Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 6, 2014

Original Article

MUCOADHESIVE BUCCAL PATCH OF CEFIXIME TRIHYDRATE USING BIODEGRADABLE NATURAL POLYMER

ASWATHY S NAIR[1], VIDHYA K.M[2], SARANYA T.R[3], SREELAKSHMY K.R[4], SREEJA C NAIR[5*]

Department of Pharmaceutics, Amrita Institute of Medical Sciences (Amrita School of Pharmacy), AIMS Health Sciences Campus, Kochi 682041 Kerala India. Email: sreejacnair@aims.amrita.edu

Received: 28 Apr 2014 Revised and Accepted: 29 May 2014

ABSTRACT

Objective: The objective behind the study was to develop a bio erodible mucoadhesive buccal patch containing Cefixime trihydrate as a therapeutic agent for the treatment of bacterial infections and their evaluation.

Methods: Cefixime trihydrate buccal patches were prepared by solvent casting method.

Results: The formulated patches were subjected to various evaluation parameters and all the physical parameters evaluated are within the acceptable limits. The formulation F5 showed maximum release 98.1% while other formulations showed less amount of drug release in 7 hr. The *in vitro* antibacterial activity by agar diffusion assay demonstrated a significant antibacterial profile of the optimized patch F5 against Streptococcus species. The morphological study by Scanning electron microscopy (SEM) confirmed that the upper surface of patch containing Cefixime (F5) was rough with numerous pores inside it. The stability study proved that the formulation F5 was found to be stable.

Conclusion: The prepared formulation also provides a desired antimicrobial sustained drug delivery into the systemic circulation.

Keywords: Chitosan, Cefixime trihydrate, Buccoadhesive patch, Sustained drug release.

INTRODUCTION

Oral transmucosal drug delivery may be of 3 types like sublingual, gingival, and buccal. Absorption of therapeutic agents from the oral cavity provides a direct entry for such agents into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal degradation. However, the buccal routes of drug delivery gain superiority because of its unique advantages over the other oral transmucosal routes. [1] A number of mucoadhesive devices has been developed in the recent era. However, buccal films offer greater flexibility and comfort than adhesive tablets. In addition, patches can overcome the problem of the relatively short residence time of oral gels on mucosa as these gels are easily washed away by salivary secretion [2]. Also the patch can be easily applied to the wound surface that can control the healing more effectively. An ideal buccal patch should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it must also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration [3].In present research work.

Cefixime is used as a model drug, a third generation cephalosporin antibiotic having bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis, acute bronchitis and acute exacerbation of chronic bronchitis, uncomplicated gonorrhea. Cefixime with pKa value of 2.5 a weak acid which will remain unionized at acidic pH. [4] It is primarily absorbed from the stomach and upper part of intestine. Cefixime is not soluble in water after its oral administration; it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability around 40-50%. So, in order to improve the therapeutic effect of the drug, by safe and effective levels are maintained for a long period time. [5]

The purpose of this study was to develop antimicrobial buccal pach formulations for the treatment of Bacterial infections and systematical evaluation of its in-vitro performances. The patches were prepared by using a natural polymer Chitosan, where Cefixime were selected to use as a model drug based on its pharmacological activity and physicochemical property. Chitosan is natural, biocompatible, biodegradable, non irritant to tissue having good film forming properties and better mucoadhesive property.

MATERIALS AND METHODS

Cefixime drug is procured as a gift sample from Karnataka antibiotics, Bangalore, India.

Chitosan was purchased from Central Institute of Fisheries and Technology (CIFT), Kochi. India. All other materials used were of pharmaceutical grade.

Preformulation studies

Preformulation studies are designed to deliver all necessary data, especially physiochemical, biopharmaceutical properties of the drug substance, excipients and packing material, as well as its compatibility. [6] The overall aim of preformulation study is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

Following studies were performed:

Melting point

Melting point of the obtained drug sample indicates the purity of the sample. The presence of relative small amount of impurity will lower the melting point. [7]

Lamda (λ) max of the drug

An absorption maximum of Cefixime trihydrate was determined using distilled water and phosphate buffer pH 6.8. [8]

Solubility

Solubility of drug was checked in different solvents such as water, ethanol, methanol, chloroform, acetone, ether, phosphate buffer pH 6.8. [9]

Analytical methods

Calibrations curve was done using phosphate buffer PH 6.8 as the solvent.

