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Gastroretentive floating matrix tablets of cephradine based on psyllium husk

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Sustained-release gastroretentive floating matrix tablets of cephradine were prepared for better patient compliance. Eight different tablets were prepared by using two natural polymers, psyllium husk powder (F1–F4) and xanthan gum (F5–F8), through the wet granulation technique. These tablets were characterized by pre- and postcompression analysis, Fourier transform infrared spectroscopy, swelling index study, in vitro buoyancy and dissolution study. Data were analyzed by model-dependent and model-independent analysis to devise the release mechanisms. The polymers exhibited excellent sustained-release behavior as well as binding characteristics. Pre- and postcompression parameters were observed in the specified official pharmacopoeia range. The drug contents of all the formulations were found in the range 95·52–99·63%. No chemical interaction was found between the drug and polymer. All formulations exhibited a good floating time – that is, >24 h – except F8, which remained buoyant for less than 1 h in simulated gastric fluid (pH 1·2). All of the formulations exhibited a direct relation between the swelling index and viscosity of polymer matrices. The significance of the wet granulation technique was indicated by the polymer action as a binding agent in wetting solution. From comparison of the two polymers, psyllium husk powder efficiently retarded the drug release owing to its high gelatinous swollen mass.

Notation

D	tablet diameter (mm)
d	diameter
d_B	bulk density
d_T	tapped density
F	force (N)
h	cone height
k	release rate constant
M	mass
M_t	amount of drug released at time t
n	release exponent
T	tablet thickness (mm)
t	time
V_b	bulk volume
V_t	tapped volume
W	weight of tablet
w_a	average weight of tablets
w_o	theoretical weight of tablets

1. Introduction

Gastroretentive floating drug-delivery systems control the release rate of the target drug to a gastric medium.[1] The effective pharmacological response of the drug is associated with its absorption behavior.[2] The absorption rate of the drug depends on various factors such as dissolution rate and gastric emptying process.[3] To improve the drug action, the retention time of drug-delivery systems is required to be increased.[4] An extended gastric retention time enhances the solubility of the drug at gastric pH by increasing the drug release time and reducing drug waste. Consequently, the therapeutic effect is improved and patient compliance is achieved. Thus, the control of drug release and gastrointestinal transit profiles is a major focus of pharmaceutical research.[5]

A drug dosage form consists of two basic components: the active ingredient and excipients.[6] The excipients help in the development of pharmaceutical formulation. They improve the physicochemical properties of the formulation.[7] As excipients, polymers play a significant role in the drug-release process from any dosage form. Polymers may be natural or synthetic. The choice of polymer is a key step in manufacturing any dosage form.[8] These days, the focus of manufacturers is tending toward the use of natural polymers because of various issues related to drug release and side effects.

Gastric drug-delivery systems are considered superior over other systems as they are based on the use of natural polymers.[9] Natural polymers are basically polysaccharides, so they are biocompatible and without any side effects. Natural polymers are non-toxic, are capable of chemical modification and have a gel-forming nature.

Various natural polymers, including pectin, chitosan, xanthan gum (XNG), gellan gum, guar gum, karaya gum, starch, psyllium husk (*Plantago ovata*) (PSH) and alginates, are utilized in the development of stomach-specific drug-delivery systems due to their promising potential.[10–12] After water absorption, PSH becomes mucilaginous gel with a larger swelling factor. A high swelling factor and the ability to form uniform viscous solution make PSH an ideal candidate as a suspending and thickening agent.[13] Hence, it is used in development of floating and sustained-release drug-delivery systems.[14] XNG is a high-molecular-weight heteropolysaccharide. It is easily soluble in water and develops high-viscosity solutions at low concentration.[15] XNG also exhibits a high level of swelling and little erosion due to polymer relaxation on water absorption. XNG swells on contact with gastric media and produces a viscous layer around the tablet. Consequently, the drug-release rate is decreased.[16] Thus, it is considered an efficient excipient in pharmaceutical industry.

Cephradine ($C_{16}H_{19}N_3O_4S$) (Figure 1) belongs to the cephalosporin group of antibiotics[17] and is effective against infections caused by various gram-negative and gram-positive bacteria.[18] Its mechanism of action involves the inhibition of bacterial cell wall synthesis.[19] Cephradine is also used in the treatment of bronchitis, rheumatic fever, pneumonia and soft-tissue infections.[20] Reportedly, gastroretentive floating matrix tablets would enable the extended release and absorption phase of several drugs, including the cephalosporin class of antibiotics. The additional benefits of this design are improved pharmacokinetic and pharmacodynamic profiles due to the prolonged gastric residence time; using this system, one can improve as well the solubility of cephradine-like drugs that are less soluble in a high-pH environment.

