Gastroretentive Sustained Release Floating and Swellable Cefadroxil Formulation: In vitro and in vivo Evaluation

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Abstract

A new Gastroretentive Sustained Release (GRSR) tablet of cefadroxil was developed with floating and swellable properties. Various release retarding polymers, swelling agent, gas generating agent and release modifying agents were evaluated. The optimized formulation was studied for various physical parameters, in vitro drug release profile and for in vitro floating properties. The formulation provided sustained drug release for about 14 h with the floating lag time of 30 s and floating duration of about 14 h. Owing to the promising in vitro floating property, the formulation was explored for in vivo floating performance in healthy human volunteers by radio-analytical technique. The developed formulation of Cefadroxil showed prolonged gastric retention in vivo for 7 h. The tablets also showed significant swelling property with excellent tablet integrity till 7 h.

The developed formulation exhibited promising gastroretention in vivo. The radio-analytical technique used to evaluate the in vivo gastroretention was found to be simple, cost-effective and was precisely used for detecting floating time and tablet integrity throughout the study.

Keywords: Cefadroxil; Gastroretentive delivery; In vivo floating study

Introduction

Gastroretentive Delivery Systems (GRDS) have been designed for achieving therapeutic benefit for drugs that are preferentially absorbed from the proximal part of the Gastrointestinal Tract (GIT) or that are less soluble in or are degraded by the alkaline pH they encounter at the lower part of GIT [1-3]. These systems offer various pharmacokinetic advantages specifically for β-lactam antibiotics with reduction of blood level fluctuations when compared to that observed from conventional forms [4].

Gastroretention depends on various factors such as density and size of dosage form, fasting/fed condition, posture, complicated and unpredictable gastric emptying with migrating myoelectric complex motility of the stomach, etc. Various approaches like floating, swellable, mucoadhesive and/or high-density formulations have been studied to achieve gastroretention by formulating various dosage forms like microparticles, pellets, tablets, capsules, etc. [5-11].

Cefadroxil (CFD) is a broad-spectrum cephalosporin antibiotic commonly prescribed in the treatment of respiratory tract, urinary tract and skin and soft tissue infections with usual dosage of 1 or 2 g daily in a single or divided doses [12]. It exhibits short elimination half-life of 1.2 h with primary excretion via renal pathway (88 to 93% of the daily in a single or divided doses [12]. It exhibits short elimination half-life of 1.2 h with primary excretion via renal pathway (88 to 93% of the daily dose) [13]. It is a relatively low-molecular weight drug that is less soluble in or are degraded by the alkaline pH they encounter at the lower part of GIT [14].

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Various approaches for evaluation of in vivo gastroretention of the formulation in experimental animals as well as in human volunteers have been studied. Some of the well-known techniques are gamma scintigraphy, use of radiopaque materials, etc. The gamma scintigraphy technique has been successfully explored in experimental animals [13,14] as well as in Human subjects [15,16] as reported in some of the literature data. The use of radiopaque materials in the experimental product with evaluation of the subject using X-ray technique post administration has also been studied in experimental animals [17-21]. The technique however has been used in animal models with the results predicted for humans. The X-ray technique is comparatively less complicated still provides accurate evaluation of the gastroretentive system in vivo.

The aim of the study was to evaluate the developed GRSR formulation of CFD in human subjects using the X-ray technique for in vivo gastroretention.

Materials and Methods

Materials

CFD was obtained as a gift sample from M/s Macleods Pharmaceuticals, India. HPMC grades (K 15M and HPMC K100M) were gifted by M/s Colorcon Asia Pvt. Ltd., India, PVP K30 by M/s Rohm Pharma, Germany. Luzenac Pharma and Ferro gifted talc and Magnesium Stearate respectively. Barium Sulfate was purchased from Merck, Germany. All the other excipients and solvents used were purchased from Merck India Ltd. and were of analytical grade.

