Original Article

Buccal mucoadhesive tablets of flurbiprofen: Characterization and optimization

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ABSTRACT: The aim of this work was to develop and optimize sustained-release mucoadhesive tablets of flurbiprofen. Mucoadhesive polymers used were chitosan as primary polymer and hydroxypropylmethyl celluose, hydroxypropyl cellulose, or sodium carboxymethyl cellulose as secondary polymer. Tablets were evaluated in terms of weight variation, thickness, hardness, friability, swelling, surface pH, *in vitro* mucoadhesive force, and *in vitro* release. The compatibility between flurbiprofen and the tablet excipients was confirmed by fourier transfer infrared studies. Both the primary and secondary polymers were found to have synergistic effects on tablet swelling, bioadhesion, and *in vitro* drug release. Formulations containing sodium carboxymethyl cellulose (F_1) showed a maximum swelling index of 4.144 after 8 h, maximum mucoadhesive force (0.27 N), and convenient *in vitro* release over 8 h. D-optimal design was employed to evaluate the effect of the ratio of the primary polymer (X_1) and the type of secondary polymer (X_2) on the swelling index after 8 h (Y_1), drug release after 8 h (Y_2) and time taken for 30% drug release (Y_3).

Keywords: Flurbiprofen, buccal delivery, mucoadhesive tablets, chitosan, D-optimal design

1. Introduction

The buccal region of the oral cavity is an attractive target for drug administration. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining the oral cavity which offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Avoiding acid hydrolysis in the gastrointestinal tract and bypassing the "first-pass" effect are some of the advantages of this route of drug delivery. Moreover, the oral cavity is easily accessible for self medication and can be promptly terminated in case of toxicity just by removing the dosage form from the buccal cavity. In addition, the buccal route enables the administration of drugs to comatose patients (*1*,*2*).

Chitosan is a natural polyaminosaccharide obtained by *N*-deacetylation of chitin. This material is non-toxic, biocompatible, and biodegradable. Chitosan has a suitable mucoadhesive profile for combating the flushing effect of saliva and mastication (*3*). Chitosan interacts with mucin, the basic component of mucous, by multiple modes, mainly due to molecular attractive forces formed by electrostatic interaction between positively charged chitosan and negatively charged mucosal surfaces. These properties may be attributed to strong hydrogen bonding groups like -OH, -COOH, strong charges, high molecular weight (MW), sufficient chain flexibility, and to surface energy properties favoring spreading into mucus (*4*).

Attempts have been made to formulate various buccal mucoadhesive dosage forms, including tablets (*5*), films (*6*), patches (*7*), disks (*8*), and gels (*9*). A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response (*10*).

Flurbiprofen (FP) is a nonsteroidal anti-inflammatory agent indicated for the acute or long-term treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis. FP is extensively metabolized in the liver. Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with FP (*11*). The short half-life value of FP which ranges from 3 to 6 h, its low MW (244.25), and the optimum log partition coefficient (3.8) (*12*) make it a suitable candidate for administration by the buccal route (*13*,*14*).

In the present study, the mucoadhesive buccal

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tablets of FP were developed using chitosan as the primary mucoadhesive polymer and a secondary polymer either hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), or sodium carboxymethylcellulose (SCMC). The effect of the secondary polymer on drug release from mucoadhesive tablets was studied. The buccal tablets were evaluated in terms of weight variation, thickness, hardness, friability, surface pH, swelling index, mucoadhesive strength, and *in vitro* drug release. The compatibility between FP and the tablet excipients was studied using Fourier transfer infrared (FTIR) spectroscopy.

2. Materials and Methods

2.1. *Materials*

Flurbiprofen (FP) was kindly supplied by the Egyptian International Pharmaceutical Company (EIPICO), Egypt; chitosan, highly viscous [2-amino-2-deoxy (1-4)-β-D-glucopyranan), agar, and HPC-NF (low viscosity) were purchased from Fluka Chemica, Switzerland; HPMC K4M was from Dow Chemical Company, NJ, USA; SCMC (low viscosity) was from Hercules Incorporation, DE, USA; D-mannitol was from Merck, Germany; magnesium (Mg) stearate was from Belike Chemical Co., China; disodium hydrogen phosphate and potassium dihydrogen phosphate were from El-Nasr Pharmaceutical Chemicals Co., Cairo, Egypt.

2.2. *Preparation of buccal tablets*

Mucoahesive buccal tablets were prepared by a direct compression procedure. Various batches were prepared by varying the chitosan:drug ratio to identify the most effective formulation. The mucoadhesive drug/polymer mixture was prepared by homogeneous mixing of the drug with chitosan, secondary polymer, and D-mannitol, in a glass mortar for 15 min. Then, Mg stearate was added and mixed for 5 min (Table 1). The mixture was compressed using a tablet machine (Type EK: O.Erweka apparatus, Frankfurt, Germany) using flat-tip punches and dies with 8-mm-diameter. Each tablet weighed 212 mg with a thickness of 3.1 mm.

