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FORMULATION DEVELOPMENT AND EVALUATION OF CEFIXIME MUCOADHESIVE TABLETS USING NATURAL POLYMERS

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Abstract

Cefixime having lower bioavailability due to narrow therapeutic absorption window in the upper gastrointestinal tract. Further, the conventional dosage form has poor patient compliance due to frequent dosage regimen. Therefore, we planned to prepare mucoadhesive tablets of Cefixime by using varying ratio of the natural gum obtained from Okra and Hibiscus rosasinensis. The six different formulations F1 to F6 were prepared by direct compression method, and were subjected to thickness, friability, hardness, weight variation, drug content, surface pH, mucoadhesive strength, mucoadhesion force, swelling index and in- vitro dissolution studies. The mucoadhesive tablets formulated with a higher concentration of gum Okra and Hibiscus rosasinensis showed good mucoadhesion strength. The in- vitro drug release studies indicated a sustained release pattern of the Cefixime for 12 h of study and the drug release was directly proportional to gum concentration. Hence the findings suggest sustained release pattern of the Cefixime for 12 h of study, and improved systemic delivery of drugs by enhancing the absorption due to higher permeable with a rich blood supply to mucus layer.

Keywords: Cefixime, Mucoadhesive, Okra, Hibiscus rosasinensis

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1 Introduction

Oral medication conveyance has been referred to for quite a long time as the most generally used course of administration among every one of the routes that have been investigated for the fundamental conveyance of medications through different drug results of various dose forms. An ideal DDS should help in the enhancement of medication treatment by conveying a suitable add up to the proposed site and at an ideal rate. Overall, a DDS might be utilized for spatial position (for example focusing on a medication to a particular organ or tissue) or transient conveyance (i.e., controlling the pace of medication conveyance to the objective tissue)[1].

Mucoadhesive drug delivery system has as of late acquired interest in pharma calling. Mucoadhesion is a feature of bioadhesion that is planned to limit the medications at a specific mucosal region in the body. Water-dissolvable polymers, those become cement on hydration, has been utilized to plan the detailing. The main points of mucoadhesion are drug focusing on, maintained/controlled delivery, expanding of gastric home time, limiting the principal pass impact and lessening the unfavourable impacts. The polymers picked for mucoadhesion should be non-absorbable, non-poisonous, biocompatible, non-covalent cement and financial. These polymers might be either characteristic (sodium alginate, gelatin and guar gum) or engineered/semi-manufactured (sodium carboxymethyl cellulose, carbopol 934 and hydroxypropyl methylcellulose). They might be utilized either alone or mixes of at least two adhesive polymers for mucoadhesive frameworks[2].

Two plants are prominently used, and have been chosen as the polymer for the formulation of mucoadhesive tablets of cefixime. These are leaves of *Hibiscus rosasinensis* and fruits of Okra (*Abelmoschus esculentus*). *Hibiscus rosasinensis* is widely grown as an ornamental plant throughout the tropics and subtropics. The mucilage of the leaves of *Hibiscus rosasinensis* reported healing of the numerous diseases. Mucilage of the Okra pods has been reported to have binder potential for tablet formulations. The fresh fruits of Okra are a common component of Indian diet. Additionally, the plant has been used medicinally in the treatment of several diseases[3]. The mucilage of *Hibiscus rosasinensis* and Okra used as a

natural polymer, biocompatible, biodegradable, non-irritant to tissue having good binding properties and better mucoadhesive property.

Cefixime belongs to third generation cephalosporin antibiotic and having potent antibacterial activity against various bacteria. Cefixime mostly used for the healing of the UTI infection, acute bronchitis, pharyngitis, gonorrhoea, otitis media, chronic bronchitis and many more. Cefixime is unionized at acidic pH due to lower pKa value of 2.5. The lower solubility about 30%-40% of the drug limited the bioavailability. Cefixime having a narrow therapeutic absorption window in the upper gastrointestinal tract, and the conventional tablets produced lower bioavailability. Hence, it is required to provide affordable formulations to improve the bioavailability and drug delivery. The mucoadhesive tablet interacts with the mucosal tissue found in stomach and improved systemic delivery of drugs by enhancing the absorption due to higher permeable with a rich blood supply[4-7]. In addition, mucoadhesive dosage form is utilized to prolonging the drug release and to improve the absorption.

