ORIGINAL ARTICLE

Mucoadhesive Buccal Films Based on Chitosan and Carboxymethylated *Feronia Limonia* Fruit Pulp Mucilage Interpolymer Complex for delivery of Opioid Analgesics

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Abstract

Aim: To develop and evaluate interpolymer complex (IPC) based buccal mucoadhesive films for delivery of opioid analgesics. The IPC was prepared using Chitosan and carboxymethylated *Feronia limonia* fruit pulp mucilage. **Materials and Methods:** In this study, the IPC is formed between mucoadhesive polymer chitosan and carboxymethylated *F. limonia* fruit pulp mucilage. The resulted IPC is used to prepare buccal mucoadhesive films of a model opioid analgesic. Other excipients include glycerin as plasticizer, a combination of sodium dihydrocholate and ethylenediaminetetraacetic acid sodium salt as permeation enhancers and a backing layer of 1% ethyl cellulose is placed on each film to ensure unidirectional drug release to systemic circulation. The solvent casting method is used to prepare buccal films and evaluated for bioadhesion strength, tensile strength, swelling index, *ex vivo* diffusion, and *in vitro* dissolution. **Results and Discussion:** Formulations are prepared and optimized by 3^2 factorial design. Formulation F7 was found to be optimized formulation which contained 50 mg drug, 100 mg IPC, and 2% glycerin as plasticizer. Thus, this study suggests that IPC between chitosan and carboxymethylated *F. limonia* fruit pulp mucilage can act as a potential mucoadhesive polymer system for buccal delivery of opioid analgesic drugs. **Conclusion:** In this study novel, buccoadhesive film was developed using IPC between chitosan and carboxymethylated *F. limonia* fruit pulp mucilage. The film was releasing drug over a period of 8-h directly to systemic circulation through buccal mucosa. The extensive first pass metabolism of a drug was prevented to a great extent.

Key words: Interpolymer complex, carboxymethylated *Feronia limonia* fruit pulp mucilage, factorial design, mucoadhesive films, optimization

INTRODUCTION

The transmucosal route has been an attractive area of research in the development of novel drug delivery systems due to its unique ability to administer medicaments directly into systemic circulation by bypassing first pass metabolism. The various drug delivery systems are very much capable of adhering to the site of the application for the duration of treatment. The direct administration of medicament into systemic circulation leads to improved bioavailability and gives quick onset of action.[1] Mucosal drug delivery systems release drug in the region of buccal cavity from which drug readily absorbed through the venous systems drains from the cheek and thus bypass the first pass metabolism.[2] Buccal mucosa is having a very high permeability compare to the transdermal route. The high permeability is attributed by the rich blood supply in the buccal mucosal region.[3] The higher patient compliance and safety can be achieved because of the possibility of removing dosage forms from site of applications on observing any side effects or toxic effects. A considerable amount of research has been done by many researchers to develop various buccoadhesive devices including tablets,[4] films,[5] patches,[6] disks,[7] and strips.[8] Among all buccal films are more preferable because of flexibility and comfort.[9]

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Advantages like biodegradability and biocompatibility make natural gums and mucilages very promising excipients in the development of novel drug delivery systems. Other benefits include cost effectiveness and easy availability.[1] In this study chitosan - *F. limonia* mucilage interpolymer complex (IPC) was used as bioadhesive polymer to increase the residence time of the dosage form in buccal cavity. This IPC swells in aqueous media to form a gel through which the drug diffuses. It shows that IPC between chitosan and biopolymer can be used to control the release rate of drug from matrix.

In this study *F. limonia* fruit pulp mucilage, a polysaccharide, acetylated glucomannan, is located within the protoplast of the parenchyma cells. *F. limonia* fruit pulp holds mainly mannose - containing polysaccharides, cellulose, and pectin polysaccharides.[10] Mucilage is neutral in nature and is subjected to introduce carboxymethyl group by Williamson synthesis method. The added carboxymethyl functional group imparts negative charge to mucilage and thus carboxymethylated mucilage can easily be used to make IPC with chitosan.