2.3. *Physicochemical parameters of tablets*

The tablets were checked for weight variation. Tablet thickness was measured using a micrometer (Mitutoyo, 103-260, Japan). Hardness of tablets was determined using a hardness tester (model: TH-16, China). Friability was determined using a Roche friabilator (Erweka Apparatebau GmbH, Germany). Drug content uniformity was determined by dissolving the crushed tablets in ethyl alcohol and filtered through 0.45-µm PTFE filter (Millipore Co., Bedford, MA, USA). The filtrate was diluted with phosphate buffer (pH 6.8) and analyzed at 248 nm (*15*) using a UV spectrophotometer (Shimadzu, model UV-1601 PC, Japan) using a reference to a standard calibration curve of the drug (r^2 = 0.998). The experiments were performed in triplicate and the average values ± standard deviation (SD) were reported.

2.4. *Swelling study*

The swelling index for each tablet was determined in triplicate and the mean ± SD was calculated. Each buccal tablet was weighed individually (W_1), placed separately in 2% agar gel plates, and incubated at 37 ± 1°C. At regular 1-h time intervals for 8 h, the tablet was removed from the petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was reweighed (W_2), and the swelling index (SI) was calculated using equation 1 (*16*):

$$SI = \frac{(W_2 - W_1)}{W_1} \quad \text{--- (1)}$$

2.5. *Surface pH study*

The surface pH of the buccal tablets was determined using the method adopted by Bottenberg, *et al.* (*17*). As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with 2 mL simulated saliva fluid (pH 6.8) for 2 h at room temperature and pH was noted by bringing the electrode of the pH-meter (Jenway 8510, Baroworld Scientific Ltd., Essex, UK) in contact with tablet surface

Table 1. Formulation of flurbiprofen buccal tablets

Codes	FP (mg)	Chitosan (mg)	SCMC (mg)	HPMC (mg)	HPC (mg)	Mannitol (mg)	Mg Stearate (mg)
F_1	50	50	100	–	–	10	2
F_2	50	100	50	–	–	10	2
F_3	50	25	125	–	–	10	2
F_4	50	50	–	100	–	10	2
F_5	50	100	–	50	–	10	2
F_6	50	25	–	125	–	10	2
F_7	50	50	–	–	100	10	2
F_8	50	100	–	–	50	10	2
F_9	50	25	–	–	125	10	2

and allowing the surface to equilibrate for 1 min. The surface pH for each tablet was determined in triplicate and the mean ± SD was calculated.

2.6. *In vitro mucoadhesive force*

The two-armed balance method reported by Parodi, *et al.* (*18*) with minor modifications was used for studying the bioadhesive force of the prepared tablets using fresh eggshell membrane (*19*) as illustrated in Figure 1. Briefly, the eggshell membrane was fixed on the bottom of a smaller beaker attached to a larger beaker. Fresh phosphate buffer (pH 6.8) was added to the beaker up to the upper surface of the membrane. A tablet was attached to the upper clamp and the platform was slowly raised until the tablet surface came in contact with membrane. After a preload time of 5 min, water was added with a polypropylene bottle until the tablet was detached from the membrane. The mass of water, in grams, required to detach the tablet from the membrane surface gives the measure of mucoadhesive strength. The force of adhesion was deduced using the following equation (*20*):

$$\text{Force of adhesion (N)} = \frac{\text{bioadhesive strength} \times 9.81}{1{,}000} \quad \text{--- (2)}$$

2.7. *In vitro drug release study*

The USP dissolution tester (Vankel Industries 750D, Weston Parkway, USA) with rotating paddle was used to study the drug release from the mucoadhesive tablets. The dissolution medium consisted of 250 mL of phosphate buffer, pH 6.8. The release study was performed at 37 ± 0.5°C with a rotation speed of 50 rpm. The buccal tablet was attached to a glass disk (by the use of rubber band) and was placed at the bottom of the dissolution vessel, thereby allowing drug release only from the upper side of the tablet. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with fresh medium. Samples were filtered through 0.45-µm PTFE filter (Millipore Co., Bedford, MA, USA) and analyzed after appropriate dilution by UV spectrophotometry at 248 nm. Dissolution tests were performed at least three times for each sample.