Received November 04, 2016; Accepted November 14, 2016; Published November 24, 2016

Citation: Chaudhari SV, Vavia PR (2016) Gastroretentive Sustained Release Floating and Swellable Cefadroxil Formulation: In vitro and in vivo Evaluation. J Bioequiv Availab 8: 294-298. doi: 10.4172/jbb.1000313

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Methods

Preparation of tablets

Tablets were prepared by conventional wet granulation method. All the excipients were passed through # 40 ASTM Sieve, mixed and granulated with PVP K30 (5% w/v in isopropyl alcohol). The wet mass was passed through # 8 ASTM Sieve and dried at 50ºC to 60ºC for about 20-30 min. The dried mass was then passed through # 18 ASTM Sieve and the granules were lubricated with magnesium stearate and talc and compressed into caplet sized tablets (21 × 11 mm) on a Cadmach single station tablet press (Formulation: CFD-173).

The formulation, CFD-173 was studied for incorporation of a radio-opaque compound, Barium Sulfate, most commonly used for clinical diagnosis of gastrointestinal tract.

Barium sulfate exhibits high density (4.7777 g/cm³) which makes it difficult to achieve the desired floating properties of the developed formulation upon its incorporation. It also exhibits poor flow property, affecting inversely the flow property of the tablet-blend.

The formulation, CFD-173 was therefore modified by changing the composition of the excipients to get the desired floating properties without significantly altering the in vitro release profile. The developed formulation CFD-173XR contained Barium Sulfate about 9.0% w/w of the tablet and to accommodate this quantity, CFD quantity was reduced by 10% of its dose.

Evaluation of tablets

Tablets were evaluated for appearance, hardness, weight variation, friability and drug content.

In vitro dissolution study

The in vitro dissolution of CFD was studied by USP dissolution apparatus I with rotation speed of 100 rpm. The dissolution was carried out in buffer change medium (900 mL as pH 1.2 buffers for first 2 h, pH 4.5 buffer for next 2 h and water till the end) and in pH 1.2 buffer (900 mL) of the dissolution maintained at 37 ± 0.5 ºC. The samples of 5 mL were withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14 and 16 h and replaced with fresh buffer each time. Samples were analyzed by the developed UV spectroscopy method at 263 nm.

In vitro floating study

The floating study was carried out using USP dissolution apparatus type II. The medium used was 0.1 N HCl (pH 1.2 buffers); 900 mL maintained at 37.5 ± 0.5 ºC throughout the experiment. The floating lag time i.e., time to float the tablet and the duration of floating were studied visually.

In vivo floating study

The floating ability of the developed GRSR formulation was studied in vivo by radio-analytical technique in healthy human volunteers (formulation CFD-173XR). The study was conducted at the K.J. Somaiya medical college and research centre, radiology department, Mumbai, India and the study design/protocol was approved by the local ethical committee. The healthy human volunteers (n=4) selected were males between (age group 20-30 years) with the body weights ranging between 60 ± 8 kg and were housed a day before in the K. J. Somaiya hospital during the entire study. The volunteers were undergone regular check-up to meet the exclusion criteria and were checked as per the protocol after completion of the study.

The volunteers were fasted overnight at least 10 h prior to dosing with water ad lib. The study was performed in fed condition and volunteers were given breakfast. The blank X-ray was taken immediately and 5 min after the breakfast. The volunteers were then given tablets (CFD173-XR) with 240 mL of water. Water was not allowed freely 1 h post dosing. Lunch, breakfast and dinner were provided at 5, 9 and 13 h after the morning breakfast to all the volunteers. During the h of food restriction, no beverages like tea, coffee, milk etc. were permitted other than water. X-ray photographs of all the volunteers were then taken at 2, 4, 7 and 10 h intervals in standing position from the front side of the stomach covering total abdominal part.

Results and Discussion

Evaluation of tablets

The various excipients were optimized for their quantities used and the prepared formulations were studied for their effect on in vitro drug release. The tablets were compressed at the hardness of 7-8 kg/cm² and showed friability less than 0.2% w/w. The assay was found to be 100% of the labelled amount of CFD (The formulation optimization data is not discussed in this work).

