. Stearate5.5 mg5.5 mg5.5 mg5.5 mg5.5 mg5.5 mgTalc5.5 mg5.5 mg5.5 mg5.5 mg5.5 mg5.5 mgTable 1: Formulation composition of Cefditoren pivoxil floating tablets of F1 to F6

Cefditoren pivoxil was mixed manually in polybags with rate

controlling polymer separately as per formulae and MCC was added as diluent and sodium bicarbonate was added as effervescent agent (Table 1) and blended for 10 mins. Then the lubrication of blend was done for 3 to 5 minutes by using magnesium stearate and talc was added as glidant. The mixed blend was then compressed into tablets by direct compression method using 9 mm punches on a four station rotary tablet punching machine (Shakthi machineries). Total six formulations were developed.

3. Evaluation

a) Characterization of tablets for physicochemical parameters

The prepared Cefditoren pivoxil floating tablets were evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content.

b) In vitro floating lag time

Floating lag time was determined to estimate the in vitro buoyancy behavior of tablets. 100 ml of 0.1N HCl was taken in a suitable beaker and the tablets were placed in the medium. The medium was kept in stagnant condition and the temperature was maintained at 37o C. The time required for the tablet to rise to the surface and float was determined as floating lag time4.

c) In vitro floating duration time

USP Dissolution apparatus II containing 900ml of simulated gastric fluid (0.1 N HCl) was used to estimate the floating capacity of the tablets. After floating lag time, for which time the tablet constantly floats on the surface of the medium was observed visually and taken as floating duration4.

d) In vitro drug release

The release of Cefditoren pivoxil from floating tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5oC temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that volume was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbances of the diluted samples were measured at λmax of 240nm for Cefditoren pivoxil by using UV-Visible double beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve5.

Results and Discussion:

1. Preformulation study

In IR spectrum (figure 1) of pure Cefditoren pivoxil, the characteristic peaks of different functional and other groups of drug were remained unaltered in the IR spectrum (figure 1) of physical mixture containing drug, polymers and other excipients. The presence of peaks at 3304.17, 3074.63, 3061.13, 3724.67 cm-1 (>N-H stretching), 1629.90, 1606.76, and 1591.33 cm-1 (>C=N stretching), 1348.29, 1334.78, 1303.92, 1284.63 and 1253.77 cm-1 (>C-N stretching), were characteristic to that of the pure drug and all of them remained unaltered in the IR spectrum of physical mixture containing drug, polymers and other excipients. IR analysis revealed that there was no evidence to the presence of known chemical interaction of drug with polymers and other ingredients.

Formulation	F1	F2	F3	F4	F5	F6
Cefditoren pivoxil	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
HPMC K4M	200 mg	200 mg	-	-	-	-
Xanthan gum	-	-	200 mg	200 mg	-	-
Guar gum	-	-	-	-	200 mg	200 mg
MCC	56.5 mg	29 mg	56.5 mg	29 mg	56.5 mg	29 mg
$NaHCO_3$	82.5 mg	110 mg	82.5 mg	110 mg	82.5 mg	110 mg
Mg. Stearate	5.5 mg	5.5 mg	5.5 mg	5.5 mg	5.5 mg	5.5 mg
Talc	5.5 mg	5.5 mg	5.5 mg	5.5 mg	5.5 mg	5.5 mg

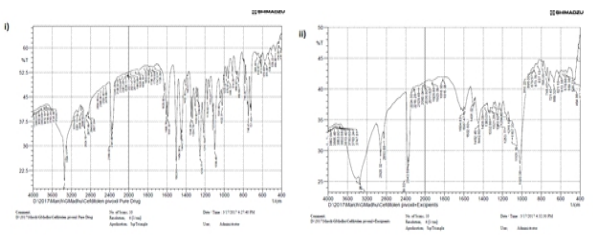

Figure 1: IR spectra of i) Pure Cefditoren pivoxil and ii) Physical mixture containing drug, polymers and other excipients.