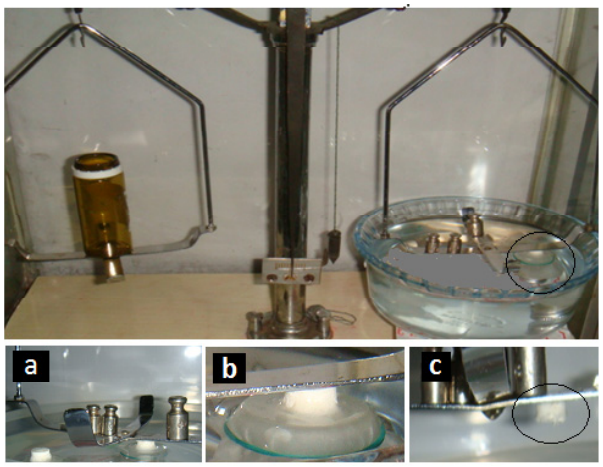

Figure 1. Developed balance for determination of mucoadhesive strength. (a) preload step, (b) adhesion step, and (c) detachment step.

2.8. *Fourier transfer infrared spectroscopy (FTIR)*

Samples (2-3 mg) of the ground tablets were each mixed with about 100 mg of dry potassium bromide, and were compressed into discs under pressure of 10-15 pounds/inch^2. The FTIR spectra were recorded using a Mattson FTIR spectrophotometer (Model Genesis II, UK).

2.9. *Data analysis*

A twelve run, two factor, three variable D-optimal design was employed to evaluate the effect of primary polymer conc (X_1) and the type of secondary polymer (X_2) on the responses studied for the drug; the swelling index after 8 h (Y_1), drug release after 8 h (Y_2) and time taken for 30% drug release (Y_3) (Table 2).

The following cubic model was built to describe the response:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{12}X_2^2 + b_{13}X_1X_2 + b_{14}X_1^2X_2 + b_{15}X_1X_2^2$$

where Y is the response, X the factors and b the coefficients of each term calculated by multiple regression analysis.

3. Results and Discussion

3.1. *Physicochemical parameters*

The results of the physical characteristics of the prepared mucoadhesive tablets of FP are shown in Table 3. Physical evaluation of the compressed matrix tablets showed that all physical parameters were within specifications. Tablet weights varied between 208 and 213 mg with SD of ± 1.81; thickness, between 2.94 and 3.36 mm with SD of ± 0.19; hardness, between 3.0 and 6.0 kg/cm² with SD of ± 1.44, and friability ranged

Table 2. Experimental domains and coding of the variables

Variables	Levels		
	–1	0	+1
Primary polymer conc. (X_1)	1:1	1:2	1:4
Type of secondary polymer (X_2)	SCMC	HPC	HPMC

Responses:
Y_1 swelling after 8 h
Y_2 drug release after 8 h
Y_3 time taken for 30% drug release

Table 3. Physical evaluation of prepared flurbiprofen tablets

Codes	Weight (mg)	Hardness (kg/cm)	Friability (%)	Thickness (mm)	% Drug content	Surface pH
F_1	209 ± 2.5	6.9 ± 0.3	0.01 ± 0.00	2.94 ± 0.06	99.0 ± 0.6	5.91 ± 0.2
F_2	210 ± 2.7	3.5 ± 0.7	0.02 ± 0.00	3.02 ± 0.03	98.4 ± 0.5	6.0 ± 0.1
F_3	213 ± 4.2	5.5 ± 0.2	0.01 ± 0.01	3.06 ± 0.02	100.7 ± 0.3	6.05 ± 0.1
F_4	212 ± 4.1	3.2 ± 0.5	0.02 ± 0.01	3.36 ± 0.10	98.4 ± 0.8	6.5 ± 0.3
F_5	208 ± 1.6	3.0 ± 0.5	0.04 ± 0.02	3.36 ± 0.12	98.1 ± 0.7	5.95 ± 0.2
F_6	213 ± 3.3	3.7 ± 0.6	0.01 ± 0.00	3.36 ± 0.10	100.2 ± 0.3	5.97 ± 0.2
F_7	210 ± 1.5	3.5 ± 0.6	0.03 ± 0.01	2.95 ± 0.04	100.4 ± 0.3	6.42 ± 0.1
F_8	209 ± 1.6	3.3 ± 0.7	0.03 ± 0.01	2.97 ± 0.03	99.5 ± 0.1	6.09 ± 0.1
F_9	210 ± 2.4	6.0 ± 0.2	0.01 ± 0.00	2.99 ± 0.02	99.9 ± 0.0	6.07 ± 0.2

Values are mean ± SD (n = 3).

between 0.01 and 0.04% with SD of ± 0.01. Tablet drug content ranged from 98.1 to 100.7% with SD of ± 0.96.