Preparation of standard stock solution:

10mg of Cefixime trihydrate was dissolved in 50ml of phosphate buffer PH 6.8 and made upto 100ml with phosphate buffer PH 6.8 in a 100ml volumetric flask. [10]

Preparation of working standard solution:

From the above stock solution 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml, 1.2ml were pipetted out and were made up to 10ml using Phosphate buffer pH6.8 in 6 separate 10ml standard flasks to produce 2, 4, 6, 8,10, 12microgram/ml respectively. [11]

Preparation of Standard Graph

From the above stock solution, 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml, 1.2ml respectively were pipetted out and were made up to 10ml using Phosphate buffer pH6.8 in 6 separate 10ml standard flasks to produce 2, 4, 6, 8,10, 12 microgram/ml respectively. The absorbance of these solutions was measured at 289.5nm by UV Spectrophotometer using Phosphate buffer pH 6.8 as the blank. The absorbance was plotted against concentration to obtain the Standard graph. [12]

Preparation of buccal patch

Dissolved chitosan in10ml of dilute acetic acid at a concentration of 1%, 2%, 3%, 4%, 5% chitosan and was kept overnight for swelling. The drug was then dissolved in 1ml of methanol and added to the chitosan solution and 2ml of propylene glycol was added as a plasticizer. Transferred the solution to a Petri dish and kept it in an oven at 45^0c until a suitable patch is obtained. The different compositions were tabulated in Table 1. [13].

Table 1: Compositions of Cefixime Trihydrate loaded buccal patches

Formulation	Polymer concentration(mg)	Plasticizer concentration(ml)	Drug concentration(mg)
F1	100	2	10
F2	200	2	10
F3	300	2	10
F4	400	2	10
F5	500	2	10

Physico chemical evaluation of prepared buccal patches

Thickness uniformity of the patches

Three patch of each formulation were taken. Patch thickness was measured using micrometer screw gauge at three different places. Mean value was calculated. [14]

Uniformity of weight of the patches

These patches of every formulation of size 1×1 cm^2 were taken and weighed individually on a digital balance. The average weight was calculated. [15]

Folding endurance

Three patches of each formulation of size 2×2 cm^2 were cut using a sharp blade. Folding endurance was determined by repeatedly folding a small strip of patch at the same place till it broke. The number of time the patch could be folded at the same place without breaking gave the value of folding endurance. The mean value is calculated. [16]

Surface pH of the patches

Three patches of each formulation are allowed to swell by keeping in contact with 0.5ml of distilled water (pH 6.5 ± 0.5) for 1 hour at room temperature. The pH was determined by bringing electrode in contact with the surface of the patch allowing it to equilibrate for 1 minute. [17]

Percentage swelling index

Patches were cut into 1×1 $cm^2$and weighed accurately and kept immersed in 50ml phosphate buffer pH 6.8. Taken out and weighed at 5,10,30,60 minutes intervals till a constant weight was obtained. [18]

Percentage moisture absorption

In order to evaluate the physical stability of the patches in high humidity condition, it is accurately weighed and placed in a desiccator containing saturated solution of Aluminum chloride (79.5% relative humidity) for 3 days. The patches were reweighed and percentage moisture was calculated using the formula. [19]

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

This is to evaluate the percentage of moisture loss from the freshly prepared film. The prepared patch is accurately weighed and placed in a desiccator containing fused anhydrous calcium chloride for 72 hours. After 72 hrs again reweighed and percentage moisture loss was calculated using the formula. [20]

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Drug content uniformity

The drug loaded chitosan chips of known weight of 7X2 mm dimension were dissolved in 10 ml of methanol and shaken until it dissolved. The drug solution was suitably diluted and absorbance was measured at 289.5 nm. The polymer solution without drug serves as a blank. [21]

***In vitro* drug release study**

The dissolution study was performed by using USP type I basket type six station dissolution apparatus where, one patch of each batches was fixed inside the basket. The dissolution media consist of 900ml of phosphate buffer of pH 6.8 at 37 ± 1^0c at 50 rpm rotation was maintained throughout the experiment. Samples were withdrawn from each station at an interval of 15 minutes and replaced with equal volume of dissolution medium.