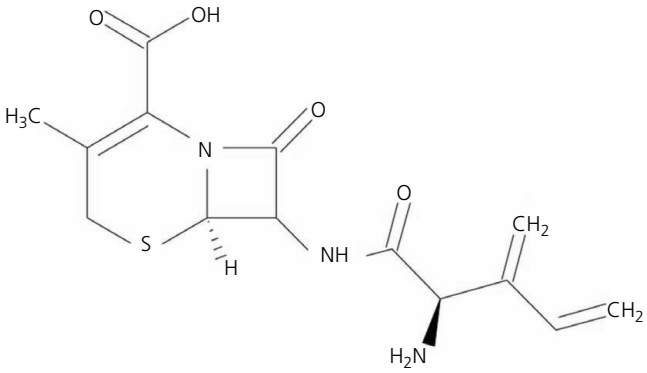

Figure 1. Structure of cephradine

Until now, no gastroretentive controlled-release form has been available in the market all over the world. Hence, the present study was carried out to develop sustained-release gastroretentive floating matrix tablets of cephradine by using natural polymers for better patient compliance.

2. Materials and methods

2.1 Chemicals

PSH was purchased from Marhaba Laboratories (Pvt.) Ltd, Pakistan. XNG, tragacanth (TRG), isopropanol, hydrochloric acid (HCl), magnesium stearate ($Mg(C_{18}H_{35}O_2)_2$) and sodium hydrogen carbonate ($NaHCO_3$) were purchased from Merck, Germany. Distilled water was used throughout the study. All of the solvents used during the study were of analytical grade.

2.2 Preparation of tablets

Eight different gastroretentive floating sustained-release tablets of cephradine (F1–F8) were prepared using varying concentrations and types of polymers by the wet granulation method.[21] The polymers PSH and XNG were ground to fine powder by using a pestle and mortar. PSH (powdered, 25 g) was further mixed with isopropanol (50 ml). Ground polymers and drugs were individually screened through sieve number 20. Table 1 shows the composition of a single tablet of each formulation (F1–F8); however, the authors prepared 152 tablets of each batch (i.e. each formulation). Cephradine (100 mg) and the polymer (used as a granulating as well as swelling agent) were mixed and homogenized evenly using a pestle and mortar. The physical mixture was wetted by using a wetting solution of TRG (as binder) uniformly. The wet mass was homogenized and granulated by passing through sieve number 16 and was oven-dried at 40°C for 12 h (keeping the moisture content at 7 ± 1%). Sodium hydrogen carbonate (as the effervescent agent) and magnesium stearate (as the lubricant) were added to the dried granules during tablet compression. The mixture was compressed

Table 1. Gastroretentive formulations of cephradine using natural polymers

Code	Cephradine: mg	PSH: mg	XNG: mg	TRG: mg	Diluent: mg	Sodium bicarconate: mg	Total weight: mg
F1	100	50	—	30	150	60	390
F2	100	100	—	30	100	60	390
F3	100	150	—	30	50	60	390
F4	100	200	—	30	—	60	390
F5	100	—	50	30	150	60	390
F6	100	—	100	30	100	60	390
F7	100	—	150	30	50	60	390
F8	100	—	200	30	—	60	390

into tablets carefully under 15 kN force on a ZP-19 rotary press fitted with 7 mm round flat punches.

2.3 Fourier transform infrared spectroscopy

Interaction between the drug and polymers were determined by Fourier transform infrared (FTIR) spectroscopy (IR Prestige-21, Shimadzu, Japan). Cephradine, PSH, XNG, TRG and all formulations (F1–F8) were analyzed in the range 4000–400 cm^{-1}.

2.4 Flow characteristics of granules

The powder blend was screened through sieve number 18 to avoid the agglomerates forming during storage. The flow properties of the powder blend were assessed by measuring the following parameters.[22] All of the precompression studies were carried out in triplicate, and mean values were determined.

2.4.1 Bulk density

Screened powder (50 g) was added to a 100 ml graduated/measuring cylinder, and the bulk volume was noted. Bulk density (d_B) was determined by applying the equation.

1. $$d_B = M/V_o$$

2.4.2 Tapped density

The tapped density (d_T) was measured by using a tapped-density cylinder. Powder (50 g) was added to a 100 ml graduated/measuring cylinder. The cylinder was dropped from a specified distance of 14 ± 2 mm at the rate of 300 drops/min. The final tapped volume (V_f) was determined to calculate the d_T of powder blend using the equation

2. $$d_T = M/V_f$$

2.4.3 Hausner's ratio and Carr's compressibility index

Data of d_B and d_T was used to determine the Hausner's ratios and Carr's compressibility indices (CIs) of all of the formulations (F1–F8) by using the following equations[22]

3. $$\text{Hausner's ratio} = d_T/d_B$$

4. $$\text{CI} = \frac{(d_T - d_B)}{d_T} \times 100$$

2.4.4 Static angle of repose

The static angle of repose (AOR) of all of the formulations was measured by using the funnel method. The cone height (h) and diameter (d) were measured, and the AOR was determined by applying the equation

5. $$\tan \alpha = 2h/d$$

2.5 Tablet compression

Granules were compressed into the tablets using a ZP-19 rotary press. Then, these tablets were subjected to following postcompression parameters for evaluation.