Therefore, it was planned to developed mucoadhesive tablets of Cefixime by using the natural mucilage obtained from the *Hibiscus rosasinensis* and Okra plants for its better bioavailability.

2 Material and Methods

2.1 Preparation of natural gum

2.1.1 Extraction of *Abelmoschus esculentus* (Okra) gum

About 1 kg of fresh immature fruits of Okra was purchased from local market. After removal of the seeds, the fresh immature fruits were sliced, homogenized and extracted with cold water containing 1% w/v of sodium metabisulphate. The crude mucilage was centrifuged at 3000 rpm for 5 min. The gum was precipitated from the supernatant with acetone. The precipitated gum was washed several times with acetone. The obtained cream colored product was dried under vacuum in desiccators. A light brown colored powder was obtained after complete removal of moisture. The dried gum was pulverized using end runner mill and screened with a 0.25 mm stainless steel sieve. This was stored in a well closed amber colored specimen bottle till ready for use.

2.1.2 Extraction of *Hibiscus rosasinensis* gum

The fresh leaves of *Hibiscus rosasinensis* Linn. were collected, washed with water to remove dirt and debris and then dried. The powdered leaves were soaked in water for 5-6 h, boiled for 30 min and kept aside for 1 h for complete release of the mucilage in to the water. The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature < 50 °C, collected, dried, powdered and passed through a sieve no: 80 and stored for further use in the desiccators[8,9].

2.2 Formulation and development of mucoadhesive tablets

2.2.1 Preparation of mucoadhesive tablets of Cefixime

Tablet containing 200 mg of Cefixime was prepared by direct compression method. Cefixime, Okra gum, *Hibiscus rosasinensis* gum, and all the excipients except the lubricant were blended homogeneously in a mortar according to the quantities given in table 1. The lubricant was added to this blend and mixed properly again for 2 min. Powdered lubricated blend was compressed into tablet by compression machine.

2.2.2 Evaluation of Cefixime mucoadhesive tablets

2.2.2.1 Weight variation test

In this process the 20 tablets were weighed separately. The average weight of one tablet was calculated by taking average mean. On I.P. it has mentioned that not more than 2 tablets produce distinctive weight. As per I.P note more than 2 of the distinctive weights from the mean weight, and none should be aberrant by longer than twice that percentage given in the monographs.

2.2.2.2 Thickness test

With the help of Vernier calliper, we measure the thickness of the tablets in terms of micrometer. The averages of three readings were noted and the results of mean were recorded (n = 3)

2.2.2.3 Hardness test

The Monsanto hardness tester was used to determine the hardness of formulated tablets. The hardness was calculated in respect to kg/cm^2. Thrice readings were measured and average was noted.

2.2.2.4 Friability test

The Roche friabilator was used to measure the abrasion rate of formulated tablets. Measure the weight of 20 tablets and kept in the friabilator chamber. The friabilator was rotated at speed of 25 rpm for 4 min. After completion of rotation of friabilator tablets were weighed and by the help of formula the percentage weight loss was calculated.

2.2.2.5 Drug content

The drug content was calculated by triturating the three tablets in a mortar with pestle to get fine powder. Taken powder equivalent weight of one tablet and was dissolved in pH 6.8 phosphate. Measure the absorbance of diluted sample of Cefixime at 287 nm, using UV-Visible Spectrophotometer. The drug content was calculated by using standard calibration curve.

2.2.2.6 Surface pH

The microenvironment pH (surface pH) of the mucoadhesive tablets was determined in order to investigate the possibility of any side effects *in-vivo*. As an acidic or alkaline pH may cause irritation to the mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Battenberg *et al*. was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 ml of distilled water (pH 7.0 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min [9].