Tramadol hydrochloride is used as a model opioid analgesic drug to study the diffusion and drug release mechanism from the films. It is a centrally acting opioid analgesic mainly used to treat moderate to severe pain conditions. It is having good absorption after oral administration, but the reason for poor oral bioavailability is extensive first pass metabolism via N and O-demethylation and glucuronidation or sulfation in the liver.[11]

IPC of chitosan and *F. limonia* fruit pulp mucilage have not been reported for the use of development of buccoadhesive drug delivery systems. An attempt has been made in this study to utilize *F. limonia* fruit pulp mucilage which is widely available, mucoprotective in nature and a more economical source of polysaccharides in the development of buccal film for systemic delivery of a model opioid analgesic.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was obtained as a gift sample from Karnataka Atibiotics & Pharmaceuticals Ltd. (Bengaluru). *F limonia* fruits were procured from local market in Vadodara. Chitosan was purchased from Pure Chem Pvt. Ltd. (Ankleshwar). All other chemicals were purchased from Merck Ltd. (Mumbai).

Experimental design

Optimization of buccal films was done by using a 3^2 randomized full factorial design as shown in Table 1 . This method includes evaluation of two factors individually at three levels. Different codes such as −1, 0 and +1 were given to lower, medium, and higher levels of both variables. Two independent variables were the amount of IPC in specific ratio of drug (X_1) and the concentration of glycerin (plasticizer) (X_2). Tensile strength (Y_1), bioadhesion force (Y_2), and % drug release at 8 h (Y_3) were selected as response variables.

Isolation of mucilage by microwave procedure

F. limonia fruit pulp (10 g) was dried and powdered for 5 min in a mechanical blender and soaked in distilled water (150 ml) for 24 h in an RB flask. It was kept in a microwave oven (LG Grill Intello wave System, Model No. MW-3291LE) along with a glass tube inside to prevent bumping. It was subjected to microwave irradiation at 800 W intensity for 3 min. The beaker was removed from the oven and kept aside for 2 h for the release of mucilage into water. It was processed in a similar way as explained in the conventional procedure, weighed and chemical tests were carried out.[12]

Carboxymethylation of mucilage

About 100 g of mucilage powder was added in a mixture of 630 ml of ethanol and 554 ml of toluene. To this 44.8%, w/v NaOH was added gradually and mixed thoroughly. This mixture was kept at room temperature for 30 min. After that Monochloro-acetic acid (120 g) was gradually added with agitation to this mixture and kept overnight. After keeping it overnight, the excess alkali was neutralized with glacial acetic acid using phenolphthalein indicator. The product was filtered, washed with ethanol and dried.[13]

Preparations of mucodhesive buccal films

Mucoadhesive buccal films were prepared by solvent casting method. Nine different formulations were prepared as shown in Table 2. Chitosan was dissolved in 60 ml 5 M acetic acid to produce 2.5% chitosan solution. To this solution, 10 ml 5 M ammonium solution was added. Drug was dissolved in 40 ml 2.5% carboxymethylated mucilage solution with constant stirring for 15 min using mechanical stirrer. Glycerin was used as plasticizer. This solution was sonicated for 45 min to remove air bubbles. This solution was poured in Petri dish of size 8 cm in diameter and was dried in vacuum oven at 55°C for 24 h. The backing layer of 1% ethyl cellulose was placed by pouring solution over medicated buccal film and dried in vacuum oven at 55°C for 4 h. Dried films were cut into 1.5 cm^2 patches containing 50 mg of drug in each patch.

Characterization of buccal films

Thickness and weight

The thickness of film was measured using micrometer screw gage. For each formulation, three films were selected randomly with surface area 1.5 cm^2. The weight of individual films was noted down using analytical balance. An average weight was then calculated.

Swelling studies

Swelling index study is useful to find out and compare the water absorption characteristics of film polymers. Pre-weighed films (designated as w_1) are placed separately in Petri plate having phosphate buffer 6.8 pH. At regular intervals (5, 10, 15, 20, 25, 30, 35, 40, 60 min), films were removed from the Petri plate. Excess water was removed carefully using filter paper. The swollen films were reweighed (w_2). The following formula was used to calculate swelling index.[14]

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100 \quad (1)$$

Measurement of surface pH

Surface pH of film was found out to see whether the film can cause irritation to the mucosa or not. The surface pH study was performed by selecting 3 films randomly. Digital pH meter was used to find out pH. The pH electrode was placed in close contact with the wetted film surface, and pH was recorded for each film.[15]