2.5.1 Preparation of buffer solution

Buffer solution (0·1 N, pH 1·2) was prepared by adding 12·2 M hydrochloric acid (8·3 ml) into distilled water (500 ml). The volume of the solution was raised to 1000 ml by adding distilled water.

2.5.2 Standard curve of cephradine in 0·1 N hydrochloric acid (1·2 pH) buffer

A stock solution of cephradine (1000 parts per million (ppm)) was prepared by dissolving pure drug (100 mg) in 0·1 N hydrochloric acid buffer (50 ml). The volume of solution was raised to 100 ml with 0·1 N hydrochloric acid buffer. Stock solutions were further diluted to prepare different sample solutions of 20, 40, 60, 80 and 100 ppm. The absorbance was measured at 254 nm.

2.5.3 Content uniformity test

Ten tablets were randomly chosen from each batch, and their average weight was determined. These tablets were crushed finely using a pestle and mortar. The powder (equivalent to 10 mg of cephradine) was weighed accurately and dissolved in 50 ml of 0·1 N hydrochloric acid (1·2 pH) buffer. The volume was raised to 100 ml using 0·1 N hydrochloric acid buffer. The volume was raised to 100 ml using 0·1 N hydrochloric acid buffer after filtration. The drug content in each dosage form was determined by taking the absorbance of the solution at 254 nm through a double-beam ultraviolet (UV)/visible spectrophotometer. A calibration curve was generated and analyzed to determine the drug content of all of the batches (F1–F8). Standard deviation (SD) and % relative standard deviation (% RSD) were determined statistically using Equations 6 and 7, respectively

6. $$\text{SD} = \left[\frac{\sum(\text{individual value} - \text{mean})^2}{\text{number of values}}\right]$$

7. $$\%\ \text{RSD} = \left(\frac{\text{SD}}{\text{mean}}\right) \times 100$$

2.5.4 Weight variation test

Ten tablets from each formulation were randomly selected and weighed individually. The average weight was calculated. The individual weight of each tablet was compared to the average weight (w_a), and the percent age difference was noted by applying the equation

8. $$\text{percent difference} = 100 - [(w_o - w_a/w_o) \times 100]$$

where w_a is the average weight of the tablet and w_o is the theoretical weight of the tablet.

2.5.5 Friability test

The friability of the tablets was determined in accordance with US Pharmacopeia (USP) 1216, 'Tablet friability'. The friability test was performed by using a friabilator (Roche friabilator). Ten tablets were randomly selected from each batch, dedusted and weighed accurately. The tablets were placed in the friabilator (height was 6 inches (15·2 cm)), and the speed of the rotating drum was set to 25 revolutions per minute (rpm). After 100 rotations, tablets were withdrawn from the friabilator and dedusted again with a camel hairbrush to remove loose powder and reweighed accurately. Friability was measured by applying the equation[23]

$$9.\quad \%\ \text{friability} = [(W_1 - W_2)/W_1] \times 100$$

where W_1 is the weight of the tablet prior to the test and W_2 is the weight of the tablet after the test.

2.5.6 Hardness and tensile strength (T_s) test

Ten randomly selected tablets from each batch were introduced to a hardness tester for determination of hardness, thickness and diameter. The SD of all the formulations was calculated. Crushing strength data, diameter and thickness values were used to measure the T_s of all of the formulations by applying the equation

$$10.\quad T_s = 2F/\pi DT$$

where F is the force expressed in newtons, D is the tablet diameter expressed in millimeters and T is the tablet thickness expressed in millimeters.

2.6 In vitro buoyancy studies

A tablet from each batch was added to 0·1 N hydrochloric acid (1·2 pH) buffer (200 ml) in a 250 ml glass beaker. The temperature of simulated gastric fluid was maintained at 37 ± 5°C by placing the beaker in a water bath for the whole length of the study (12 h). The floating lag time and total floating time were noted carefully. Each test was carried out in triplicate, and results were calculated as their mean.

2.7 Swelling index study

A tablet from each batch was randomly selected, and its initial weight (W_i) was noted. Each tablet was added to 0·1 N hydrochloric acid solution (200 ml, 1·2 pH buffer). Tablets were taken out from the solution after regular intervals of time, and excess fluid was wiped off using filter paper. The final weight (W_f) of each tablet was measured to find the swelling index (SI) by applying Equation 11. The study was performed in triplicate, and results were determined as average.

$$11.\quad \text{SI} = [(W_f - W_i)/W_i] \times 100$$

where W_i is the weight of the tablet before the test and W_f is the weight of the tablet after the test.

