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DEVELOPMENT AND EVALUATION OF LORNOXICAM BASED BUCCAL MUCOADHESIVE TABLETS: A PRELIMINARY STUDY

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Abstract
This preliminary investigation was aimed to optimize the fabrication of lornoxicam (LRX) loaded buccal mucoadhesive tablets for local management of pain and inflammation in oral mucosa. The direct compression method was used to produce buccal mucoadhesive tablets. Chitosan, HPMC and sodium alginate were screened in preliminary study to find out requisite concentrations for optimization purpose. Solid state characterization test, such as Fourier Transform Infrared (FTIR) spectroscopy, was carried out to investigate drug excipient compatibility in physical mixtures of drug and polymers. This was followed by further assessment of formulations at *in-vitro*, *ex-vivo* and *in-vivo* levels to determine swelling index, matrix erosion, mucoadhesive strength and time, *in-vivo* residence time and drug release. The findings deduced from preliminary investigations on mucoadhesive buccal tablets showed that all sodium alginate containing formulations, except F8, did not sustain drug release up to 6 h, and showed poor mucoadhesivity. The mucoadhesive character as well as drug release pattern was influenced by the concentration of HPMC in mucoadhesive buccal tablets. Chitosan containing formulations indicated lower values in terms of swellibility, mucoadhesion and drug release as compared to HPMC containing formulations, due to the presence of reduced hydrophilic interactions between chitosan particles. Additionally, it was noted that swelling index values were greater for formulations containing sodium alginate as compared to formulations containing HPMC, due to greater swelling capability of sodium alginate. The values of surface pH ranged from 6.38 – 7.14 and fall within physiological salivary pH range. The matrix erosion data revealed significantly higher values for sodium alginate containing formulations, whereas HPMC containing formulations showed increased values for *ex-vivo* mucoadhesive strength, time, *in-vivo* residence time and *in-vitro* drug release i.e. 9.55 ± 1.84 g, 5.82 ± 1.11 h, 2.01 ± 0.85 h and sustained

drug release for 4 h, respectively, for F4. Thus, it is concluded that mucoadhesive tablet formulation batch F4 was considered as an optimized formulation based on mucoadhesive strength and time and could be subjected to main study.

Keywords: Lornoxicam, Direct Compression, Mucoadhesion, Sodium Alginate, *In-vitro* drug release

1. Introduction

The buccal route of the oral cavity has been regarded as the most appealing and the most preferred location for administering dosage forms, owing to the simplicity and comfort associated with this route (1). Since the buccal mucosal lining provides a relatively gentle environment for drug absorption, buccal administration safely protects medicinal substances from the harsh gastric environment, preventing enzymatic as well as acidic degradation, like proteins and polypeptides (2). The buccal mucosal delivery system comprises of buccal tablets, buccal gels and ointments. The former is produced as either double layer matrix tablets or as a monolithic system. Monolithic tablets are composed of drug and polymer blend and possess unidirectional drug release. Furthermore, they may be either uncoated or coated with various polymers. Two layers make up double layered matrix tablets. For locally acting dosage forms, the outside layer is generally composed of non-bioadhesive agent, while for systemic release, outer layer is rendered inactive and inner layer is composed of active moiety. Consequently, this approach supports the controlled drug release from the formulation (3). Buccal gels and ointments are primarily composed of various polymers that increase gel viscosity and provide controlled drug release (4).

Oral mucositis is referred to as an inflammatory disease of the oral mucosa, after radiation or chemotherapy. Patients frequently experience considerable challenges in eating and drinking due to the severe discomfort, ulceration and erythematous lesions linked to this condition. This ultimately results in weight loss, exhaustion, and a decreased quality of life (5). Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat a variety of oral cavity pathologies, including stomatitis, periodontitis, gingivitis and oral ulcers, and their administration requires the use of peroral route. Several studies have conclusively shown that the risk of upper gastrointestinal (GI) problems rises with increasing dosages and frequency of NSAID usage (6). The systematic management of oral mucositis-related discomfort may exacerbate NSAID adverse effects. As a result, local therapy is recommended since it allows for greater drug delivery to the target tissues while minimizing systemic absorption.

Lornoxicam (LRX), a potent NSAID, is widely used to treat pain as well as inflammation. Its conventional dosage forms have unequivocally shown greater risk of upper GI disorders with its increased dose and frequency. Moreover, the drug exhibits poor water solubility (BCS class II), substantial plasma protein binding (99 %) and short half-life (3-4 h), which is an excellent choice for its local administration (7). Buccal mucosal drug administration is now regarded as the most viable replacement for the oral route because it overcomes the majority of the problems with oral drug delivery. There has only been a limited investigation carried out on the buccal delivery of LRX, according to a systematic literature review from several database sources. Hence, the current investigation is aimed at developing LRX loaded buccal mucoadhesive drug delivery system for efficient and rapid management of pain and inflammation linked to oral cavity pathologies. The buccal mucoadhesive drug delivery system of LRX is expected to favor improved drug solubility as well as bioavailability and achieve a pattern of controlled drug release for superior analgesic and anti-inflammatory effects.