3.2. *Swelling study*

Appropriate swelling behavior of a buccal adhesive tablet is essential for uniform and prolonged release of the drug and effective mucoadhesion (*21*). The swelling index was dependent on the type of secondary polymer and its ratio to primary polymer in each formulation as shown in Figure 2. Tablets containing SCMC as secondary polymer showed maximum swelling index (F_1 = 4.14) as illustrated in Figure 3. This finding may be due to the fast-swelling properties of SCMC compared to either HPMC or HPC. Results also show that increasing the amount of chitosan led to an increase in the swelling behavior in formulations containing either of the two hydrophilic polymers HPMC or HPC (F_5 = 2.838 and F_8 = 0.668, respectively). This may be attributed to the increase in the ionized NH_2 group of chitosan, which results in loosening of the tablet matrix as a result of electrostatic repulsion between the polymers and decreased hydrogen bonding possibilities caused by charged NH_3^+ species. Moreover, protonation favors hydration and hence a higher water absorption capacity is observed.

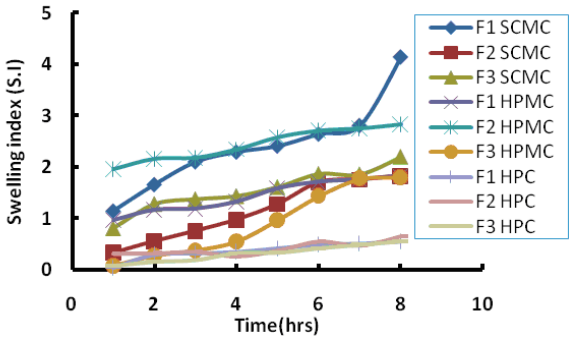

Figure 2. *In vitro* swelling studies of flurbiprofen buccal tablets.

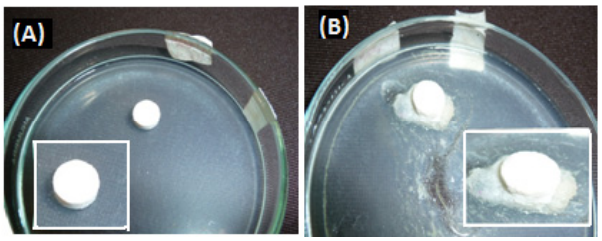

Figure 3. Mucoadhesive buccal tablet F_3 in 2% agar at zero time (A) and after 8 h (B).

3.3. *Surface pH study*

Surface pH of all tablets was found to range from 5.91 to 6.5 with SD of ± 0.21 (Table 3). These results reveal that all formulations provide an acceptable pH in the range of salivary pH (5.5 to 7.0) and that they will not produce any local irritation to the mucosal surface.

3.4. *In vitro mucoadhesive force*

As already indicated by several authors, the bioadhesive properties of polymeric materials are significantly affected by the model mucous membrane employed as a substrate for *in vitro* bioadhesion measurements and due to the use of either tissues or mucous membrane of various animals or different regions of the gastrointestinal tract of these animals, a wide variability was noted due to variation in the thickness of the layer covering the epithelium of these organs or tissues (*22*). In this study, egg shell membrane was employed as a natural substrate. The outer surface of the shell is covered with mucin protein which acts as a soluble plug for the pores in the shell (*23,24*). Therefore, egg shell membrane possesses an intricate lattice network of stable and water-insoluble fibers and has high surface area resulting in various applications such as adsorbent (*25*).

The force of adhesion was calculated from the bioadhesive strength as indicated in equation 2 and the results are shown in Figure 4. Chitosan is a cationic polymer and its mucoadhesion is mainly based on ionic interactions with anionic substructures of the mucus layer. The type of secondary polymer affected the mucoadhesion force significantly. SCMC, which is a polyanionic polymer, had a faster hydration rate and achieved maximum swelling more quickly. That is why F_1 showed a maximum bioadhesive force (0.27 N). HPMC and HPC tablets, which hydrated at a slower

rate than SCMC, showed a smaller bioadhesive force. The rank order for bioadhesive force can be represented as $F_1 > F_2$, $F_8 > F_6 > F_3 > F_4$, and $F_7 > F_9 > F_5$.

3.5. *In vitro drug release study*

The most significant factor affecting the rate of drug release from buccal tablets is the drug to polymer ratio. Figure 5 shows that complete drug release occurred within 4 h from tablets containing drug alone, while tablets prepared with chitosan alone, as primary polymer, showed complete drug release within 8 h. The reason for this delay in drug release is that chitosan, being a hydrophilic polymer, retains water in its structure forming gel spontaneously which is swellable and erodible, thus retarding drug release (*26*).

An increase in the concentration of the secondary polymer not only causes an increase in the viscosity of the gel structure surrounding the tablet upon hydration, but also leads to the formation of a gel layer with a longer diffusional path. This leads to a decrease in the diffusion of the drug and therefore a reduction in the rate of drug release (*27*). In the present study, the rate of drug release from formulations prepared with HPMC followed this predictable pattern. As seen in Figure 6, the percent drug released after 8 h from formulations containing least HPMC ratio (F_5) was 46.328%, while tablets containing highest HPMC concentration showed least drug release (F_6 = 22.086%). This is probably due to high gelling properties of HPMC. Formulations containing HPC showed the highest drug release among all prepared tablets (Figure 7). This is because HPC swells and partly dissolves, thus enabling chitosan to swell to its maximum size. On the other hand an explanation for slower drug release in formulations containing HPMC than those with HPC can be explained by the fact that HPMC has a higher swelling ability than HPC.