2.8 In vitro dissolution studies

2.8.1 Preparation of simulated gastric fluid

In vitro dissolution studies of cephradine (250 mg) and gastroretentive floating matrix tablets of cephradine were performed using USP dissolution apparatus II (paddle type) in 0·1 N hydrochloric acid (900 ml, 1·2 pH) buffer for 8 h. The dissolution apparatus was set at 50 rpm. The temperature of the dissolution chamber was maintained at 37 ± 0·5°C to study drug release. Aliquot (5 ml) was withdrawn from chamber and replaced with fresh buffer after 0·5, 1, 1·5, 2, 2·5, 3, 4, 5, 6, 7 and 8 h to restore its original volume (900 ml). The withdrawn sample was filtered and analyzed at 254 nm by using a double-beam UV/visible spectrophotometer (UV-1700 PharmSpec, Shimadzu, Japan). Percentage drug release was determined through a standard calibration method for all the batches (F1–F8). Each measurement was performed in triplicate, and mean values are reported and evaluated. Drug-release kinetics were studied by using model-dependent analysis and model-independent analysis. Equation 12 was applied to evaluate the mean dissolution time (MDT) of all the batches from F1 to F8.

$$12.\quad \text{MDT} = [n/(n+1)] \times k^{-1/n}$$

where n is the release exponent and k is the release rate constant.

2.9 Drug-release kinetics

The drug-release mechanism and release rate from the natural polymeric system were determined by applying different kinetic equations such as zero-order, first-order, Higuchi and Korsmeyer–Peppas models. Cumulative drug release (%) was plotted against time t to get a zero-order graph applying Equation 13. The absorption and/or elimination rate of certain drugs from the biological system is expressed by using the first-order model. The first-order plot was attained by plotting log cumulative percentage drug released against time t as shown in Equation 14. The Higuchi model describes the drug dissolution from a non-eroding insoluble matrix system. According to this, liquid penetrates into the insoluble matrix system and dissolves the drug, which then diffuses to the exterior/outside the dosage system. Mathematically, the Higuchi model is expressed as in Equation 15. The Korsmeyer–Peppas model, also called power law, is used to describe the mechanism of drug release from the matrix system. Mathematically, the power law is expressed as in Equation 16.

$$13.\quad M_t = k_0 t$$

where M_t is the amount of the drug released at any time t and k_0 is the zero-order release rate constant represented as concentration per time.

14. $$\log M = \log M_o - k_t/2{\cdot}303$$

where M_o is the initial amount of the drug in the solution, k_1 is the first-order release rate constant and t is time.

15. $$M = k_H t^{1/2}$$

where M is the amount of released drug at time t, k_H is the dissolution rate constant of the system and t is time.

16. $$\ln(M_t/M_\infty) = \ln k_p + n \ln t$$

where M_t/M_∞ is the fraction of the drug released in time t, k_p is a kinetic constant and n is the diffusion exponent for drug release.

2.10 Model-independent analysis

The model-independent approach allows the pair-wise comparison of two release profiles. As the gastroretentive floating cephradine is not market available, F1 and F5 were thus chosen as reference. The difference factor (f_1) of the respective batches was calculated using Equation 17. In the same way, the similarity factor (f_2) was measured by applying Equation 18.

17. $$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100$$

where n is the number of samples, R_t is the % drug dissolved from the reference product at $t = 1$ and T_t is the % drug dissolved from the test product at $t = 1$.

18. $$f_2 = 50 \times \log\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0{\cdot}5} \times 100$$

where n is the number of samples, R_t is the % drug dissolved from the reference product at $t = 1$ and T_t is the % drug dissolved from the test product art $t = 1$.

3. Results and discussions

Biocompatible natural polymers were applied in the fabrication of sustained-release gastroretentive tablets of cephradine through the wet granulation method. The polymers exhibited an excellent sustained-release behavior as well as binding characteristics. All formulations were studied for different precompression parameters and showed good results, as discussed in the following sections.

3.1 Drug–polymer interaction

Cephradine, all polymers and all formulations (F1–F8) were analyzed by FTIR spectroscopy. The spectrum of cephradine was compared to that of all the formulations (F1–F8). Cephradine showed characteristic absorptions at 1766·80 cm^{-1}, indicating C=O stretching, and 1687·71 cm^{-1}, due to amide C=O stretching. The spectra of the formulations consisting of PSH (F1–F4) showed the characteristic absorption bands of cephradine at 1762·94 and 1687·07 cm^{-1}. The spectra of formulations consisting of XNG showed the characteristic absorption bands of cephradine at 1761·01 and 1674·21 cm^{-1}. The spectra of all formulations (F1–F8) revealed the same position of characteristic absorption bands of cephradine. All spectra showed that there was no chemical interaction between the drug and polymers in all the formulations (Figure 2).

3.2 Precompression study of powder blends (F1–F8)

The flow characteristics of the powder blend of each batch were evaluated for different rheological parameters. Hausner's ratios of 1·21–1·32, Carr's indices of 17·10–24·12 and static AORs of 25·71–30·27 were found for formulations F1–F8. These values indicated that the granules possessed fair to passable flow characteristics in terms of Carr's index. Hence, all of the batches (F1–F8) revealed other good rheological characteristics (Table 2).