Folding endurance

The Folding endurance was determined to check flexibility of films. All selected films were folded repeatedly at same place until they broke to determine folding endurance. The action was repeated until films broke or were folded for 300 times whichever is less.[16]

Tensile strength

Texture analyzer (CT-3/10,000, Brookfield, USA) equipped with a 10 kg load cell was used to check tensile strength of the formulation. The film of 200 mm^2 was randomly selected and was fixed between the two clamps of probe TA-DGA and for a hold time of 60 s. The lower clamp was held stationary, and the film was pulled apart by the upper clamp. The film was pulled at a speed of 2.0 mm/s to a distance of 6 mm with trigger load 0.05 N. The force of the film at the point when the film broke was recorded.[17]

Texture - Pro CT V1.3 Build 14 software was used for data collection and calculations. The tensile strength break value was calculated using formula as follows:

$$\text{Tensile strength (kg/mm}^2\text{)} = \frac{\text{Force at break}}{\text{initial cross-sectional area}} \quad (2)$$

In vitro bioadhesion force

Texture Analyzer (CT-3/100, Brookfield, USA) equipped with a 100 g load cell was used to determine the bioadhesion force of buccal patches. The porcine buccal mucosa was used as the model membrane for the measurement of buccal mucosa. The mucosal membrane was isolated by removing the underlying connective tissue. The mucosal membrane was washed thoroughly with phosphate buffer (pH 6.8). Then, the membrane was fixed between two circular discs which were at lower Perspex support. The upper circular disc had a cavity of 12.7 mm diameter through which the mucosal membrane was exposed to the probe. The discs were lowered into the jacketed glass container filled with phosphate buffer (pH 6.8) which was maintained at 37 ± 1°C. The test was started once the membrane was equilibrated at 37 ± 1°C for 30 min. The buccal film was firmly tight with the help of thread on lower side of probe. The probe and circular cavity were aligned in such a way that film comes into direct contact with exposed surface of mucosal membrane. Exposed area of buccal film was moistened with phosphate buffer pH 6.8 before test starts. The probe was lowered at a speed of 0.5 mm/s to contact the tissue with load, 90 g and with contact time 120 s. It was removed at the speed of 2 mm/s.[18]

Texture - Pro CT V1.3 Build 14 software was used for data collection and processing. The adhesive force and adhesiveness were found out to evaluate the bioadhesive strength of film. Bioadhesion force (N) was calculated using formula as follows:

Table 1: Translation of coded levels in actual units

Variable levels	Low (–1)	Medium (0)	High (+1)
IPC: Drug (X_1)	0.5:1	1:1	2:1
% plasticizer glycerin (X_2)	2	4	6

IPC: Inter polymer complex

Table 2: Composition of various buccal film formulations

Ingredients	Formulations and quantity								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tramadol hydrochloride (mg)	50	50	50	50	50	50	50	50	50
Inter polymer complex (mg) (CH:CM, 60:40)	25	50	100	50	100	25	100	25	50
Glycerin (% w/v)	2	4	6	2	4	6	2	4	6
Sodium dihydrocholate (% w/v)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
EDTA disodium salt (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethyl cellulose (1% w/v)	Backing layer on F1-F9 formulations								

EDTA: Ethylenediaminetetraacetic acid

Table 3: Factorial design with corresponding 9 formulations

Batch no.	Variable levels in coded form		Tensile strength (kg/mm²) Y_1	Bioadhesive force (N) Y_2	Drug release (%) Y_3
	X_1	X_2			
F1	−1	−1	11.67±0.12	0.41±0.10	83.62±0.5
F2	−1	0	14.50±0.17	0.48±0.09	85.46±0.6
F3	−1	+1	16.28±0.18	0.53±0.10	87.56±0.5
F4	0	−1	12.49±0.14	0.79±0.09	91.52±0.7
F5	0	0	15.68±0.14	0.84±0.11	93.45±0.4
F6	0	+1	17.42±0.11	0.93±0.10	92.28±0.5
F7	+1	−1	16.54±0.14	1.13±0.11	95.06±0.6
F8	+1	0	18.32±0.16	1.17±0.12	88.22±0.5
F9	+1	+1	19.12±0.12	1.22±0.09	87.39±0.5

Bioadhesion force (N) = [Bioadhesive strength (g)/1000] × 9.81 (3)

RESULTS AND DISCUSSION

Nine different formulations were prepared by 3^2 randomized full factorial design. Design Expert software 8.0.6 was used to process various data collected by experimental processes. Various models such as Linear, 2FI, Quadratic, and Cubic were fitted to the data for two responses simultaneously using and adequacy and good fit of models were tested using analysis of variance (ANOVA). The formulation chart prepared by factorial design is shown in Table 3.