Results also demonstrate that the incorporation of SCMC results in a delay in FP release compared with tablets containing chitosan alone (Figure 5). This may be attributed to the possible ionic interaction between chitosan (a cationic polymer) and anionic SCMC within the tablet. In fact, it is already known that the cationic nature of chitosan permits the formation of complexes with oppositely charged drugs and polymers (*28*). There was a direct relationship between the SCMC ratio in tablet and the percent of drug released (F_1 = 66.783% while F_3 = 92.54%) as increasing the polymer ratio was accompanied by a decrease in chitosan amount within the tablet which resulted in the formation of the mentioned complex.

3.6. *Fourier transfer infrared spectroscopy (FTIR)*

Figure 8 demonstrates the FTIR spectra of FP, chitosan, SCMC, HPMC, HPC alone and F_3, F_6 and F_9 formulations. In the FTIR spectrum of FP powder,

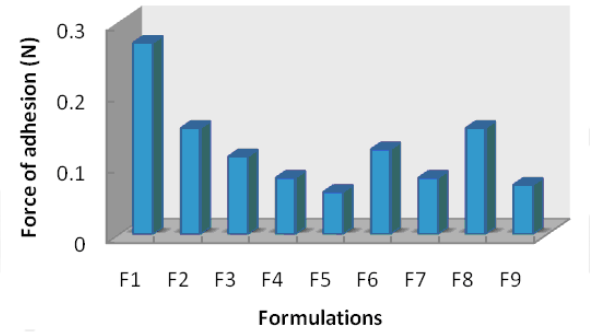

Figure 4. *In vitro* bioadhesive force of prepared buccoadhesive tablets.

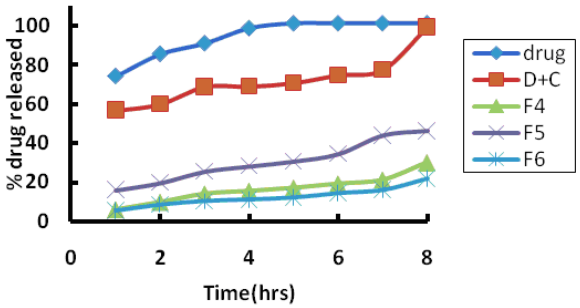

Figure 6. Release profile of different HPMC formulations compared to drug alone and to drug with chitosan (D+C).

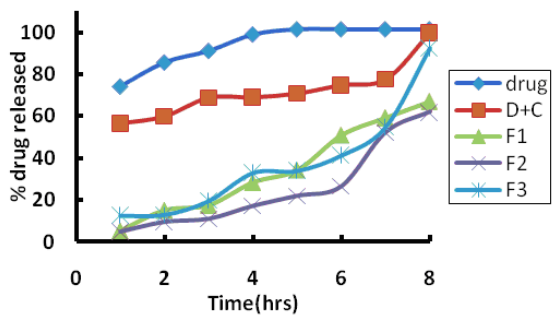

Figure 5. Release profile of different SCMC formulations compared to drug alone and to drug with chitosan (D+C).

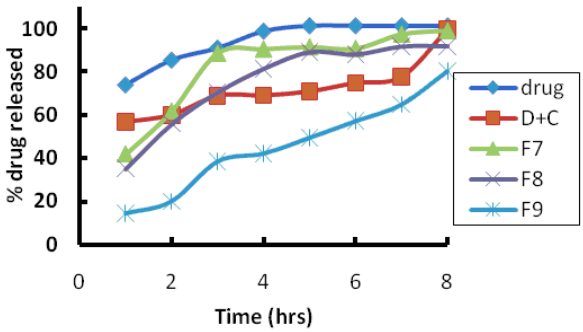

Figure 7. Release profile of different HPC formulations compared to drug alone and to drug with chitosan (D+C).

a carbonyl stretching band at 1,701 cm^{-1}, a hydroxyl stretching peak related with carbonyl group at 3,525 cm^{-1} and CF stretching peak at 1,216 cm^{-1} were seen as observed in previous literature (*29*). The FTIR spectrum of chitosan shows a characteristic band at 3,434 cm^{-1} which is attributed to amine and hydroxyl groups stretching vibration and the band for carbonyl stretching of the secondary amide I at 1,644 cm^{-1} (*30*). Characteristic peaks of FP were observed in the spectra of all formulations. These results showed that there was no chemical interaction during tablet preparation and that FP was stable in all mucoadhesive tablet formulations. Moreover, the FTIR spectrum of F_3 proved that there was an interaction between the amine group of the positively charged chitosan and the carboxylic acid group of the negatively charged SCMC through hydrogen bonding at 3,289 cm^{-1} (*31*).