3.3 Postcompression evaluation

All gastroretentive floating matrix tablets of cephradine (F1–F8) were subjected to various pharmacopoeial and non-pharmacopoeial tests. The standard calibration curve of cephradine in 0·1 N hydrochloric acid buffer solution was a straight line with a regression coefficient of 0·999. The uniformity

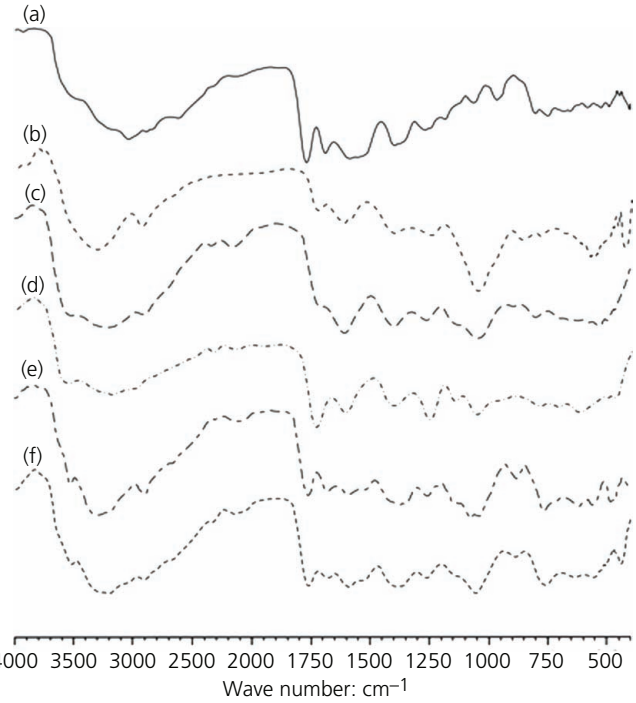

Figure 2. Overlay of FTIR spectra of cephradine (a), PSH (b), XNG (c), TRG (d), formulation F1 (e) and formulation F6 (f)

Table 2. Precompression parameters (n = 3) of powder blend of all the batches (F1–F8)

Formulation code	Bulk density	Tapped density	AOR	Carr's index	Hausner's ratio
F1	0·649 ± 0·05	0·817 ± 0·08	27·03 ± 0·54	20·59 ± 1·23	1·26 ± 0·08
F2	0·639 ± 0·04	0·814 ± 0·09	28·89 ± 0·61	21·45 ± 1·18	1·27 ± 0·12
F3	0·647 ± 0·02	0·791 ± 0·11	27·49 ± 0·59	18·18 ± 1·31	1·22 ± 0·14
F4	0·613 ± 0·07	0·761 ± 0·07	30·27 ± 0·70	19·44 ± 1·19	1·24 ± 0·19
F5	0·649 ± 0·09	0·855 ± 0·12	25·71 ± 0·82	24·12 ± 1·29	1·32 ± 0·11
F6	0·632 ± 0·10	0·791 ± 0·13	26·97 ± 0·94	20·05 ± 1·24	1·25 ± 0·22
F7	0·639 ± 0·06	0·771 ± 0·09	29·82 ± 1·08	17·10 ± 1·30	1·21 ± 0·28
F8	0·649 ± 0·08	0·796 ± 0·14	28·57 ± 0·97	18·53 ± 1·31	1·23 ± 0·30

of drug content and percent drug-release data of all of the batches were determined from the standard calibration curve. Content uniformity of all of the batches was observed in the range 95·52–99·63% with SD less than 9% within the range of USP30-NF27 (2007).[24] Friability values were found to be less than 1%, which meets the official USP requirements for this test. Moreover, the weight variation test data were uniform with a low SD, indication of excellent mixing of the drug with all of the excipients. Hardness values were in the range 5·17–5·50 kg/cm^2, indicating excellent hardness as well as mechanical strength. Dried and powdered PSH as well as XNG has poor binding strength in dry granulation but is highly efficient for wet granulation where polymers themselves act as binders in the wetting solution. The postcompression parameters of gastroretentive floating matrix tablets of cephradine (F1–F8) are presented in Table 3.

3.4 In vitro buoyancy studies

The results of in vitro buoyancy studies of tablets consisting of formulations F1–F8 in simulated gastric fluid (pH 1·2) are shown in Table 4. Carbon dioxide (CO_2) gas is produced by reaction of the effervescent agent sodium hydrogen carbonate and hydrochloric acid present in the dissolution medium. The gas evolved is trapped within the tablet; hence, the density of tablet is decreased.[21] The tablet becomes buoyant when its density falls below that of the aqueous medium (1 mg/l). The ideal amount of sodium hydrogen carbonate required to obtain a short floating lag time together with prolonged buoyancy is 50 mg.[25] In the current study, the duration of flotation of all of the tablets (containing sodium carbonate (Na_2CO_3) = 60 mg) (F1–F7) ranged from 8 to 24 h, while F8 floated for less than 1 h in simulated gastric fluid. XNG formulations F5 and F6 exhibited the highest floating time – that is, about 24 h – among all formulations. At high water content of the gastric medium, the fluid penetrates highly into the tablet. Therefore, carbon dioxide is readily produced and the floating lag time is reduced.[21] Tablets F1–F4 containing PSH showed sustained release of the drug, and the floating lag time ranged from 4 to 21 min. Tablets F5–F8 containing the polymer XNG showed a shorter floating lag time as these started floating earlier in the range 1–5 min. Among all formulations, F6 was confirmed as the best formulation, due to its short floating lag time and a prolonged total floating time.

