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Development and Characterization Buccoadhesive Film of Ciprofloxacin Hydrochloride

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ABSTRACT: The purpose of the experimental study was to design a sustained release film formulation of ciprofloxacin hydrochloride for the treatment of periodontal diseases and investigate different experimental parameters to conclude in details about its different characteristics.Films were formulated using different concentration hydroxypropylmethyl cellulose and polyvinyl alcohol. The prepared films were subjected to different evaluation like determination of weight, thickness, surface pH, folding endurance, swelling index, mucoadhesion time, mucoadhesion strength, drug content, in-vitro drug release study, ex-vivo release study and release kinetic behavior. From the results of evaluation it was concluded that all the prepared films having desire flexibility and mucoadhesive properties, along with that they shows good in-vitro and ex-vivo drug release performance. Drug release from the films follows desire sustained release phenomenon as needed in buccoadhesive drug delivery.
KEYWORDS: - Buccoadhesive film, Ciprofloxacin hydrochloride, Periodontal diseases.

INTRODUCTION

Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time to get the desire benefit, not only for local targeting of drugs but also for the better control of systemic drug delivery[1]. The concept of mucosal adhesion or mucoadhesive was introduced into controlled drug delivery area in the early 1980's, which is become a major part of novel drug delivery system in the recent era. Some of the potential sites for attachment of any mucoadhesive system are include buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route and gastrointestinal area. Amongst the various routes of administration tried so far for novel drug delivery systems localized delivery to tissue of the oral cavity has been investigated for a number of applications including the treatment of toothaches, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis and facilitating tooth movement with prostaglandins [2]. Oral transmucosal drug delivery may be of 3 types like sublingual, gingival, and buccal [3]. 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[4]. However, the buccal route of drug delivery gain superiority because of its unique advantages over the other oral transmucosal routes.[5] A number of mucoadhesive devices has been developed in the recent era includes tablet[6], films[7], patches[8], disks [9] strips,[10]ointments,[11] and gels[12] etc. However, buccal films offer greater flexibility and comfort than adhesive tablets. In addition, films can circumvent the problem of the relatively short residence time of oral gels on mucosa. Since the gels are easily washed away by saliva[13]. Again it can be introduced to the wound surface that can control the healing more effectively[14]. An ideal buccal film 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[15].

A significant proportion of total world populations are affected by the periodontal diseases [16], which is mainly caused by periodontal pathogens such as *Porphyromonas gingivalis, Prevotella intermedia* and *Actinobacillus actinomycetemcomitans*[17]. Therefore, an objective of periodontal treatment is to suppress or eliminate subgingival periodontal pathogens. Ciprofloxacin is a second generation fluroquinolone derivative; exhibiting activity against a wide range of Gram-negative and Gram-positive facultative bacteria, as well as it also shows its potentiality against periodontal pathogens[18, 19]. The physicochemical properties of ciprofloxacin hydrochloride like short half life (3-5 hours), low molecular weight and extensive first-pass metabolism (25%), makes it a suitable candidate for administration by buccal route[20].

The purpose of this study was to develop buccoadhesive film formulations for the treatment of periodontal diseases and systematical evaluation of its in-vitro and ex-vivo performances. The film were prepared by introducing polymer like hydroxypropyl methyl cellulose (HPMC) and polyvinyl alcohol (PVA), where ciprofloxacin hydrochloride were selected to use as a model drug based on its pharmacological activity and physicochemical property. The prepared film were subjected to different evaluation parameters like folding endurance, study of surface pH, thickness of film, mucoadhesion property of film, swelling index study etc.

MATERIAL AND METHODS

MATERIALS

Ciprofloxacin hydrochloride was supplied by the Dr. Reddy's Laboratory, Hyderabad, India. Hydroxypropyl methylcellulose (HPMC K4 M) was purchased from Loba Chemie Pvt. Ltd. Polyvinyl alcohol (PVA) was punched from Burgoyne Urbidgis & co. India, Mumbai. All the other analytical grade ingredient was procure from commercial chemical supplier.