3.7. *Data analysis*

The concentration of primary polymer (X_1) and the type of secondry polymer (X_2) were chosen as formulation variables and the swelling index after 8 h. Drug release after 8 h and the time taken for 30% drug release were selected as response variables (Y_1-Y_3), as shown in Table 2. The causal factors and response variables were related using a polynomial equation with statistical analysis through Design-Expert® software (*32*).

Tables 4-6 sumarize the experimentaly observed yeilds, swelling indices, drug release after 8 h and time taken for 30% drug release. The relationship between the dependent and independent variables was further elucidated using contour and response surface plots. The effects of X_1 and X_2 and their interaction on Y_1-Y_3 are given in Figures 9-11. At low and high levels of

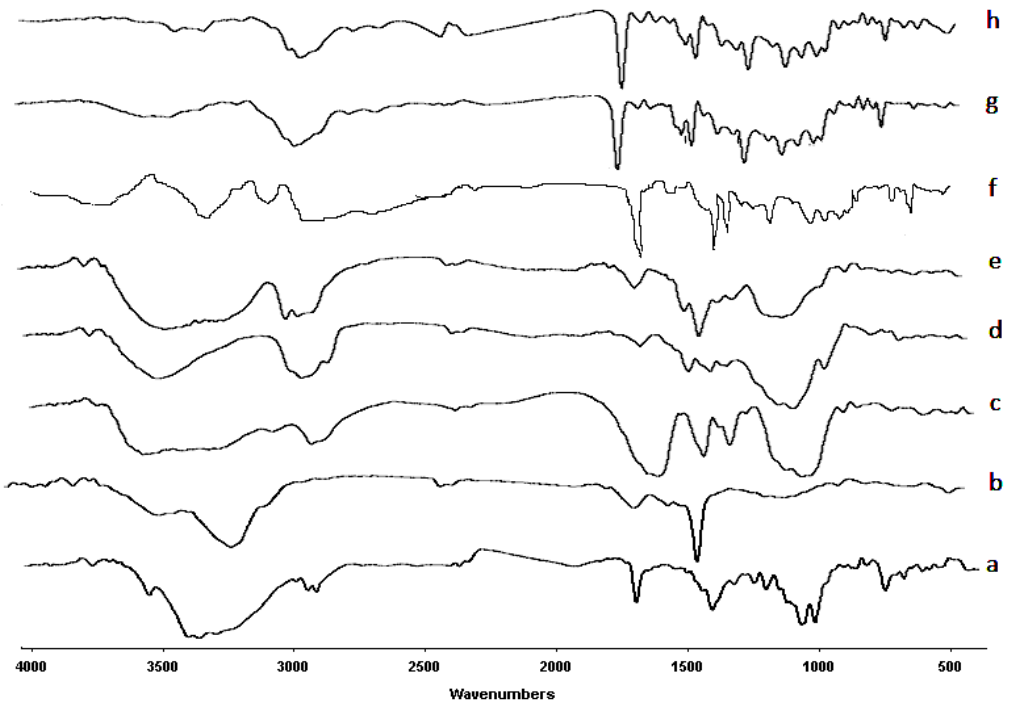

Figure 8. FTIR spectra. (a) flurbiprofen, (b) chitosan, (c) SCMC, (d) HPMC, (e) HPC, (f) formulation containing SCMC (F_3), (g) formulation containing HPMC (F_6) and (h) formulation containing HPC (F_9).

Table 4. Actual, predicted, residual values for swelling index after 8 h as a function of primary polymer concentration (X_1) and type of secondary polymer (X_2)

Standard order	X_1	X_2	Actual value	Predicted value	Residual	Run order
1	1	–1	2.20	2.19	–0.01	10
2	–1	1	1.83	1.82	–0.01	6
3	0	–1	1.84	1.87	0.03	5
4	1	1	1.67	1.66	–0.01	3
5	–1	–1	4.14	4.13	–0.01	8
6	1	0	0.56	0.59	0.03	1
7	–1	–1	4.14	4.13	–0.01	7
8	–1	1	1.83	1.82	–0.01	4
9	1	1	1.67	1.66	–0.01	9
10	0	0	0.56	0.58	0.02	12
11	–1	0	0.56	0.55	–0.01	11
12	0	1	2.83	2.86	0.03	2

X_2, Y_1 increases compared with the middle value. The same observation was found for Y_3, while the reverse was found for Y_2, that at low and high levels of X_2, Y_2 decreases.