Spectral analysis of carboxymethylated mucilage

A slight modification can be observed in the well-defined spectrum of purified mucilage in Figure 1. The infrared spectrum of carboxymethyl polysaccharide shows a reduced intensity of the absorption band located at 3418 cm^{-1}, due to OH stretching, indicating that some OH groups were carboxymethylated. The band due to water (bending of water), which appeared at approximately 1650 cm^{-1} in the asymmetrical and symmetrical vibrations due to moiety were assigned to 1615 and 1780 cm^{-1}, respectively, which may be attributed to the incorporation of carboxymethyl groups into the polysaccharide.

Characterization of buccal films

Physicochemical characteristics of the bilayer films are shown in Tables 3 and 4.

Thickness and weight

The average thickness of buccal films is found out ranging from 0.36 to 0.46 mm. The weight variation values for films are ranging from 104 to 467 mg. Thus, it can be concluded that the increase in weight is well supported by the increase in thickness of films. This data indicates that the film was casted uniformly.

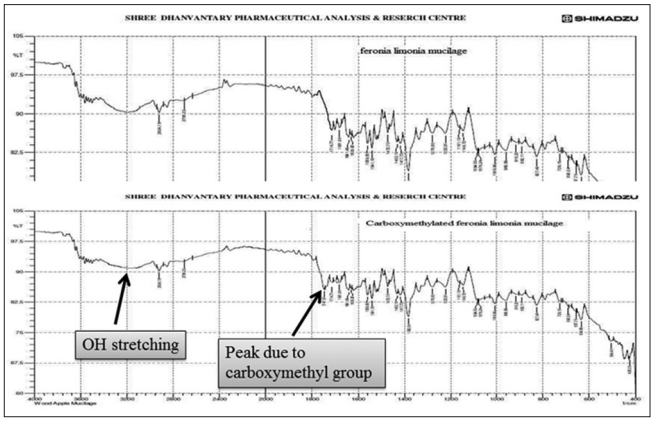

Figure 1: Infrared spectra of pure mucilage and carboxymethylated mucilage

Swelling studies

Swelling characteristics of films shows that as the concentration of IPC increases more swelling was observed in films. Values for the swelling index are in the range of 33.08-47.35. Thus, this study confirms that increase in swelling index is mainly because of increase in the concentration of IPC. Swelling index of film is directly associated with the release of drug.

Measurement of surface pH

Surface pH for formulation F1-F9 was found to range from 6.66 to 7.17. Since pH values of films are near to the salivary pH, no mucosal irritation was expected.

Folding endurance

The folding endurance of films was found to increase with increase in glycerin concentration. The values range from 247 to 320 which show that all films have high mechanical strength. This is highly desirable because it would not allow easy dislocation of the film from the site of application or breaking of film during administration.

Table 4: Result of physic-chemical characteristics of the bilayer films

Code	Thickness (mm)	Weight uniformity (mg)	Swelling index	Surface pH	Folding endurance	Permeation study (%)
F1	0.36±0.01	143.13±7.65	33.08±0.2	6.85±0.3	309±1.25	83.26±0.6
F2	0.37±0.02	242.64±7.63	39.23±0.3	6.66±0.2	296±2.50	86.23±0.7
F3	0.42±0.02	411.30±5.71	37.88±0.2	6.78±0.4	247±1.55	84.12±0.5
F4	0.36±0.01	159.50±5.52	37.47±0.3	7.11±0.3	253±1.50	87.76±0.8
F5	0.46±0.02	467.61±7.11	39.81±0.3	7.16±0.5	264±2.30	88.81±0.4
F6	0.39±0.01	301.30±7.41	34.03±0.2	7.08±0.3	257±2.30	89.53±0.6
F7	0.42±0.01	321.37±5.57	46.49±0.3	7.19±0.4	269±1.70	93.24±0.7
F8	0.38±0.02	104.21±6.64	47.35±0.2	7.17±0.4	320±2.75	91.21±0.8
F9	0.42±0.02	320.98±5.83	45.56±0.3	7.15±0.5	265±1.60	90.37±0.5

Effect of formulation variables on tensile strength

Tensile strength test data for all formulations show that films are sufficiently strong to withstand wear and tear occurring during handling, packaging, and transportation. The tensile strength of formulations is in the range of 11.67-19.12 kg/mm^2. Results indicate satisfactory mechanical strength.