The release study was carried out for 6 hours. Each withdrawn sample was filtered, diluted suitably and then analyzed spectrophotometrically at 289.5nm. The experiments were performed in triplicate. [22]

***In vitro* Antibacterial Activity**

The procedure utilizes the strain streptococcus with the principle of agar diffusion assay method. S.*pneumoneia* should be inoculated directly and the plates were streaked to obtain isolated colonies, immediately placed in an anaerobic atmosphere and incubated at 35-37oC for 18-48 hours. Sterile NA plates were prepared and 0.1 ml of the inoculums of test organism (*Streptococcus* sp.) was spread uniformly. Patches were cut using a sterile blade with a diameter of 2mm and were placed on the NA plates. The plates were then incubated at 37oC for24 hours. The zone of inhibition of microbial growth around the well was measured in mm. Zone of Inhibition was calculated from the fully grown plates, Also calculated the MIC (minimum inhibitory concentration).

Scanning Electron Microscopy (SEM)

The morphology and surface topography of the optimized patch F5 were examined by SEM (Joel jsm-6490l analytical SE). Spherical samples (5 mm^2) were mounted on the SEM sample stab using a double sided sticking tape. The samples were coated with gold under reduced pressure (0.001 torr) for 2 min using an ion sputtering device (model JFC-1100 E, Jeol, Japan). The gold coated samples were observed under the SEM at room temperature and photomicrographs of suitable magnifications were obtained. [23]

Stability studies

The stability of the F5 patches was studied at 2 different temperatures. The patches of size (7 × 2 mm) were weighed in three sets and were wrapped individually in aluminum foil and also in butter paper and placed in Petri dishes. These containers were stored at room temperature (30±2^{0}C) and in a refrigerator (4 ± 2°C) for a period of 45 days. All the polymeric patches were observed for any physical changes and the % drug release was estimated at an interval of one week. [24]

RESULT

The procedure adopted results in the fabrication of uniform and reproducible Cefixime loaded polymeric buccal patches. All the prepared patches were translucent and showed good flexibility also.

Preformulation studies

To confirm the identity, purity and suitability of drug for formulation and to establish a suitable drug profile, preformulation studies were undertaken.

Melting point of the drug

The melting point of the drug was found to (218-225ºC) and it was accordance with the monograph.

λ-max of the drug

The λ max of the drug was found to be 289.5 nm (Figure 1) at an absorbance of 0.599 it was in accordance with the official standard.

Solubility of the drug

The solubility of the pure drug was compared with reference sample and it was tabulated in Table 2.

Calibration curve of Cefixime in phosphate buffer pH 6.8

Figure 2 shows the absorption reading of standard drug solution containing 10-100 µg/ml of drug in pH 6.8 phosphate buffer at the maximum wavelength of 289.5 nm. Analyses were done in triplicate.

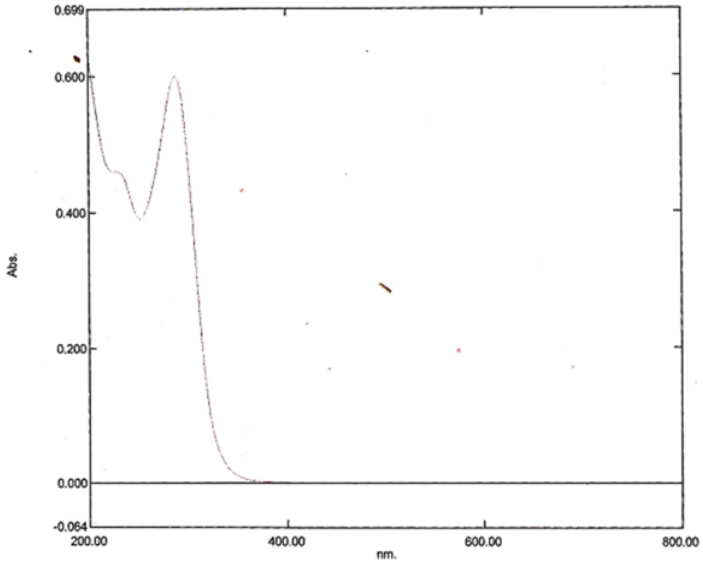

Fig. 1: Absorption maxima of Cefixime trihydrate in Phosphate buffer pH 6.8.