Also, contour plots were used to illustrate the simultaneous effect of the casual factors on individual and combined response variable. This expression gives an insight into the effect of the different independent variables (response). A positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. The larger coefficient means the causal factor has a more potent influence on the response. As shown in Table 7, the coefficient of X_1X_2 and $X_1^2X_2$ were largest, showed that the effect of combination of the two independent factors, polymer type and concentration was the main influence on the responses, swelling and drug release. The value of coefficients of X_2 was less than that of X_1, indicated that the influence of the polymer type is less than that of polymer concentration.

We can also conclude from Table 7 that there was a high and significant R^2 between independent variables

Table 5. Actual, predicted, residual values for drug release after 8 h as a function of primary polymer concentration (X_1) and type of secondary polymer (X_2)

Standard order	X_1	X_2	Actual value	Predicted value	Residual	Run order
1	1	–1	92.54	91.88	–0.66	10
2	–1	1	30.13	29.80	–0.33	6
3	0	–1	52.33	53.66	1.33	5
4	1	1	22.08	21.75	–0.33	3
5	–1	–1	66.78	66.45	–0.33	8
6	1	0	80.30	81.63	1.33	1
7	–1	–1	66.78	66.45	–0.33	7
8	–1	1	30.13	29.26	–0.78	4
9	1	1	22.08	21.75	–0.33	9
10	0	0	91.92	89.26	–2.66	12
11	–1	0	99.18	100.5	1.32	11
12	0	1	46.33	47.77	1.33	2

Table 6. Actual, predicted, residual values for time taken for 30% drug release as a function of primary polymer concentration (X_1) and type of secondary polymer (X_2)

Standard order	X_1	X_2	Actual value	Predicted value	Residual	Run order
1	1	–1	4.0	3.94	–0.06	10
2	–1	1	8.0	7.97	–0.03	6
3	0	–1	6.0	6.12	0.12	5
4	1	1	9.0	8.97	–0.03	3
5	–1	–1	5.0	4.97	–0.03	8
6	1	0	2.5	2.62	0.12	1
7	–1	–1	5.0	5.12	0.12	7
8	–1	1	8.0	7.97	–0.03	4
9	1	1	9.0	8.97	–0.03	9
10	0	0	1.0	0.77	–0.23	12
11	–1	0	0.5	0.62	0.12	11
12	0	1	5.0	4.97	–0.03	2

Table 7. Optimal regression equation (cubic model) for each response variable as a function of primary polymer conc (X_1) and type of secondary polymer (X_2)

Model	Coefficient	Y_1	Y_2	Y_3
	B_0	0.5	89.26	0.77
	$b_1(X_1)$	–0.1	–9.44	1.0
	$b_2(X_2)$	0.49	–3.0	–0.5
	$b_{11}(X_1^2)$	0.087	1.81	0.85
	$b_{12}(X_2^2)$	1.86	–38.6	4.85
	$b_{13}(X_1X_2)$	3.75	3.75	–11.75
	$b_{14}(X_1^2X_2)$	–1.2	–23.69	2.51
	$b_{15}(X_1X_2^2)$	–0.53	13.78	–1.01
Quadratic	CV	2.12	3.34	3.24
	R^2	0.9996	0.9983	0.9988
	Adjusted R^2	0.9988	0.9953	0.9966
	PRESS*	0.50	1,087.01	8.27

* Predicted residual error sum of squares.

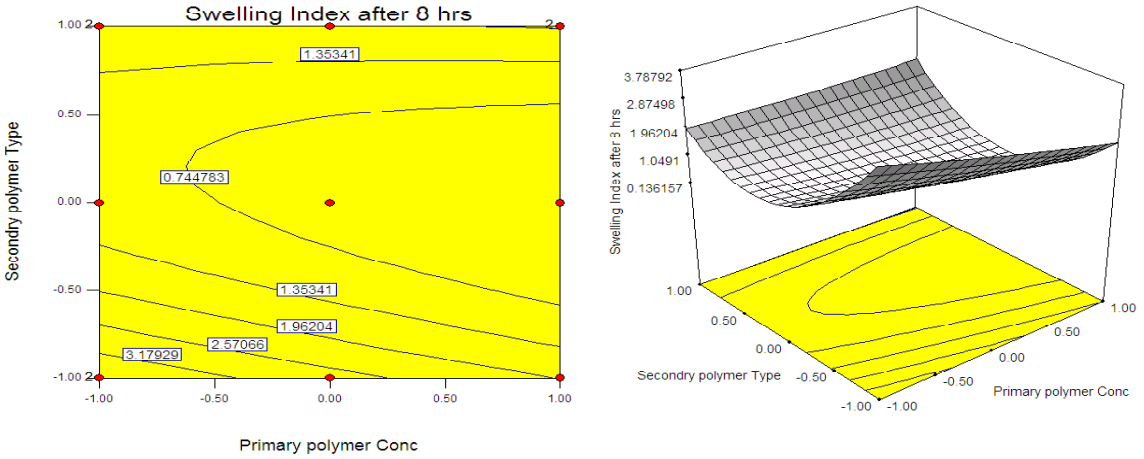

Figure 9. Contours of swelling index after 8 h (Y_1) as a function of primary polymer concentration (X_1) and secondary polymer type (X_2).