PREPARATION OF FILM:

The buccoadhesive film of ciprofloxacin was prepared using different concentration of polymers like HPMC and PVA. The calculated amount of polymer was shocked in 20 ml of distilled water for 24 hours. Than drug (ciprofloxacin hydrochloride 250 mg) was added as solution form in polymeric solution with continues stirring. Desire quantity of glycerin was added in homogenized drug polymer solution and kept aside for some time at room temperature .The above polymeric solution was transferred to previously prepared glass block and kept for drying in room temperature. The dried film was then cut into 2x2 cm pieces, wrapped in aluminum foil and was kept in desiccators until further use. The formula of the prepared films is mention in table no-I.

FILM WEIGHT AND THICKNESS:-

For evaluation of film weight, three films of every formulation were selected randomly and individual weight of each 2x2cm film was taken on digital balance. The average weight was calculated similarly, three film of each formulation were selected randomly and the film thickness was measured using micrometer screw gauge at three different places and the mean value was calculated [21].

SURFACE pH OF FILM

For determination of surface pH three films of each formulation were selected randomly and are allowed to swell for 2 hours on the surface of previously prepared 1% agar plate. The surface pH was measured by using a pH paper placed on the surface of swollen film[2].

FOLDING ENDURANCE

Folding endurance of the 2x2cm films was determined by repeatedly folding one film at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on two individual films of each formulation batches. [22]

SWELLING INDEX

Buccal films were weighed individually (designated as W1) and placed separately in 1% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1hour time intervals until 3 hours, patches were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen patches were then reweighed (W2), and the swelling index (SI) was calculated using the following formula[23]. The experiments were performed in triplicate, and average values were reported in table no – II.

$$SI = \frac{(W2 - W1)}{W1} \times 100$$

CONTENT UNIFORMITY

Drug content uniformity was determined by dissolving each 2x2cm films of different batches in 100mL distilled water. The whole content was then shake continuously 5 hours with the help of rotary shaker and then kept aside for 24 hours. Then the solution was filter with Whatman filter paper (0.45 µm). Form the filtrate 5ml solution was taken and suitably diluted

with distilled water and analyzed at 278nm using a UV spectrophotometer[15]. The experiments were performed in triplicate, and average values were reported in table no – II.

MUCOADHESION TIME

For determination of mucoadhesion time or residence time of the prepared formulation a fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water[15]. The residence time was determined using a locally modified USP disintegration apparatus [24]. Distilled water (500ml) was used as disintegration medium and a 37°C ± 1°C was maintained throughout the experiment. A segment of fresh sheep buccal mucosa, 3 cm long, was glued to the surface of a glass slide, which was vertically attached to the apparatus using thread. The mucoadhesive film was hydrated from one surface using distilled water and then the hydrated surface was brought into contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to move up and down so that the film was completely immersed in the water at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the film from the mucosal surface was reported in table no – II.[25]

EX VIVO MUCOADHESIVE STRENGTH

To perform the ex-vivo mucoadhesive strength fresh sheep buccal mucosa was obtained from a local slaughter house and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water. The bioadhesive strength of films was measured on a modified physical balance using the method.[21] A piece of buccal mucosa was tied in the open mouth of a glass vial, filled with distilled water. This glass vial was tightly fitted into a glass beaker filled with distilled water, so it just touched the mucosal surface and temperature of 37°C ± 1°C was maintain throughout the experiment. The film was stuck to the lower side of a rubber stopper with adhesive. Two pans of the balance were balanced with a 5g weight on the right-hand side pan. The 5g weight was then removed from the left hand side pan, which lowered the pan along with the film over the mucosa. The balance was kept in this position for 10 minutes of contact time. The water was added slowly at 100 drops/min to the right-hand side pan until the film detached from the mucosal surface. The weight, in grams, required to detach the film from the mucosal surface was measured manually which provided the measurement of mucoadhesive strength. The experiments were performed in triplicate, and average values were reported.

***IN-VITRO* DRUG RELEASE STUDY**

The Veggo VDA-6D USP six station dissolution apparatus was used throughout the study. The dissolution study was performed by using basket type setting where, one film of each batches was fixed inside the basket. The dissolution media consist of 500ml of distilled water. The release study was performed rotation speed of 50 rpm and a temperature of 37°C ± 1°C was maintained throughout the experiment. The release study was carried out for 6 hours. After every 30 min. interval 5ml of sample was withdrawn from each station and the same was replaced back to the station. Each withdrawn sample was filtered, diluted suitably and then analyzed spectrophotometrically at 278nm. The experiments were performed in triplicate, and average values were reported.