2.2.2.7 Mucoadhesion studies

The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by using sheep mucosa as model mucosal membrane. A double beam physical

balance was taken, the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass vial of 30 ml capacity with uniform surface was tied. A clean 500 ml glass beaker was placed below hanging glass vial within which was placed another glass beaker of 100 ml capacity in inverted position. The temperature control system involves placing the thermometer in 500 ml beaker and intermittently adding hot simulated saliva (pH 6.8) into 500 ml beaker containing simulated saliva (pH 6.8) maintained at 37.0 ± 0.5 °C. The balance was so adjusted that right-hand-side was exactly 5 g heavier than the left [10-12].

Force of adhesion (N) = Mucoadhesive strength/100 × 9.81.

2.2.2.8 Swelling index

The tablets were individually weighed (W_1) and placed separately in Petri dishes with 5 ml of simulated saliva of pH 6.8. At the time interval of 0.5, 1, 2, 4, 6, 8, 10 and 12 hrs, tablet was removed from the petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W_2) and the percentage hydration were calculated using the following formula [13, 14].

% Swelling Index (S.I) = $[(W_2-W_1)/ W_1] \times 100$

W_1 = initial weight; W_2= final weight

2.2.2.9 *In-vitro* drug release study from cefixime mucoadhesive tablets

In -vitro study was carried out in USP II apparatus, employed paddle stirrer at 50 rpm and 900 ml of phosphate buffer pH 6.8 as dissolution medium maintained at 37 ± 0.5 °C. The tablets were designed to release drug from one side only, therefore, one side of tablet was fixed to a glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed it at 287 nm using UV-Visible spectroscopy[4, 10-13].

2.3 Statistical analysis

Each experiment was repeated at least three times. The results are expressed as the mean±S.D.

3 Results and Discussions

After formulation of tablets, it required to check the suitability of dosage form for proper therapeutic response. The various parameters were used for evaluation of compression of tablets. The thickness, friability, hardness, weight variation, drug content, surface pH, mucoadhesive strength, mucoadhesion force, swelling index and *in-vitro* dissolution test were evaluated for prepared tablets using standard procedures.

3.1 Characteristics of Cefixime mucoadhesive tablets

The six different formulations i.e. C1 to C6 were prepared by direct compression method, and physiochemical properties were evaluated. The thickness of the formulation C1 to C6 were found to be in between 4.1±0.17 to 4.7±0.08 mm (Table 2). The hardness of the formulation C1 to C6 were varied between 4.3±0.54 to 5.5±0.74 Kg/cm^2, demonstrating good binding and satisfactory strength of tablet (Table 2). The results demonstrated on increasing the concentration of gum it increases the hardness of the tablets.

The weight of the tablets was found to be uniform with low standard deviation values from 426.2±0.78 to 426.9±1.13 mg (Table 2)**.** All the formulated tablets comply with the weight variation evaluation as per IP. All the tablets were circular with no visible cracks and smooth on appearance.

The percentage friability of the formulation C1 to C6 were ranged between 0.31±0.12 to 0.52±0.08 (Table 2). The results expressed percentage friability was less than 1% for all formulation. The findings complied the official requirement mentioned in the IP.

The percentage of drug content in the formulation C1 to C6 were found in the range of 97.8±0.27 to 99.6±0.57 (Table 2). The values of drug content were under the limit mentioned in the Pharmacopoeial.

The outcomes indicate the gel forming property of the gum present in the tablet matrix in line with the comparable findings reported earlier by various researchers[12,13]. The results of the tablet hardness demonstrated the tablets can withstand the mechanical shocks. This is combined with the friability (less than 1%) of all the formulations, which demonstrated the effectiveness of the gum for its use as a binder. The findings of the physicochemical properties of the tablets show that formulations were within acceptable levels.

3.2 Surface pH

Table 3 showed the surface pH of the formulations C1 to C6 were in the range of 7.22±0.72 to 7.44±0.25. The findings of the surface pH suggested that the formulation will not cause any local irritation to the mucosal surface, and all the formulation can be used safely.