The constant and regression coefficient for Y_1 (tensile strength) are shown below:

$$Y_1 = 15.61+1.92\ X_1+2.02\ X_2-0.50\ X_1X_2 +0.85\ X_1^2-0.60\ X_2^2 \quad (4)$$

The quadratic model was found to be significant with *F* value 64.20 ($P < 0.0001$) which shows that the model is significant. Figure 2 represents the contour plot showing the effect of different proportions of independent variables on the response Y_1. The increase in glycerin concentration at the same concentration of IPC is responsible for increase in tensile strength. The combined effect of factor X_1 (IPC) and X_2 (glycerin) can be further understood with the help of response surface plot [Figure 2]. High level of factor X_2 gave a high value of tensile strength at all levels of factor X_1 which shows that the factor X_2 has significant positive effect on tensile strength. Increase in concentration of glycerin and IPC were responsible for increase in tensile strength of buccal films.

Effect of formulation variables on in vitro bioadhesion force

Bioadhesion force is necessary to hold drug delivery system at the site of application during the course of treatment. Bioadhesion force is directly related to the swelling index. Higher the swelling index of polymer greater will be the bioadhesion force. Formulations F7, F8, and F9 show higher values of bioadhesion force to its good swelling index. Increase in concentration of IPC mainly responsible in higher bioadhesion force of buccal films.

The constant and regression coefficient for Y_2 (bioadhesion force) are as follows:

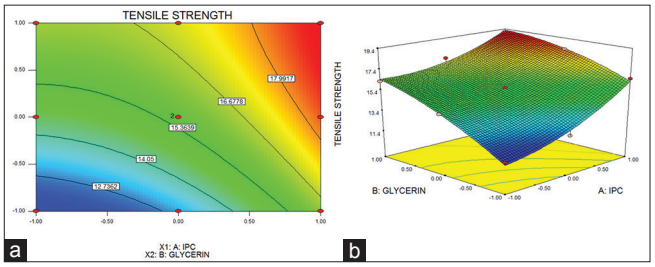

Figure 2: (a and b) Two-dimensional contour plot, three-dimensional response surface plots for Tensile strength

$$Y_2 = 0.83+0.35\ X_1+0.058\ X_2+2.50\ X_1X_2 -0.01\ X_1^2+7.14\ X_2^2 \quad (5)$$

The quadratic model was found to be significant with *F* value 936.47 ($P < 0.0001$) that shows that the model is significant. Figure 3 represents the contour plot showing the effect of different proportions of independent variables on the response Y_2. Increase in Bioadhesion force of buccal films is mainly because of increase in IPC concentration. The combined effect of factor X1 (IPC) and X2 (Glycerin) can be further elucidated with the help of response surface plot [Figure 3]. High level of factor X_1 gave high value of bioadhesion force at all the levels of factor X_2 which indicates that the factor X_1 has significant positive effect on bioadhesion force.

Effect of formulation variables on in vitro release of tramadol hydrochloride from buccal film

No significant release of drug was observed in any formulation until polymers swell completely, i.e., for 60 min. Formulations with higher concentration of IPC show good swelling index values, greater hydration rates, which would permit faster and ready disentanglement of individual chains, thus increasing the porosity of the film and gives good release. Formulation F7 showed highest drug release (95.06%) in 8 h. This optimized formulation (F7) was subjected to various mathematical models to understand the release pattern. The value of coefficient of regression (R^2) was found to be 0.9635 for Korsemeyers-Peppas and release exponent (n) was 0.5217 indicating that drug transport mechanism is mainly

anomalous transport, i.e., drug release is being governed by both diffusion as well as erosion.