Table 2: Solubility profile of drug Cefixime trihydrate

Parameters	Solubility
Methanol	Freely soluble
Ethanol	Sparingly soluble
Water	Slightly soluble
Chloroform	Insoluble
Hexane	Insoluble
Ethyl acetate	Insoluble

Physicochemical evaluation of the prepared Patches

The physicochemical evaluation data were tabulated in Table 3. It reveals that the mean thickness (Figure 3) of the patches increases as the concentration of the polymer chitosan increases from 1 to 5%. The average weight (Figure 4) of patches varies from 6.33 mg to 11.42 mg for F1 to F5.The folding endurance study (Figure 5) confirmed that the patches did not show any cracks even after folding for more than 300 times. Surface pH (Figure 6) for all formulations of chitosan which ranges from 5.6 ±0.02 to 6.3 ±0.01. Swelling index value (Figure 7) increases as the concentration of polymer increases from 18.48 ±0.01 to 28.8 ±0.01 % for F1 to F5. The results revealed that the % moisture absorption (Figure 8) was found to increase with increasing concentration of chitosan polymer. The percentage moisture loss (Figure 9) decreased from 2.85 ±0.02 to 1.24 ±0.01 for F1 to F5. All the formulations (Figure 10) exhibited good drug content which indicates good reproducibility.

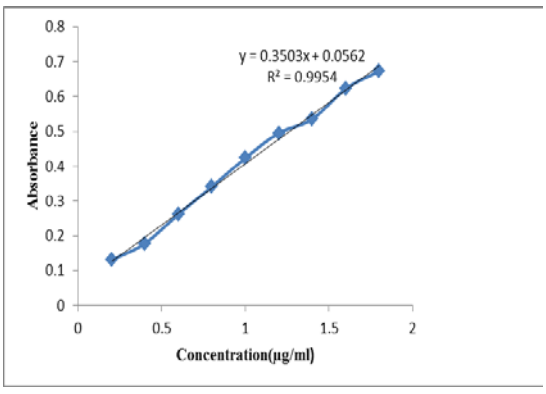

Fig. 2: Calibration curve in phosphate buffer pH 6.8

In vitro drug release and kinetic studies

The drug release time profile from different concentration of Chitosan patches were shown in Figure 11.

The curve was obtained after plotting the cumulative amount of drug released from each formulation vs. time. The *in vitro* drug release studies showed maximum percentage drug release of 85.442 % for F1, 89.023% for F2, 92.153% for F3, 94.106 % for F4, 98.01% for F5 respectively for a maximum of 7 hours. After 7 hours, the patch had lost their integrity and hence was not fit for further release study. Formulation F5 98.01% showed maximum release while other formulations showed less amount of drug release in 7 hr.

In vitro Antibacterial Activity

The *in vitro* antibacterial activity by agar diffusion assay demonstrated a significant antibacterial profile of the optimized patch F5 against S.*pneumoneia*. The optimized formulation showed greater growth inhibition area for streptococcus species with no zone of inhibition for the blank patch (with out drug) were shown in Figure 12.

Scanning Electron Microscopy (SEM)

The morphological study by Scanning electron microscopy (SEM) in Figure 13 showed the upper surface of patch containing Cefixime (F5) was rough with numerous pores inside it.

Stability studies

From the stability studies (Figure 14) it was confirmed that the optimized patch F5 of 5% chitosan concentration remained stable at room temperature (30 ± 2°C) and at refrigerator temperature (5 ± 2°C).

