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Original Article

Studies on development and characterization of gastroretentive drug delivery system for antibiotics: Cefdinir

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ABSTRACT

Aims/objective: Oral SR gastroretentive dosage forms offer many advantages for drugs having absorption from upper GIT and improve the bioavailability of medications that are characterized by narrow absorption window. Cefdinir is a third generation cephalosporin with broad spectrum of activity with low bioavailability (20–30%) and short biological half life (1–2 h). It has better absorption from upper part of gastrointestinal tract. The purpose of present study was to formulate and develop a new GRDDS using bilayered tablet technology for cefdinir as a model drug.

Methods: Cefdinir bilayer tablets (CBT) were prepared by using double compression cup and core method. First layer, floating matrix layer contained different rate retarding polymers and effervescent mixture. Second layer is loading layer contained cefdinir and fast releasing components (soluble starch, sodium bicarbonate and citric acid). All CBT were evaluated for their pre and post compression parameters.

Results: Precompression and post compression parameter of all CBT were within the pharmacopeial limits. In vitro buoyancy behavior and matrix integrity study revealed that FLT of optimized formulation was 1.57 ± 0.52 min and the tablet remained floatable throughout the study. In vitro drug release of optimized CBT follows initially first order release upto 30 min (till their release of loading layer), then zero order release upto 12 h and kinetic profile followed the Peppas ($R^2 = 0.9838$) and zero order ($R^2 = 0.9986$). FTIR studies revealed no drug–excipients interactions. Stability studies conducted for optimized formulation did not show any change in physical appearance, drug content, floatability, matrix integrity.

Conclusion: Kinetics of CBT showed biphasic release in the first phase, immediate dose was released in less than 60 min and second phase was released from matrix layer as a controlled zero order fashion. Cefdinir is a suitable drug for development of gastroretentive bilayer tablet.

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1. Introduction

Gastroretentive drug delivery systems (GRDDS) are reported beneficial to many drugs for improving their bioavailability, therapeutic efficacy and by possible reduction of dose. These systems offer various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutics levels minimizing the risk of resistance especially in case of antibiotics.[1–5]

Cefdinir is a semi-synthetic, broad spectrum, β-lactamase-stable antibiotic in the third generation of the cephalosporin class. It was approved by the U.S. Food and Drug Administration (FDA) in December of 1997.[6] Oral bioavailability of cefdinir is 20–25% and short biological half life (1–2 h).[7] Cephalosporin drugs show incidence of antibiotic-associated colitis, which might have been caused by the high concentration of antibiotic entering the colon. To avoid the drug absorption in the colon gastroretentive dosage form would be required to ensure drug delivery within drug-absorbable intestinal regions.[8] Cefdinir is administered with the antacid as its activity is lost due to increase in the gastric pH suggested that the absorption of drug is confined mainly to the upper part of the gastrointestinal tract.[9] Cefdinir had higher absorption in the proximal region of the GI tract and poor absorption, as well as antibiotic-associated colitis, when a large amount of drug entered the colon suggest it is an ideal candidate for a gastroretentive drug delivery system that will prolong the gastric residence time of the dosage form, giving prolonged drug release in the upper GI tract, where absorption of cefdinir is well confined.[8,9]

2. Materials and methods

2.1. Materials

Cefdinir was obtained as a gift sample from Aurobindo Pharma Ltd., Hyderabad, HPMC (K4M, K100M, and K15M) were kindly gifted by Dr. Reddy's Laboratories, Hyderabad. All other materials and solvents used were of analytical grade or pharmaceutical grade.

2.2. Methods

2.2.1. Preparation method of cefdinir tablet for 12 h release (cup and core type)

Step-1 (matrix layer): accurately weighed quantities (as specified in Tables 1 and 2)[10,11] of cefdinir, HPMC K4M (& other polymer), MCC, sodium bicarbonate and citric acid were passed through #40 to get uniform size particles, then they were mixed geometrically for 5–10 min to ensure homogenous mass. Accurately weighed quantity of PVP K30 was dissolved in Isopropyl alcohol (IPA) which was to be used as a binder solution. The binder solution was added to the dry blend gradually with constant kneading to form homogenous mass. The dough mass was passed through #16 and the granular mass was allowed to dry at room temperature. The granules were passed through #16. These granules were lubricated with magnesium stearate and talc and compressed into tablet on low compression force on 10 station punching machine using 8 mm punches.

Step-2 (loading layer): drug-loading granules (as an immediate dose) were prepared by mixing cefdinir (200 mg), soluble starch (50 mg), sodium bicarbonate (50 mg), citric acid (25 mg), PVP K30 (10 mg), using IPA as granulating agent. The granules were dried at room temperature for 20 min then mixed with talc and magnesium stearate.

Step-3: the granules were prepared in step-2 was poured in to the 9 mm die in 10 station punching machine, then tablet prepared in step-1 was kept over the granules and compressed into tablets at high compression force using 9 mm punches.[10,12,13] The prepared tablets were shown in Fig. 1.

2.2.2. In vitro buoyancy behavior

The in vitro buoyancy behavior was characterized by floating lag time and total floating time ($n = 6$). The test was performed using USP 23 dissolution apparatus II was 900 ml of 0.1 N HCl at paddle speed 75 rpm at 37 °C ± 0.5 °C. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as floating lag time and total buoyancy time, respectively.[14,15]

Table 1 – Composition of cefdinir floating layer of bilayer tablet.

Ingredients (mg)	Formula code											
	FM 1	FM 2	FM 3	FM 4	FM 5	FM 6	FM 7	FM 8	FM 9	FM 10	FM 11	FM 12
Cefdinir	150	150	150	150	150	150	150	150	150	**150**	150	150
HPMC K4M	5	10	15	20	25	25	35	45	55	**65**	75	85
Sodium bicarbonate	–	–	40	50	60	70	70	70	70	**70**	70	70
Citric acid	–	–	25	25	25	25	25	25	25	**25**	25	25
MCC[11]	195	190	70	75	80	80	70	60	50	**40**	30	20
PVP K30[10]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Magnesium stearate (7.5)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Talc (7.5)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total weight	375	375	375	375	375	375	375	375	375	**375**	375	375

Bold indicates optimized formulation among all the formulations.