EX-VIVO DRUG RELEASE STUDY

The Veggo VDA-6D USP six station dissolution apparatus was used throughout the study. The setup were slightly modified, where a two side open ended glass tube were set by replacing the basket. One end of the glass tube was attached with the dissolution apparatus and in the other end the membrane was attached. The film was introduced inside the glass tube. The dissolution media used for the study was 500ml of distilled water. The release study was performed at 37 ± 0.5°C with rotation speed of 50 rpm. The release study was carried out for 6hours. After every 30 min. interval 5ml of sample was withdrawn from each station and the same was replaced back to the station. Each withdrawn sample was filtered, diluted suitably and then analyzed spectrometrically at 278nm.

RESULTS & DISCUSSION:

The main goal of this experimental work was to develop a new polymeric film containing ciprofloxacin hydrochloride as an active constituent and to perform different experimental study to conclude in details about its different characteristics of the prepared film.

Physical characteristics of all the prepared films are represented in Table II. The prepared films were of 2x2cm in size and 0.22-0.31 mm in thickness. The weight of films was found within the range from 53 to 72 mg. The surface pH of all formulations was within 6-7 that is close the neutral pH and hence no mucosal irritation was expected. The recorded folding endurance of all the prepared films was > 300 times, that can be consider as a sign of good flexibility. Assessment of the swelling behavior was done by measuring percentage swelling. In the case of films

intended for local therapy, the contact area should be as large as possible, a requirement that must be balanced with patient compliance; excessive increase swelling index might cause discomfort and/or dislodgment of the swollen film. The recorded data show that films prepared with PVA having high swelling tendency ranges from 42.46 - 47.46 as compare to the film prepared with HPMC ranges from 35.93 – 42.42. These differences in swelling were may be due to the difference in resistance of matrix network structure (hydrogen bond) towards the movement of water molecules. The recorded data obtain from mucoadhesion time study suggest that films prepared by introducing HPMC as polymer having higher mucoadhesion time ranges from 211 -238 min, as compare to the PVA films which ranges from 133 -156 min, the reason behind this may be due to higher bonding attachment (hydrogen bonding) between buccal layer and polymer.

All the results of other evaluation parameters like, mucoadhesion strength, % drug content, in-vitro cumulative percentage release study, ex-vivo release study, R^2 value of higuchi release kinetics study are introduced in table no- III. From the resultant data of mucoadhesive strength study it can be conclude that films composed of HPMC shows higher mucoadhesion strength as compare to films composed of PVA and among the several formulations of HPMC F4 formulation shows highest mucoadhesion strength. It may be due to increased amount of solid content of polymer which ultimately improves the adhesive strength of the fabricated formulation. As per the results of drug content study it has been found that all the prepared formulation contain not less than 95 % of drugs which can be consider as a sign of good formulation. All the films are design by considering a well understandable fact that if the films gives too sustained release profile it means the films should kept in contact of buccal mucosa for prolong period of time which may cause discomfort to patient. The data obtained from in-vitro drug release study performed up to 6 h gives a clear indication that prepared films shows necessary sustained release profile desire for buccoadhesive drug delivery. Amongst them, Formulations like F5 and F6 shows highest drug release at 6^{th} hours 92.04%, 91.61% respectively. On the other side F4 formulation shows lowest release profile 71.39% at 6^{th} hours among all. Again all the formulation shows more than 70 % of drug release at 6^{th} hours. The differences of release profile may be due to differences in characteristics and presence of different functional groups of introduced polymers. Again it has been found that increase solid content of polymer has a negative effect on drug release. The graphical representation in-vitro release profile of different formulation batches are shown in fig-I and II. Based on the % drug content four formulations have been selected for ex-vivo study. All the four formulation shows more than 55% of drug release among them F7 formulation gives highest ex-vivo drug release of 62.20%. The graphical representation ex-vivo release profile of different formulation batches are shown in fig-III. The R^2 value represented for in-vitro release kinetic study perform based on higuchi kinetic release shows that, formulations like F1, F2, F3 and F7 are best fit to the higuchi plot. The graphical representation in-vitro release kinetics of different formulation batches are shown in fig-IV.