2. Weight variation, hardness, friability and assay

The weight variation of the tablets (Table 2) was within the limits of uniformity. The mass ranged from 551.50 to 549.40 mg with SD values 0.39–1.02. The mass of all compressed tablets were within the limits as per USP. The drug content ranged from 98.64 ± 0.16 % in formulation F1 to 97.87 ± 0.48 % in formulation F6 and the friability was ranged from 0.31 to 0.88. Friability and assay of all compressed tablets were within the limits as per USP. The hardness of all prepared tablets was in the range of 3.6 to 4.1 kgs.

Table 2: Weight variation, Friability and Assay

Formulation	Mass (mg) Mean ± SD	Friability (%)	Assay (%)
F1	549.80 ± 0.97	0.75	98.64 ± 0.16
F2	551.50 ± 0.39	0.31	101.27± 0.29
F3	549.68 ± 0.96	0.32	103.28± 0.33
F4	550.21 ± 0.57	0.65	108.87±1.01
F5	549.40 ± 1.02	0.85	94.57±0.58
F6	549.53± 0.78	0.88	97.87±0.48

3. In vitro floating lag time and floating duration

All formulations had floating lag times below 4 minutes (Table 3). The formulations containing 20% w/w of effervescent agent have shown less floating lag time compared to the formulations with 15% w/w effervescent agent. The formulations containing HPMC K4M (F1, F2) and Guar gum (F5, F6) have floated in the medium for more than 12 hours where as the formulations containing Xanthan gum have dissolved immediately after floating. This may be due to high capacity of HPMC K4M and Guar gum to retain the produced gas within the dosage form thereby reducing the density of tablets compared to Xanthan gum. It may also be due to high capacity of HPMC K4M and Guar gum to form gel like barrier around the dosage form compared to Xanthan gum6.FormulationFloating lag time Floating duration time (hrs)F11 min 38 secMore than 12 hrsF21 minMore than 12 hrsF33 min 50 secImmediately dissolved after floatingF41 min 05 secImmediately dissolved after floatingF53 min 47 secMore than 12 hrsF62 min 57 secMore than 12 hrs

Table 3: Floating lag time and Floating duration

Formulation	Floating lag time	Floating duration time(hrs)
F1	1 min 38 sec	More than 12 hrs
F2	1 min	More than 12 hrs
F3	3 min 50 sec	Immediately dissolved after floating
F4	1 min 05 sec	Immediately dissolved after floating
F5	3 min 47 sec	More than 12 hrs
F6	2 min 57 sec	More than 12 hrs

4. In vitro drug release

The release of Cefditoren pivoxil from prepared floating tablets was greatly affected by the concentration of effervescent agent present in the dosage form (table 4). In the formulations F1, F3 and F5 with 15% w/w effervescent agent, the drug release was extended up to 8 hours irrespective of the rate controlling polymer present in the dosage form (figure 2). But in the formulations F2, F4 and F6 with 20% w/w effervescent agent, the drug release time was decided by the nature of rate controlling polymer in the dosage form (figure 3). Formulations F2 and F4 containing HPMC K4M and Xanthan gum as rate controlling polymer respectively, have released the drug completely within 2 hours. But in the formulation F6 containing Guar gum as rate controlling polymer, the drug release was extended beyond 8 hours.

Table 4: In-vitro release profiles of formulations F1 to F6

Time (hrs)	Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	
1	15.65	91.17	77.48	80.02	5.67	13.11
2	30.72	105.65	88.43	97.83	7.83	16.04
4	54.98		90.98		8.96	16.43
6	60.07		93.52		10.17	17.80
8	72.00		101.54		14.87	24.07

From the results it was clear that in the formulations F1, F3 and F5, 15% w/w of effervescent agent has not disturbed rate controlling capacity of polymer in the dosage form. But in the formulations F2 and F4, 20% w/w of effervescent agent has disturbed the cross-linking nature of polymer chains thereby rate controlling capacity of polymers like HPMC K4M and Xanthan gum in the dosage forms. This may be because of weak cross-linkings of polymer chains of polymers like HPMC K4M and Xanthan gum which leads to poor gel formation in tablet to control the diffusion of drug in to medium10. On the other hand, in the formulation F6, the same 20% w/w of effervescent agent was unable to affect the polymer chains to form the cross-linkings. So the gel formation capacity of Guar gum in the dosage form has been not disturbed by the amount of effervescent agent in formulations F5 and F6.