Table 3: Physio-chemical evaluation data of different patches

Code	Mean Thickness (mm)	Average Weight (mg)	Folding Endurance	Surface pH	Swelling index (%)	Moisture Absorbed (%)	Moisture Loss (%)	Drug Content (%)
F1	0.180 ±0.02	6.33 ±0.12	309 ±0.02	5.6 ±0.02	18.24 ±0.01	5.06 ±0.01	2.85 ±0.04	87.31 ±0.36
F2	0.211 ±0.03	8.10 ±0.11	320 ±0.03	5.7 ±0.01	20.7 ±0.01	5.23 ±0.03	2.41 ±0.05	89.02 ±0.27
F3	0.280 ±0.01	9.78 ±0.12	346 ±0.02	5.6 ±0.05	22.5 ±0.04	5.46 ±0.02	2.20 ±0.02	90.46 ±0.37
F4	0.326 ±0.03	10.36 ±0.13	374 ±0.01	6.1 ±0.01	25.8 ±0.03	6.37 ±0.01	1.88 ±0.03	95.38 ±0.28
F5	0.368 ±0.02	11.42 ±0.14	390 ±0.03	6.3 ±0.01	28.8 ±0.03	6.96 ±0.02	1.24 ±0.04	96.35 ±0.32

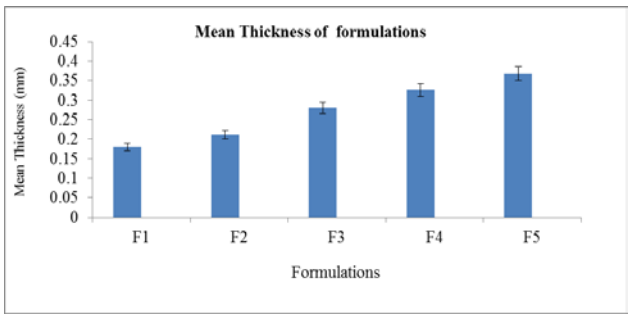

Fig. 3: Mean Thickness of the formulations

Each value indicates the mean ± SD (n = 3)

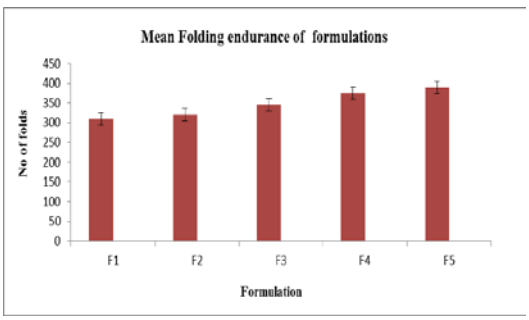

Fig. 5: Mean Folding Endurance of the formulations

Each value indicates the mean ± SD (n = 3)

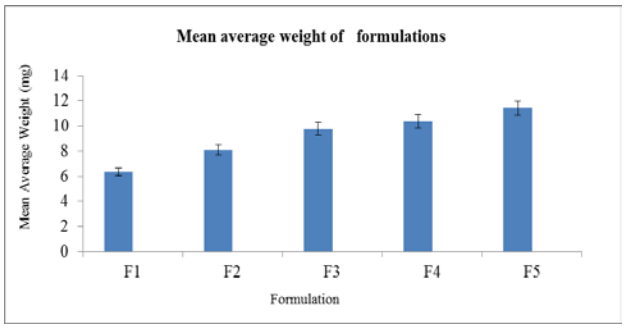

Fig. 4: Mean Average Weight of the formulations

Each value indicates the mean ± SD (n = 3)

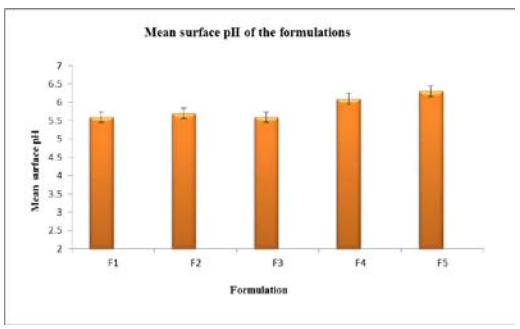

Fig. 6: Mean surface pH of the formulations

Each value indicates the mean ± SD (n = 3)