3.3 Bioadhesive strength

Table 3 exhibited mucoadhesive strength of formulations C1 to C6 ranged from 34.12±0.12 to 43.56±0.05 gm and mucoadhesion force were found to be in the range of 3.347 to 4.273 N. The bioadhesion characteristics were affected by the concentration of bioadhesive gum used. It has been observed that on increasing in concentration of gum increased the bioadhesive strength of the formulation. The C6 containing *Hibiscus rosasinensis* gum showed higher mucoadhesive strength and mucoadhesion force compared to C3 containing Okra gum.

3.4 Swelling studies

The swelling index of the formulations C1 to C6 was found in the range of 20 to 83 for 12 hr (Table 4). The results expressed the swelling index of the tablets increases on increasing the polymer concentration. The gum of the okra increased the swelling index of C3 to 73, while the gum of *Hibiscus rosasinensis* enhances the swelling index of C6 to 83. This may be due to the quick hydration of gum on keeping the tablets in contact with water for 1 h to 12 h. An appropriate swelling index is mandatory for the uniform and sustained release of the drug and effective mucoadhesion. Hence the C6 containing *Hibiscus rosasinensis* gum showed higher swelling index compared to C3 containing Okra gum.

3.5 *In-vitro* release studies

The results showed that all formulations released the drug within 12 h (Fig 1). The C2, C3 and C6 released drug 98.56±0.64%, 93.15±0.41% and 98.23±0.61%, respectively from formulations. It was found that the rate of drug release was different for formulations with different proportions of gum present in the formulations. The gradual decrease in the percentage of drug release from C1 to C5 and C4 to C6 in 12 hr may be due to the increase in the concentration of gum of Okra and *Hibiscus rosasinensis*, respectively. It may be due to the *in-situ* gelling property of Okra and *Hibiscus rosasinensis*, which slows the dissolution

rate of the drug Cefixime. The formulation C2, C3 and C6 were remaining intact during the entire 12 h study period.

4 Conclusion

The mucoadhesive tablets of Cefixime were formulated by incorporating different ratio of gum of Okra and *Hibiscus rosasinensis* to reduce the frequency of the administration and better compliance of patient. The finding of thickness, friability, hardness, weight variation, drug content, surface pH, mucoadhesive strength, mucoadhesion force and swelling index of formulations C1 to C6 were acceptable according to Pharmacopoeial limit. The *in-vitro* dissolution studies indicated a sustained release pattern of the Cefixime for 12 h of study. The results of this study revealed that increasing the concentration of the gum leads to a decrease in the release rate and also increases the adhesion strength of the formulation. The outcomes of release studies concluded that these novel formulations can by-pass first pass metabolism and enhance the release for extended period of time.

5 References

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Table 1: Quantity of raw materials for preparation of mucoadhesive tablets of Cefixime

Ingredients	C1	C2	C3	C4	C5	C6
Cefixime	200	200	200	200	200	200
Okra	100	125	150	-	-	-
Hibiscus rosasinensis	-	-	-	100	125	150
PVP K30	25	25	25	25	25	25
MCC	30	30	30	30	30	30
Talc	1	1	1	1	1	1
Magnesium stearate	70	45	20	70	45	20

Table 2: Evaluation characteristics of Cefixime mucoadhesive tablets

Formulation	Tablet Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Average weight (mg)	Drug content (%)
C1	5.2±0.56	0.44±0.06	4.6±0.16	426.5±1.06	99.1±0.64
C2	4.8±0.49	0.52±0.08	4.2±0.19	426.9±1.13	98.6±0.85
C3	5.5±0.74	0.36±0.03	4.7±0.08	426.6±1.25	99.3±0.39
C4	4.6±0.28	0.31±0.12	4.3±0.05	426.2±0.78	97.8±0.27
C5	4.3±0.54	0.48±0.07	4.1±0.17	426.4±0.61	98.4±0.41
C6	4.7±0.44	0.41±0.05	4.5±0.09	426.8±0.46	99.6±0.57

Values are mean ± SD, n=3

Table 3: Evaluation parameters of Cefixime mucoadhesive tablets

Formulation code	Surface pH	Mucoadhesive strength (g)	Mucoadhesion force (N)
C1	7.32±0.53	34.12±0.12	3.347
C2	7.41±0.19	36.53±0.09	3.583
C3	7.44±0.25	37.42±0.11	3.670
C4	7.22±0.72	38.31±0.22	3.758
C5	7.25±0.48	41.73±0.17	4.093
C6	7.23±0.86	43.56±0.05	4.273