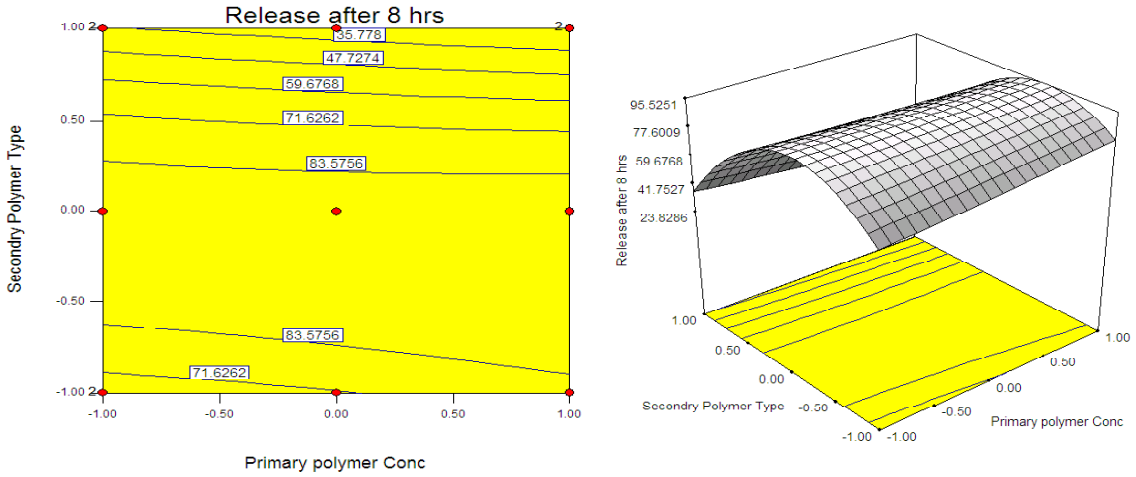

Figure 10. Contours of drug released after 8 h (Y_2) as a function of primary polymer concentration (X_1) and secondary polymer type (X_2).

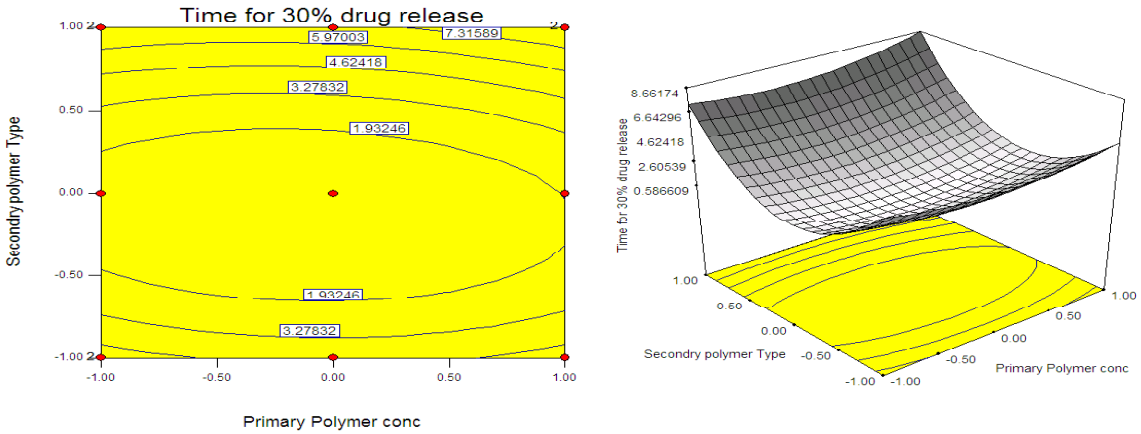

Figure 11. Contours of time for 30% drug release (Y_3) as a function of primary polymer concentration (X_1) and secondary polymer type (X_2).

(polymer type and concentration) and dependent variables (Y_1-Y_3). R^2 value of 0.99 and above for all the models in this study suggested adequate modeling. The R^2 values for Y_1-Y_3 were 0.9996, 0.9983, and 0.9988, respectively, which are in reasonable agreement with the adjusted R^2 of 0.9988, 0.9953, and 0.9966.

4. Conclusions

The prepared mucoadhesive buccal tablets of flurbiprofen

can help bypass extensive hepatic first-pass metabolism and improve drug bioavailability. The *in vitro* release studies showed that 66.78% of drug was released from F_1 by the end of 8 h, which can be used in a twice-a-day tablet, thus allows for reduction in daily drug dosage and subsequent side effects. Moreover, it adheres well to the mucous membrane and is simple to apply.

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