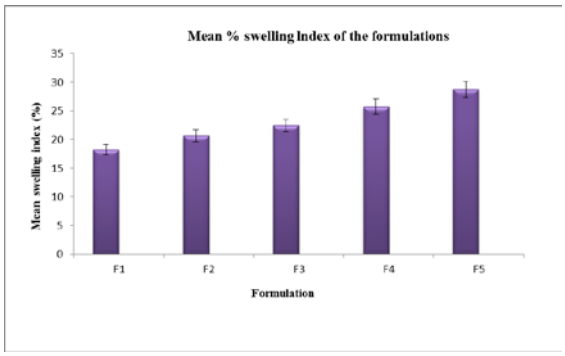

Fig. 7: Mean swelling index of the formulations

Each value indicates the mean ± SD (n = 3)

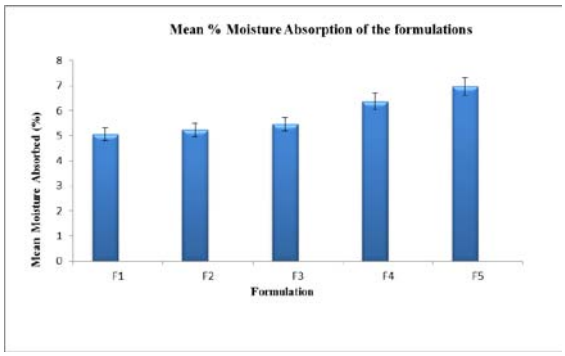

Fig. 8: Mean Percentage moisture absorption of the formulations

Each value indicates the mean ± SD (n = 3)

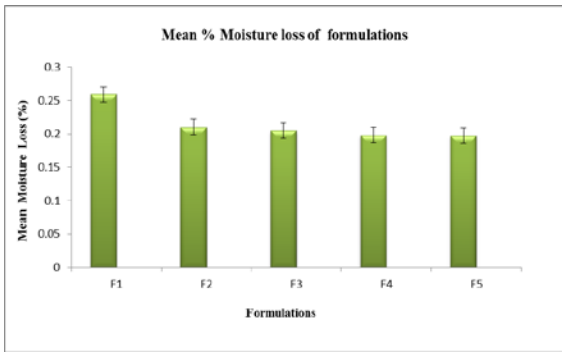

Fig. 9: Mean Percentage moisture loss of the formulations

Each value indicates the mean ± SD (n = 3)

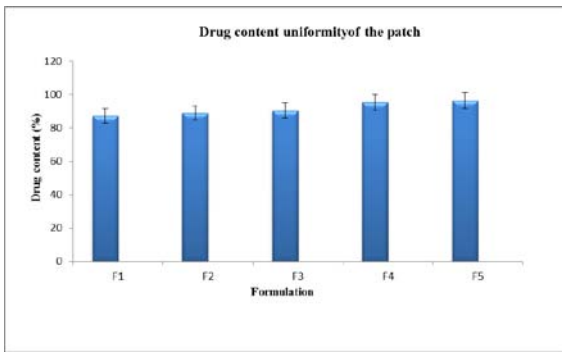

Fig. 10: Mean Drug Content Uniformity of the formulations

Each value indicates the mean ± SD (n = 3)

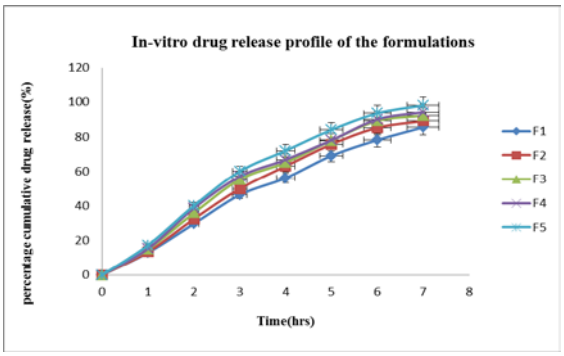

Fig. 11: *In vitro* drug release profile of F1 to F5 formulations

Each value indicates the mean ± SD (n = 3)