3.5 SI study

Matrix tablets of cephradine were designed using the natural polymers PSH (F1–F4) and XNG (F5–F8) as sustained-release agents. At higher water concentration of the medium, chains of polymer are in a relaxed position. Therefore, the volume of the tablet increases; consequently, the system becomes highly swollen.[21] The SIs of the formulations F1–F8 kept on increasing

Table 3. Postcompression evaluated parameters of gastroretentive floating matrix tablets of cephradine

Formulation code	Postcompression parameters (n = 10)					
	Drug content: mg	Weight variation: mg	Friability: %	Hardness: kg/cm^2	Thickness: mm	Diameter: mm
F1	98·01 ± 0·04	389·99 ± 0·81	0·747 ± 0·06	5·30 ± 0·17	4·14 ± 0·02	9·025 ± 0·002
F2	97·76 ± 0·01	389·71 ± 1·21	0·658 ± 0·08	5·37 ± 0·21	4·10 ± 0·03	9·018 ± 0·004
F3	97·67 ± 0·06	389·99 ± 0·81	0·465 ± 0·11	5·50 ± 0·20	4·15 ± 0·01	9·057 ± 0·003
F4	95·52 ± 0·02	390·48 ± 1·99	0·591 ± 0·13	5·38 ± 0·18	3·96 ± 0·04	9·062 ± 0·002
F5	96·40 ± 0·01	389·75 ± 1·40	0·483 ± 0·21	5·40 ± 0·24	3·91 ± 0·06	9·068 ± 0·004
F6	99·63 ± 0·81	389·53 ± 1·31	0·529 ± 0·18	5·17 ± 0·21	4·18 ± 0·05	9·048 ± 0·003
F7	95·63 ± 0·04	389·72 ± 1·21	0·545 ± 0·16	5·35 ± 0·19	3·99 ± 0·09	9·078 ± 0·001
F8	98·13 ± 0·05	390·12 ± 0·94	0·655 ± 0·23	5·38 ± 0·23	4·16 ± 0·08	9·052 ± 0·002

Table 4. In vitro buoyancy studies of tablets (F1–F8) in simulated gastric fluid (pH 1·2)

In vitro buoyancy	F1	F2	F3	F4	F5	F6	F7	F8
Floating lag time: min ± s	16 ± 24	4 ± 8	21 ± 28	13 ± 12	2 ± 2	5 ± 4	1·5 ± 3	1 ± 3
Total floating time h	>12	>12	>8	>9	>24	>24	>8	<1

with the passage of time due to water uptake of polymers up to 8 h (Figure 3). PSH formulation F4 had gained the highest SI owing to the largest amount of high-viscosity hydrophilic polymer. XNG formulations (F5 and F6) exhibited an increase in SIs on increasing polymer concentration. Therefore, it can be concluded that there is a direct relation between the viscosity of polymeric matrices and their swelling. F7 and F8 formulations exhibited a decrease in SI that may be attributed to high pH responsiveness chain relaxation. Due to the hydrophilic nature of natural polymers, a gelatinous layer is developed around the tablets in simulated gastric medium. Thus, the gelatinous layer controlled the release rate of the drug.[26] The swelling phenomenon is characterized as a determinant element of floating as well as the dissolution of the drug.[27]

3.6 Cumulative drug-release studies

Gastroretentive and sustained-release properties of PSH and XNG were studied. The aim of the study was to get a better drug-release profile over an extended time period using natural polymers. The sustained-release process of drug from the polymer matrix follows the three steps: hydration, swelling and drug release. The dissolution medium is diffused into the polymer matrix of the tablet. After diffusion, the polymer matrix swells and the drug is transported to the surroundings from the matrix. Swelling of the tablet results in enhancement of the dimensions of the tablet.[28,29] Siepmann *et al.*[30] showed that the diffusion rate of a drug considerably depends on the water content of the tablet. The effect of natural polymers on the drug-release rate was investigated by a dissolution study of eight different formulations (F1–F8) of floating matrix tablets and compared with the cephradine tablet. The amounts of cephradine released from the formulations consisting of PSH, F1, F2, F3 and F4, after 8 h were 91, 69, 60 and 58%, respectively. Drug release from polymeric matrices of PSH decreased on increasing PSH concentration. During the dissolution study, a slow release rate was observed (Figure 4). This sustained-release property was due to the swelling nature of PSH. Formulations F1–F4 maintained their integrity throughout the dissolution study due to the high matrix-forming ability of natural biocompatible polymers PSH. F4 exhibited excellent sustained characteristics as obvious from its drug-release profile due to having the highest SIs; the increase in the diffusion path length led to a decreased drug-release rate,