Drug release studies

In our previous work [22,23], the GRSR of ofloxacin was developed and successfully studied for in vitro (drug release and swelling property) and in vivo pharmacokinetic studies. Based on this the similar formulation approach was explored for the development of GRSR formulation of CFD.

The in vitro drug release was for CFD173-XR determined in the similar way as of CFD-173 in both; the buffer change method and in acid medium (Figures 1 and 2). The drug release in both the media was found to be more than 90% in 14 h and comparable with f² values in buffer change method and in acid medium for CFD-173 and CFD-173 XR formulations were found to be 62.37 and 58.28 respectively (Figures 1 and 2).

In vitro floating study

The floating lag time and duration of floating in pH 1.2 buffer and in 0.01 N HCl medium (pH 3.5) (to simulate the fed condition environment) were found to be 50 ± 8 s (N=6) and 12 ± 1 h (N=6) respectively for both the formulations; CFD-173 and CFD-173XR.

In vivo floating study

To locate the tablet upon administration in the X-ray photographs, the specific vertebrae locations were used as background.

As specified in the literature [24], the stomach is located under the diaphragm in the left region of the abdomen. Although the exact position and size of stomach vary continually and depends largely on the fed condition, the location can be traced out in X-ray photos against the vertebrae locations. Generally, the stomach lies in between 10th, 11th and 12th thoracic vertebrae while the distal part of the stomach and upper intestinal part may be located against the 1st and 2nd lumbar vertebrae.

The formulation included Barium Sulfate (9.0% w/w of tab) in the optimum quantity that it was sufficient enough to provide the maximum radio-opacity in the abdomen X-ray.

The X-ray photographs are shown in Figure 3.
The X-ray photograph taken at 0 h ensured the absence of any radio-opaque substance before commencing the study. After 2nd h the X-ray photographs showed the bright, very well and sharp edged tablet in the stomach region (seen against 10th to 11th thoracic vertebrae in all the volunteers).

After 4 h of the study, the tablet was found to be at slightly lower regions of the stomach (could be located against 11th and 12th thoracic vertebrae). The tablet at this point was observed with larger dimensions and with reduced sharpness of the tablet size. The tablet was observed as a single unit in all the volunteers with no spreading of the Barium Sulfate indicating the retention of the integrity of the tablet. Barium Sulfate being practically insoluble in aqueous medium it cannot diffuse out of the tablet unless it is disintegrated.

At the end of the 7th h, the tablet was further moved down and could be located before the 1st lumber vertebra and between 1st lumbar and the 12th thoracic vertebra, indicating the residence of the product in the distal part of the stomach or in upper part of intestine. At this point the tablet could be vividly seen as a swollen matrix and the boundaries were further diffused. Again, in all the volunteers the tablets were found to be intact. The tablet brightness was reduced with time which could be attributed to the reduced tablet integrity owing to substantial drug release by the end of 7 h. Further the food (meal) might have affected adversely on the tablet brightness.

At the end of 10 h, the tablet could not be seen even in the distal part of the abdomen. Thus, the tablet could have either become much diffused to differentiate or lost its integrity dispersing Barium Sulfate

![Figure 1: Comparative in vitro release profiles of CFD in buffer change medium.](image1.png)

![Figure 2: Comparative in vitro release profiles of CFD in pH 1.2 buffer.](image2.png)
in the intestinal part. Further the 10 h observations also ensured that the tablet did not block the GIT leading to appropriate exit from the body. No adverse events were seen in all the subjects till 48 h after administration.

**Conclusion**

The developed GRSR system for CFD formulation provided significant floating property *in vitro* and *in vivo* thus supporting the successful development of gastroretentive dosage form. The Radio-analytical technique was successfully used in human subjects for evaluation the floating properties as well as the tablet size and integrity, providing the *in vivo* performance of the developed formulation.

**Acknowledgements**

We are thankful to University Grant Commission and NAPTEC, India for providing financial assistance.

**Note:** The research work was exclusively conducted at Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai, India.

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