Fig. 12: *In vitro* antibacterial study of F5 formulation and blank patch

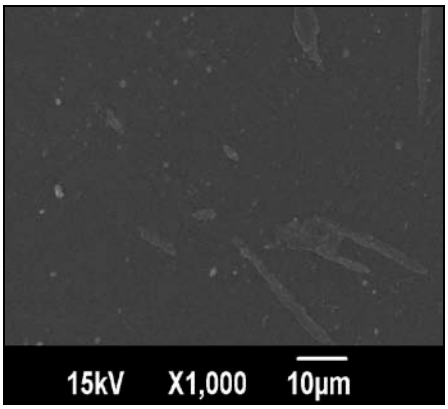

Fig. 13: SEM image of F5 formulation

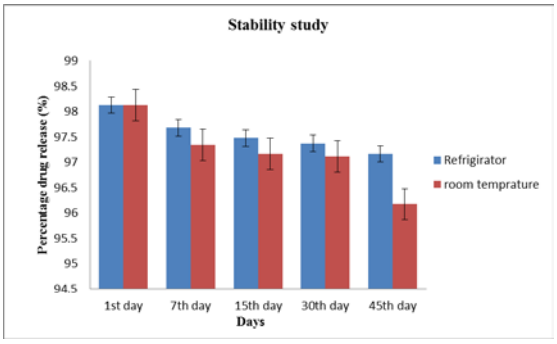

Fig. 14: Stability data of F5 formulation

Each value indicates the mean ± SD (n = 3)

DISCUSSION

In the present study, Chitosan patches (F1 – F5) containing drug Cefixime (1%) were prepared by solvent casting method with the incorporation of propylene glycol as a plasticizer. The drug loaded patches were flexible and the physicochemical evaluation parameters were found to be satisfactory. The average weight and thickness of patches increase as the polymer concentration increases. The surface pH of the all the formulations was very close to the neutral pH indicated negligible irritation to the mucosal membrane. The percentage moisture loss decreases as the polymer concentration increases due to the greater compactness and hence lower porosity of the F5 patch. The small moisture content in the formulations helps them to remain stable and from being a completely dried and brittle patch. All formulations exhibited good folding endurance exceeding 300, indicating that they are tough and flexible due to hydrophobic characteristics of chitosan. The drug content studies showed uniform and homogeneous distribution of drug inside the formulation. *In vitro* release studies performed using PBS 6.8 released the drug in a biphasic manner and showed an initial burst release by more than 40%, which is expected to kill most of the periodontal organism, followed by controlled release for about 3 to 7 hrs for different formulations, which was above the minimum inhibitory concentration of drug cefixime. .In the present investigation it was observed that as the concentrations of polymer increased in the formulations, the drug release rate increased substantially. The percentage cumulative drug release is greater in F5 formulation than F1, as these lesser polymer concentration are easily degraded by the saliva and other buccal secretions and it may also be due to formation of more pores which result in drug entrapment to a larger extent and amount. The above formulation (F5) with zero order kinetics showed that the F5 formulation of chitosan is a better formulation for delivering the drug into the buccal region for 7 hrs with maximum drug release The formulation F5 showed greater growth inhibition area against Streptococcus species with an MIC value of 0.29microgram/ml. Scanning electron microscopy (SEM) showed that the upper surface of patch was rough with numerous pores inside. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions. The drug remained intact and stable in the buccal delivery system during storage, with no significant chemical interaction between the drug and the excipients. These findings suggested that the developed formulation was a viable alternative to conventional dosage form against bacterial infections.

CONCLUSION

The advantages of a buccal delivery over systemic delivery is that it is less time-consuming, economically viable and rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. The present study was aimed to develop a low-dose local controlled delivery system of antibacterial drug Cefixime in the form of a buccal patch to overcome the problems like low solubility, low bioavailability and half-life of the drug, thereby prolonging the duration of action for treating bacterial infections and to maintain the concentration of the drug above its minimum inhibitory concentration for a prolonged period of time at the site of infection. From this experimental study it can be concluded that the prepared bucco adhesive patches shows promising physical characteristics along with desire in-vitro drug release and antibacterial profile, which is suitable to achieve the goal of this work. Further work is necessary for commercialization of the experimental thought.

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