TABLE NO – I, FORMULA OF DIFFERENT FORMULATION BATCHES.

Slno.	Ingredients	Formulation batch							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Ciprofloxacin HCL (mg)	250	250	250	250	250	250	250	250
2	HPMC K4M (mg)	250	500	750	1000	-	-	-	-
3	Polyvinyl alcohol(mg)	-	-	-	-	-	500	750	1000
4	Glycerin (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
5	Distill water(ml)	30	30	30	30	30	30	30	30

TABLE NO – II, DIFFERENT PHYSICAL PARAMETER OF ALL THE PREPARED FILMS*.

Slno	Batch code	Weight variation (mg)	Surface pH	Folding endurance	Thickness	Swelling index	Mucoadhesion time (min)
1	F1	56 ± 2	7	>300	0.22 ± 0.02	35.93 ± 1.26	211 ± 4
2	F2	53 ± 4	6	>300	0.25 ± 0.03	37.75 ± 2.22	221 ± 5
3	F3	55 ± 2	6	>300	0.23 ± 0.02	42.42 ± 4.11	232 ± 3
4	F4	57 ± 3	7	>300	0.25 ± 0.01	41.76 ± 2.11	238 ± 3
5	F5	65 ± 3	7	>300	0.28 ± 0.03	47.46 ± 1.36	133 ± 7
6	F6	55 ± 4	6	>300	0.29 ± 0.02	43.22 ± 1.63	142 ± 5
7	F7	72 ±5	6	>300	0.31 ± 0.04	44.22 ± 2.35	153 ± 2
8	F8	62 ± 3	6	>300	0.29 ± 0.03	42.46 ± 2.87	156 ± 6

- Values are presented as average ± SD, n=3

TABLE NO – III, RESULTS OF DIFFERENT OTHER IMPORTANT STUDY ALONG WITH IN-VITRO AND EX-VIVO RELEASE DATA.

Batch code	% Drug content	In-vitro cumulative % drug release after 6th hours	Ex-vivo cumulative drug release after 6th hours	Mucoadhesion strength (dyne/cm^2)	Higuchi release kinetics R^2 value
F1	98.80	80.15	58.77	10.48 + 0.7	0.973
F2	98.11	79.96	55.90	11.02 + 0.2	0.981
F3	99.20	73.95	-	12.33 + 0.5	0.979
F4	96.00	71.39	-	12.78 + 0.4	0.826
F5	95.78	92.04	-	7.23 + 0.3	0.871
F6	97.65	91.61	-	7.98 + 0.4	0.723
F7	98.88	79.92	62.20	8.56 + 0.6	0.904
F8	98.54	76.13	57.07	9.02 + 0.3	0.892

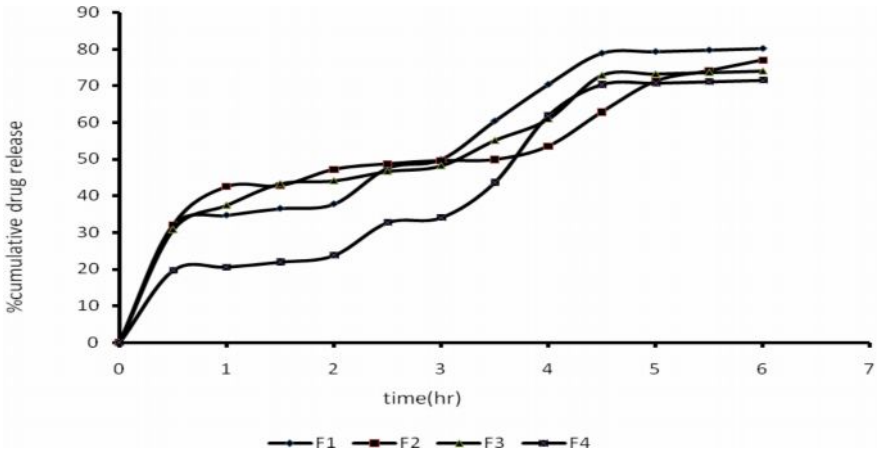

Fig – I, Graphical Representation of In-vitro Drug Release Study of Different Formulations F1, F2, F3 and F4.