2. Materials and Methods

2.1. Materials

Lornoxicam was kindly gifted by Wilshire Pharma Pvt Limited, Lahore, Pakistan; chitosan (low molecular weight), sodium alginate, poly-vinyl pyrrolidone K30 (PVP K30) (Sigma Aldrich, USA), hydroxy propyl methyl cellulose (HPMC K15M) (Dow Chemical Company, Washington, Midland,

MI, USA), sucralose, talc, magnesium stearate and lactose (Sigma Aldrich, USA). Entirely, the chemicals were seemed to ensure the analytical quality & utilized except additional purification.

2.2. Drug Excipients Compatibility Study

FTIR analysis was carried out to investigate any possible interaction between the drug and physical mixtures with various polymers. FTIR spectrophotometer (Spectrum 100, Perkin Elmer, USA) was utilized to measure FTIR spectra in the 4000-600/cm range. The infrared spectral examination for the polymers, pure drug and physical combinations was conducted to determine the existence of normal functional groups, in addition to finding any unusual or new peaks (8).

2.3. Dosage Form Fabrication

2.3.1. Mucoadhesive Buccal Tablet

The fabrication of optimized mucoadhesive buccal tablets was achieved through a preliminary study during which the physical characteristics and polymers concentration were modified such that the polymer concentration was determined to fulfill the criteria for sustained release of lornoxicam lasting up to 6 h.

The drug was precisely weighed and manually blended with excipients using a spatula. Other pharmaceutical constituents, such as mucoadhesive polymers (chitosan, HPMC-K15M and sodium alginate) in various ratios were added to this mixture. The addition of sucralose as a sweetener, PVP as a binder and lactose as a diluent was done in the quantities specified in Table 1. Ultimately, the mixture was mixed slowly with magnesium stearate for 3-5 min before being compressed into tablets using single punch tablet machine (AR 400, Erweka, GMBH, Germany) having flat faced punch (8 mm) at 2.5 tons force for 10 sec. The formulated compressed tablets were then subjected to various characterization tests (9).

2.4. Characterization of Buccal Mucoadhesive Tablets

In the preliminary study, the methods used for evaluating buccal tablets comprised both physical & physico-chemical characterization. The physical characterization tests included friability, diameter, hardness, thickness and weight variation. Furthermore, matrix erosion, surface pH, swelling index, *ex-vivo* muco-adhesive strength and time, *in-vivo* residence time and *in-vitro* release of drug are all part of the physico-chemical characterization testing (10).

2.4.1. Physical Characterization

2.4.1.1. Physical Appearance

The buccal formulated tablets were evaluated to observed physical appearance. The surface smoothness of these tablets was checked out and any intra batch variation was documented (11).

2.4.1.2. Dimensional Specifications

The tablets thickness and diameter were assessed for each formulation batch after randomly picking the tablets samples. A digital vernier caliper (Erweka, Germany) having zero error was used and the results were shown as an average of standard deviation (12).

2.4.1.3. Weight Variation

Digital electronic weighing balance (AX-200, Shimadzu, Japan) was used to measure the variability in tablet weight for each formulation batch. The mean weight of each formulation was subsequently determined in order to determine the level of variability in each formulation code, which is outlined in official USP standards (13).

2.4.1.4. Hardness Test

The hardness of formulated mucoadhesive tablets was tested using an Erweka hardness tester (Erweka, Germany), and the results were represented as mean ± SD (14).

2.4.1.5. Friability Test

Friability testing & evaluation were carried out according to the USP criteria (15), by using Roche friabilator to estimate tablets friability. The speed of rotation was set to 25 rpm for duration of four min. The tablets were taken out, de-dusted & then re-weighed after the specified interval. The % age of particle loss resulted from friability was subsequently determined for all formulations employing equation 4 and represented in terms of percentile loss.

$$Percent\ Loss = \frac{Initial\ tablet\ weight - Final\ tablet\ weight}{Initial\ tablet\ weight} * 100 \qquad \text{(Equation 4)}$$

2.4.2. Physico-chemical Characterization

2.4.2.1. Surface pH

Buccal tablets from each formulation batch were placed in individual petri dishes containing PBS pH 6.8 (10 ml) and left undisturbed for 2 h. The pH was determined by slightly pressing the electrode of pH meter (Accumet meter 21039, Denver, USA) to the tablet surface. The procedure was carried out three times for each formulation batch (16).