The constant regression coefficient for Y_3 (% drug release) is as follows:

$$Y_3 = 92.55+2.33\ X_1-0.49\ X_2-2.90\ X_1X_2 -4.82\ X_1^2+0.23\ X_2^2 \quad (6)$$

The quadratic model was found to be significant with *F* value 9.29 ($P < 0.0001$) which shows that the model is significant. Figure 4 represents the contour plot displaying the effect of different quantities of independent variables on the response Y_3. Increase in cumulative percentage release was because of increase in the concentration of IPC and then declined. The combined effect of factor X_1 (IPC) and X_2 (glycerin) can be further understood with the help of response surface plot. Medium level of factor X2 gave high value of drug release which shows that the factor X_1 has significant positive effect on drug release.

Ex vivo permeation studies

All films have shown satisfactory results for *ex vivo* permeation of tramadol hydrochloride. Films containing higher amount of IPC have shown good permeation of drug compare to other formulations. The highest diffusion of around 94.24% was shown by formulation F7 followed by F8 and F9. Drug diffusion of formulation F1, F2 and F3 was less than other formulation. It may be because of poor swelling due to the lowest concentration of IPC. The rate limiting factor here is swelling index and which is directly related to concentration of IPC in individual formulation.

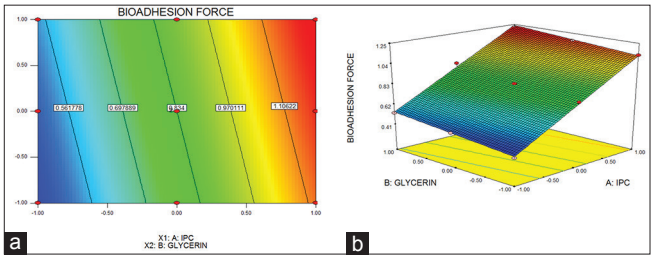

Figure 3: (a and b) Two-dimensional contour plot, three-dimensional response surface plots for bioadhesion force

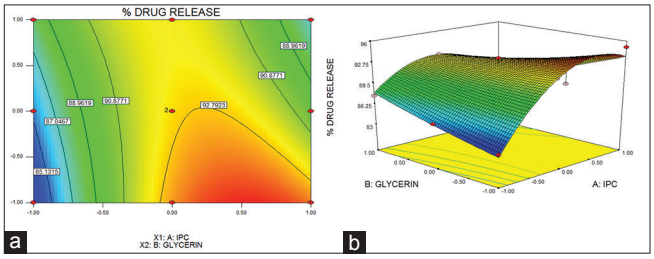

Figure 4: (a and b) Two-dimensional contour plot, three-dimensional response surface plots for *in vitro* drug release

Optimization

The computer optimization technique by setting desirable values was selected to find out the optimum formulation. The process was optimized for the response variables Y_1-Y_3. The optimized formula was found out by setting maximum percentage drug release at 8 h. The values for bioadhesion force were set in the range of 0.8-1.2 N and the tensile strength greater than 14 kg/mm^2. Formulation F7 was emerged as optimized formulation with 50 mg drug, 100 mg IPC and 2% glycerin.

CONCLUSION

In this study novel, buccoadhesive film was developed using IPC between chitosan and *F. limonia* fruit pulp mucilage. Film was releasing drug over a period of 8-h directly to systemic circulation through buccal mucosa. The extensive first pass metabolism of a drug was prevented to a great extent. The formulation chart was prepared by 3^2 level factorial design. The effect of formulation variables on bioadhesion force, drug release, and tensile strength was studied and analyzed with the help of computer-based optimization method. After analyzing all data and results formulation F7 designed based on quadratic model were selected as optimal formulation.

Thus, an IPC based mucoadhesive buccal films of a model opioid analgesic drug was developed by optimization technique. The main objective of developing buccal fims was to deliver a model opioid analgesic drug to systemic circulation without any painful procedures. IPC is more suitable for the preparation of buccal film as it exhibited good film forming ability and satisfactory bioadhesion force in comparison to chitosan alone. The study also shows that economical and widely available *F. limonia* fruit pulp mucilage can be a promising excipient for systemic drug delivery of a water-soluble drugs belong to opioid analgesic class via oral mucosal route. The *in vitro* dissolution studies confirmed that drug released at satisfactory rate from buccal films which are very much important for achieving therapeutic targets.

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