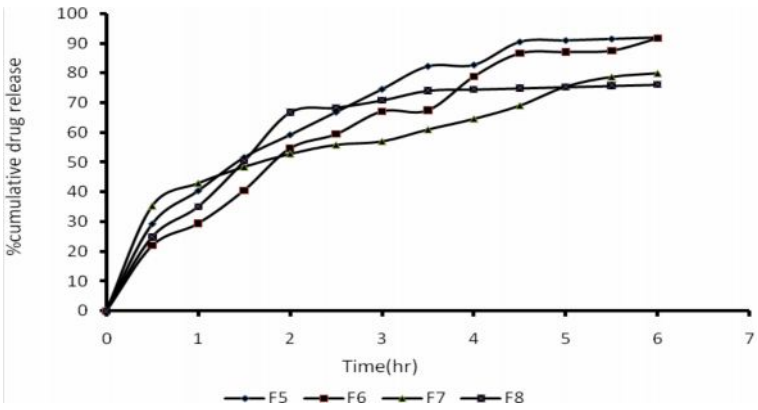

Fig – II, Graphical Representation of In-Vitro Drug Release Study of Different Formulations F5, F6, F7 and F8

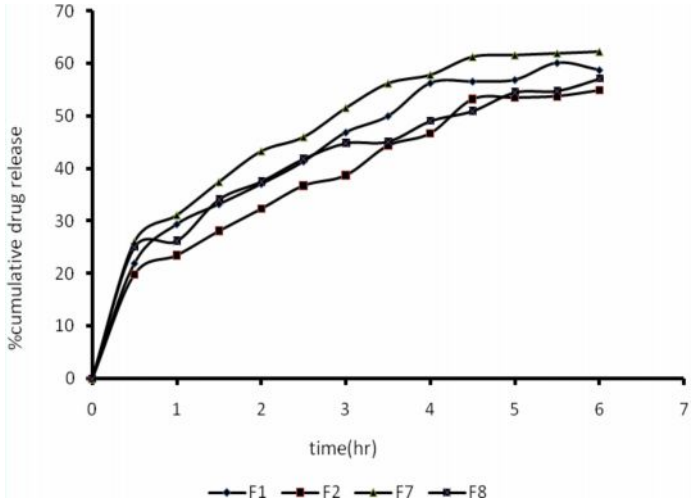

Fig – III, Graphical Representation of Ex-Vivo Drug Release Study of Different Formulations F1, F2, F7 and F8.

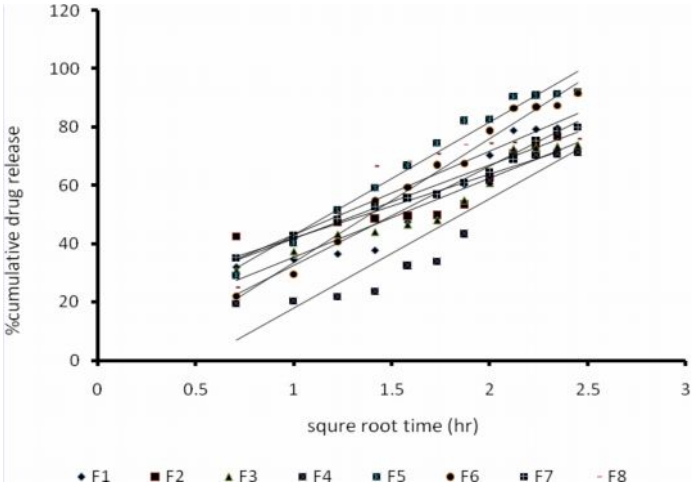

Fig – IV, Graphical Representation of Higuchi Kinetic Release Profile of All the Prepared Formulation

CONCLUSION

The advantages of buccoadhesive film delivery over systemic delivery in periodontitis are like administration is less time-consuming than mechanical debridement and a lower dose of drug would be required to achieve effective therapeutic concentration at the site of action. From this experimental study it can be concluded that the prepared buccoadhesive films shows promising physical characteristics along with desire in-vitro drug release profile, which is suitable to achieve the goal of this work. It was also found that in respect to mucoadhesion time, mucoadhesion strength study and in-vitro drug release study the performance of films composed of HPMC gives better results as compare to the films composed of PVA. Further work is necessary for commercialization of the experimental thought.

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