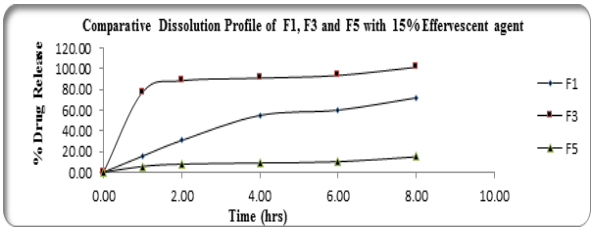

Figure 2: Dissolution Profile of F1, F3 and F5 with 15% w/w Effervescent agent

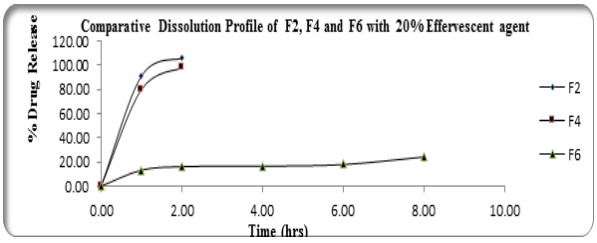

Figure 3: Dissolution Profile of F2, F4 and F6 with 20% w/w Effervescent agent

The release data of all formulations except F2 and F4 with 20% w/w of effervescent agent seem to fit better with the first order kinetics and Higuchi model i.e. the release rate in these formulations, is dependent of its concentration or amount of drug in tablet at given time and the release mechanism is diffusion. Among all formulations more extended pattern of drug release was observed in formulations F5 and F6 with Guar gum as polymer. So the complete drug release may be expected after 24 hours.

Conclusion:

A novel attempt has been made to study the effect of concentration of effervescent agent on floating and drug release properties of tablets. New gastro retentive delivery systems for Cefditoren pivoxil were developed and evaluated. From the results, it can be understood that the amount of effervescent agent in the formulation will greatly influence the floating and drug release properties. It can also be suggested that optimum concentration of effervescent agent must be used to get good buoyant properties and controlled release. It can be concluded that the antimicrobial action of Cefditoren pivoxil may be increased in the stomach due to increased retention and absorption by using formulations containing 15% w/w effervescent agent. The results obtained for used combination and ratio of polymers and effervescent agent in the present work, were not reported earlier in any work. Further work is needed to check the in-vitro drug release up to 24 hours and also to claim the results in animals by in-vivo studies.

References:

1. Meenakshi J, Ujjawal N, Jyotsana K, Singh D. A review: Gastro retentive drug delivery system. International journal of pharmaceutical and biological research. 2015; 3(1): 82-92.
2. Sanap Sunil A, Mahale NB, Salunkhe KS, Chaudhari SR. A review on floating drug delivery system. Journal of advanced drug delivery. 2014; 1(2): 96-113.
3. Venugopalarao G, Lakshmipathy R, Ganesh G, Sarada NC. Absorption and bioavailability of cefditoren pivoxil in hydrogels in vitro and in vivo. Journal of Taibah University for Science. 2015; 9: 1-6.
4. Rao GK, Praveen Kumar M, Rajendraprasad M, Prabhakar reddy V. Development and in vivo evaluation of gastroretentive delivery systems for cefuroxime axetil. Saudi Pharmaceutical Journal. 2012; 13(1): 154-167.
5. SSathiyaraj S, Ramya DD, Vedha BN. Lornoxicam gastro retentive floating matrix tablets: design and in vitro evaluation. Journal of Advanced Pharmaceutical Technology & research. 2011; 2(1): 156-162.
6. Pramod Patil, Someshwara Rao B, Suresh VK, Basavaraj, Chetan Surpur, Anand A. Formulation and In Vitro Evaluation of Floating Matrix Tablets of Ofloxacin. Asian J. Res. Pharm. Sci. 2011; 1(1): 17-22.
7. Vipul Chaudhari, Hetangi Rathod, Moin Modasia. Formulation and evaluation of floating drug delivery system containing theophylline as a model drug. Int. J. of Pharm. & Life Sci. 2011; 2(4): 695-703.
8. Josephine LJ, Mehul RT, Wilson B, Shanaz B, Bincy R. Formulation and in vitro evaluation of floating microspheres of anti-retro viral drug as a gastro retentive dosage form. International journal of research in pharmacy and chemistry. 2011; 1(3): 519-527.
9. Praveen N, Sheefali Mahant. Floating drug delivery system using Methocel K100M and E50: Formulation and characterization. Acta Pharmaceutica Sciencia. 2011; 5(3): 57 – 65.
10. Anuradha KS, Remeth JD, Kailas KM, Niranjan SM, Vishwajeet SG. Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate. Scholars Research Library Der Pharmacia Lettre. 2011; 3(3): 147-160.
11. Nagesh C, Venkatesh JS, Santhosh RM, Jagadish R, Sindhu Patil, Shankraiah M. Intragastric Floating Drug Delivery System of Levofloxacin: Formulation and Evaluation. J. Pharm. Sci. & Res. 2011; 3(6): 1265-1268.
12. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research J. Pharm. and Tech. 2008; 1(4): 345-348.
13. Debjit B, Chiranjib B, Margret C, Jayakar B, Sampath Kumar KP. Floating Drug Delivery System-A Review. Scholars Research Library. 2009; 1(2): 199-218.
14. Vimal kumar S, Abhay U. Gastro-retentive floating drug delivery systems. International Journal of Biomedical Research. 2011; 2(6): 381-390.
15. Gopalakrishnan S, Chenthilnathan A. Floating Drug Delivery Systems: A Review. Journal of Pharmaceutical Science and Technology. 2011; 3 (2): 548-554.
16. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: a review. Int.J. PharmTech Res. 2009; 1(3): 623-633.
17. Samyuktha RB, Vedha Hari BN, Brahma Reddy A, Punitha S, Parimala Devi, Rajamanickam V. The recent developments on gastric floating drug delivery systems: an overveiw. Int.J. PharmTech Res. 2010; 2(1): 524-534.
18. Natasha S, Dilip Agarwal, Gupta MK, Mahaveer PK. A Comprehensive Review on Floating Drug Delivery System. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011; 2(2): 428-441.
19. Padmavathy J, Saravanan D, Rajesh D. Formulation and evaluation of ofloxacin floating tablets using HPMC. Int J Pharm Pharm Sci. 2010; 3(1): 170-173.
20. Anuj Purohit, Abhishek Jain, Shailendra SP, Ankur Sharma. Formulation and evaluation of cephalexin extended release tablets. Int J of Pharm & Life Sci. 2011; 2(3): 606-609 .
21. Anilkumar JS, Manojkumar SP, Harinath N. Formulation and Evaluation of an Oral Floating Tablets of Cephalexin. Indian J Pharm Educ. Res. 2010; 44(3):56-63.
22. Daniel LM, Rosane AS, Leandro BB, Monica RC, Andre L. Evaluation of polymorphs in cephalexin medicines by solid state NMR. Int J Pharm Pharm Sci. 2011; 3(3): 293-298.
23. Chander Shekar B, Shireesh Kiran R, Nagendra Babu B. Preparation and Evaluation of Gastroretentive Floating Tablets of Ketoconazole. Int J Pharm .Reserch & Development. 2010; 2(9):174-184.
24. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: In Vitro and In Vivo evaluation of bilayer tablet formulations. Drug Dev Ind Pharm. 2000; 26 (8): 857-66.
25. Yang L, Eshraghi J, Fassihi R. A new intra-gastric delivery system for the treatment of H. pylori associated gastric ulcer: in vitro evaluation. J Contr Rel. 1999; 5(7): 215-22.
26. Prakash Rao B, Neelima AK, Snehith VS, Ramesh C. Development of Gastro Retentive Drug Delivery System of Cephalexin by using Factorial Design. ARS Pharm. 2009; 50(1): 8-24.