Values are mean ± SD, n=3

Table 4: Swelling index (%) of Cefixime mucoadhesive tablets

Formulation code	1 hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs
C1	20	27	34	40	46	49	54
C2	23	30	38	43	49	56	60
C3	30	38	43	56	63	69	73
C4	23	30	38	43	49	53	58
C5	28	34	41	47	55	62	65
C6	35	41	49	61	69	76	83

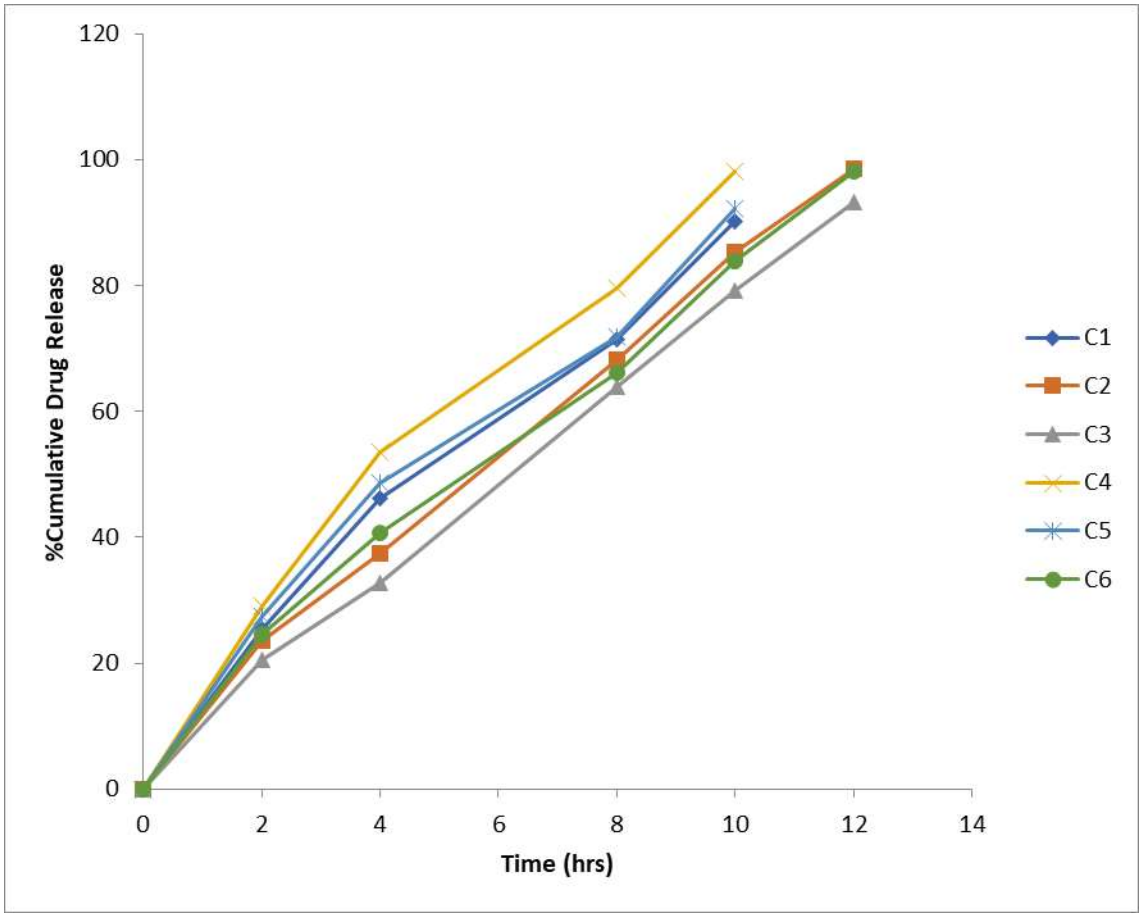

Fig 1: *In-vitro* drug release profile of Cefixime mucoadhesive tablets