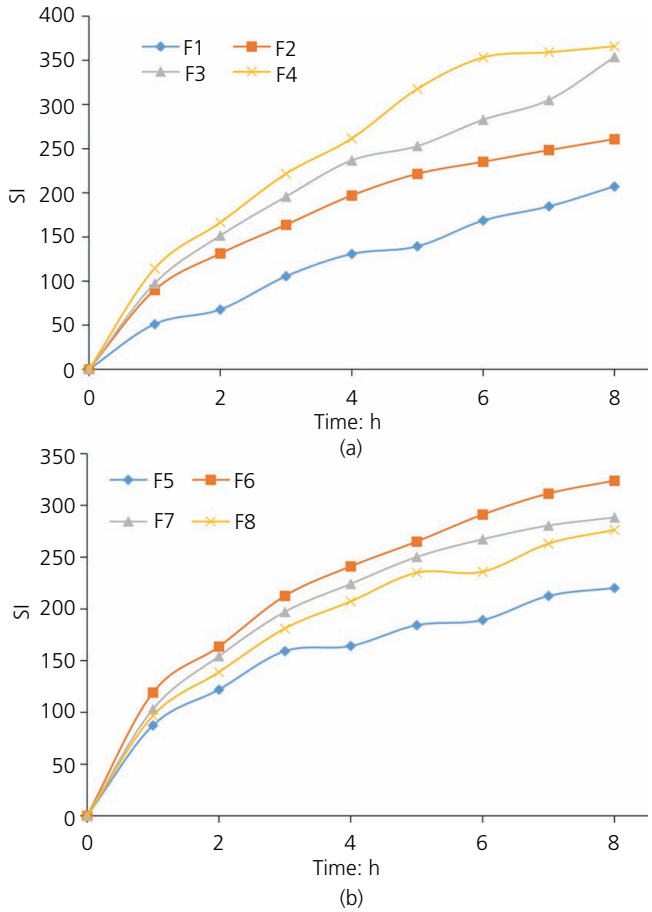

Figure 3. Swelling behavior of formulations (a) F1–F4 and (b) F5–F8

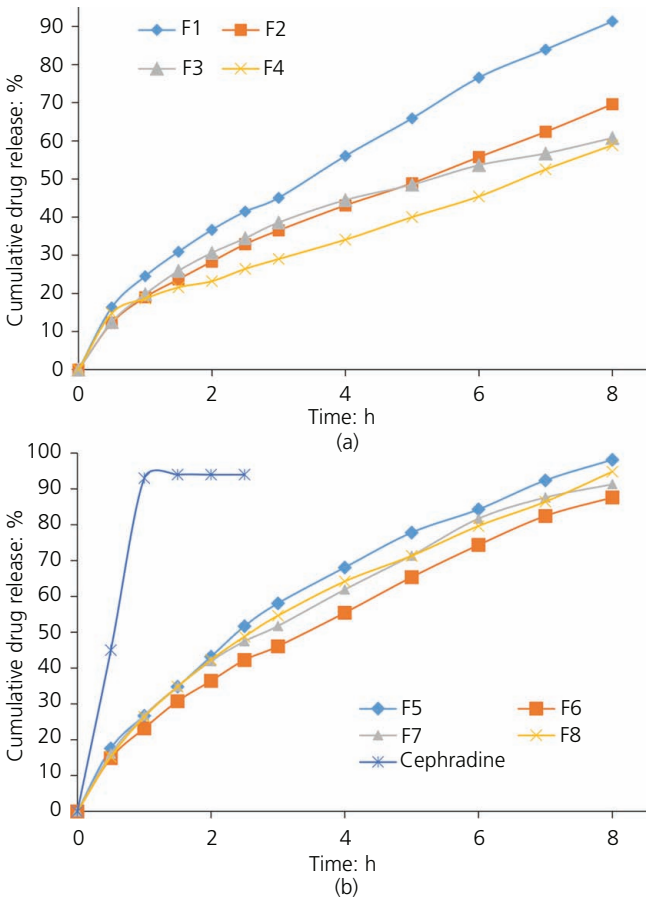

Figure 4. Cumulative drug release of formulations (a) F1–F4 and (b) F5–F8 and cephradine

Table 5. Fitness of release parameters to the various mathematical models

Code	Cumulative% drug release after 8 h	Zero-order model		First-order model		Higuchi model		Korsmeyer–Peppas model		
		k_0	R^2	k_1	R^2	k_h	R^2	k_p	R^2	N
F1	91·31	14·82	0·785	0·232	0·973	29·55	0·954	23·03	0·997	0·661
F2	69·59	10·07	0·801	0·147	0·968	22·37	0·966	18·22	0·998	0·632
F3	60·75	9·18	0·586	0·140	0·877	21·62	0·994	21·02	0·995	0·518
F4	58·84	8·01	0·764	0·112	0·888	18·63	0·954	16·05	0·973	0·597
F5	98·16	19·36	0·859	0·299	0·992	33·43	0·970	28·49	0·996	0·614
F6	87·63	14·78	0·811	0·226	0·985	29·01	0·963	23·20	0·999	0·644
F7	91·31	17·88	0·766	0·268	0·987	31·58	0·978	27·23	0·997	0·596
F8	94·85	18·42	0·836	0·269	0·994	31·49	0·977	27·23	0·997	0·596

The MDT of formulations from F1–F8 was determined on the grounds of the Korsmeyer–Peppas model, and F4 formulations depicted the highest value (3·32 h)

contributing to slow drug-release properties. The quantities of cephradine released from the formulations consisting of XNG, F5, F6, F7 and F8, after 8 h were 98, 87, 91 and 94%, respectively.

Among all of the formulations containing XNG, F5 exhibited an excellent drug-release profile due to the decreased swelling factor.

On comparison of the two polymers, PSH showed higher gelling and swelling properties. PSH is a polymer therefore used in the preparation of controlled-release formulations and also because of its mucilaginous and viscous gel-forming property.[31,32] On increasing the concentration of PSH powder in the drug formulation, the swelling factor increased as reflected in drug-release profiles. In contrast, on enhancing the amount of XNG, formulations showed increase in the swelling factor up to a certain concentration and, after that, the swelling factor was decreased. The release of drug from gelatinous swollen matrices was decreased due to the increase in the diffusion path length. Thus, PSH has a great potential to be used effectively in designing novel sustained-release matrix systems on a commercial scale.

3.7 Drug release kinetics

The mechanism of drug release from the formulations was investigated by applying zero-order, first-order, Higuchi and Korsmeyer–Peppas models on drug-release data. The results are represented in Table 5. All kinetic models exhibited a linear relationship between the drug release rate and concentration. In the first-order plot, the R^2 value obtained for all formulations except F3 and F4 ranged from 0·968 to 0·994. The best linearity was found in the Higuchi equation plot (R^2 = 0·954–0·994), indicating the release of drug from matrix as a square root of the time-dependent process based on Fickian diffusion. The release data of all formulations were fitted into the Korsmeyer–Peppas equation (power law) as well. All of the dosage units (F1–F8) showed excellent linearity (R^2 = 0·973–0·999) in this model as well.

The times taken to release 25% (t_{25}), 50% (t_{50}) and 75% (t_{75}) of the drug from different formulations were determined (Table 6). Tablets containing the highest concentration of PSH (F4) required 2·1, 6·7 and 17·98 h to release 25, 50 and 75% of the drug, respectively. Among the tablets consisting of XNG formulations,

Table 6. Successive fractional dissolution time (h) of floating matrix tablets of cephradine (F1–F8)

Formulation	t_{25}	t_{50}	t_{75}	MDT
F1	1·13	3·23	7·87	3·22
F2	1·65	4·93	12·50	3·25
F3	1·39	5·32	16·53	2·66
F4	2·10	6·72	17·98	3·32
F5	0·81	2·50	6·52	2·88
F6	1·12	3·29	8·20	3·09
F7	0·87	2·77	7·43	2·84
F8	0·87	2·77	7·43	3·00

F6 exhibited the best sustained-release characteristics. It required 1·1, 3·29 and 8·2 h to release 25, 50 and 75% of the drug, respectively. Thus, it is concluded that the tablet formulation (F4) consisting of PSH revealed higher MDT and better sustained-release properties compared to the formulation based on XNG (F6).

3.8 Model-independent analysis

Tablet formulations F1 and F5 were considered as reference formulations as they contained the minimum amount of polymers. The amount of polymers was higher in formulations F2–F4 and F6–F8. A model-independent analysis was carried out to analyze and compare the effects of varying concentrations of polymers in the rest of formulations with those of reference formulations. In this way, one can access the minimum range of the additive polymers in matrix tablets. The difference (f_1) and similarity (f_2) factors were evaluated by pairing up the reference batch F1 with the batches containing PSH (F2–F4) and F5 with batches containing XNG (F6–F8). The formulations consisting of PSH (F2–F4) showed a different release behavior compared to the reference (F1). Contrarily, all formulations containing XNG exhibited a difference factor as well as a similarity factor within

Table 7. Difference and similarity factors between formulations

Factor	F2/F1	F3/F1	F4/F1	F6/F5	F7/F5	F8/F5
f_1	23·96	25·10	35·91	14·40	6·16	5·25
f_2	42·70	39·70	33·60	51·59	67·07	70·70

f_1, dissimilarity factor; f_2. similarity factor

prescribed limits. Among these formulations, F7 and F8 resembled more the reference formulation with the lowest difference factor (6·16 and 5·25) and the highest similarity factor (67·07 and 70·70), respectively. The results are presented in Table 7.

4. Conclusions

Cephradine gastroretentive tablets were prepared using natural polymers, namely, PSH and XNG, through the wet granulation method. For the development of sustained-release gastroretentive tablets of antibiotics such as cephalosporin, the use of naturally occurring water-swellable polysaccharides proved as an effective tool/alternate to synthetic polymers. All tablets showed promising drug content, hardness, high SI, floatability and controlled-release properties. Comparatively, PSH was found to be a better sustained-release agent than XNG in the study of different parameters such as in vitro buoyancy, SI and drug-release kinetics. Natural-polymer-based gastroretentive drug-delivery systems are eco-friendly and a desirable approach to the targeted delivery of antibiotics.

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