2.4.2.2. Swelling Index & Matrix Erosion

For swelling analysis, tablets from all formulations were chosen, weighed (W1) and put on glass slides dipped in petri dishes with PBS, pH 6.8 (10 ml). The entire system was kept in incubator oven (BIOBASE, China) at 37.5 ± 0.5 ºC. The weight which was achieved by individual formulation (W2) over various time intervals i.e. 0.5, 1, 2, 4 and 6 h, was calculated by electric weighing balance. Swelling index was then calculated using equation 5 as follows (17):

$$Swelling\ Index\ (\%) = \frac{W2 - W1}{W1} * 100 \qquad \text{(Equation 5)}$$

Similarly, to calculate matrix erosion, the swollen formulation at 6 h was maintained at 60 ºC over 24 h unless uniform weight (W3) was obtained for assessing moisture loss by using equation 6 (18):

$$Matrix\ Erosion\ (\%) = \frac{W1 - W3}{W1} * 100 \qquad \text{(Equation 6)}$$

2.4.2.3. *Ex-vivo* Mucoadhesive Strength

A modified mechanical balance was utilized to calculate an *ex-vivo* mucoadhesive strength. The experimental setup comprised customized balance, with one pan arm adjusted via a stage for assessing detachment force. The tablet was soaked on both sides utilizing distilled water & gently pressed against two glass slide surfaces. Previously, every single glass slide was attached to freshly excised buccal mucosa of rabbit. The first glass slide was adhered to the base, while another one was linked to moving pan thread, while fixation of tablet was done between two slides. Before conducting the experiment, an ethical approval was granted by Ethical Review Board (ERB) (801/GCPS/GU, dated 09/06/2023)

Mucoadhesion force was measured on the basis of weight (g) needed to remove the tablet from either buccal-mucosa, with the help of adding weight to the left arm of pan. The *ex-vivo* mucoadhesive strength of the formulation was determined through the minimal weight needed for removing the tablet from the mucosa. Triplicate readings were taken for each formulation (19).

2.4.2.4. *Ex-vivo* Mucoadhesive Time

This experiment required freshly excised rabbit buccal mucosa attached to glass slide with the help of acrylate adhesive. The slide was submerged into a beaker having PBS, pH 6.8 (800 ml) in an inclined position at 45º, as previously reported (20). Prior to submerging the slide, the buccal tablet was attached to it and the mucoadhesive time was recorded. A single side of each tablet was soaked using PBS, pH 6.8 and carefully pressed over the buccal mucosal surface for 20 sec. The apparatus was

rotated at 100 rpm through magnetic stirrer (VELP Scientifica, Italy) and the entire system was kept at 37.5 ºC during the course of the experiment. Mucoadhesion time was noted as time during which tablets disintegrated, dissolved or removed from the attached site (21). This experiment was performed three times, and results were averaged as mean ± SD.

2.4.2.5. *In-vivo* Residence Time

In-vivo residence time of mucoadhesive buccal formulations was evaluated in healthy human volunteers who agreed to participate in this investigation. For this purpose, five tablets without drug, were taken and subjected to testing. The participants weren't allowed to take any food; however, they were permitted to drink as long as the formulation was not dislodged. The tablet was cautiously administered into the frontal gingival region and slightly compressed for 20 sec to start the experimental process. The respondents received instructions to not disrupting the dosage form with their tongues nor apply force to it. *In-vivo* mucoadhesive residence time of the formulation was defined as the period of time when the respective formulation disintegrated, degraded, or finished (22).

2.4.2.6. *In-vitro* Drug Release

The *in-vitro* release of drug from buccal formulations was investigated utilizing USP type II dissolution apparatus (PTWS-11/P, TPT Germany). In this study, the experimental parameters involved a paddle speed of 50 rpm, PBS, pH 6.8 as dissolution medium and 37.5 ± 0.5 °C temperature. Samples of 5 ml were taken out at predetermined time intervals (0.5, 1, 2, 4 and 6 h) for analysis, and equal volume of PBS, pH 6.8 was replenished immediately for the maintenance of sink conditions. The quantitative estimation of LRX was performed using UV spectrophotometer (1601, Shimadzu, Japan) by taking maximum wavelength of 376 nm. Triplicate readings were noted and results were represented as mean ± SD (23).

2.5. Statistical Analysis

Each experiment was carried out in triplicate and the results were presented in the form of mean ± SD. The results were statistically analyzed utilizing ANOVA and Student's t-tests with level of significance as $p < 0.05$ by GraphPad Prism (version 8.0.2).

3. Results

3.1. FTIR Analysis

FTIR spectral analysis of lornoxicam showed characteristic bands around 3065.60 cm^{-1} that corresponds to -CH stretching of heteroatomic ring. The peaks observed at 1593.56 cm^{-1} and 1536.42 cm^{-1} were attributed to the N-H bending vibrations of secondary amide. The sharp peaks at 1380.84 cm^{-1} and 1325.15 cm^{-1} were assigned to the C-S group and O=S=O group stretching vibrations. The peaks at 1145.99 cm^{-1} and 1037.04 cm^{-1} corresponded to C-N stretching vibration. The bending vibration of C-Cl group was observed at 788.34 cm^{-1}. Similar peaks have been observed in literature (24). FTIR spectrum of HPMC showed several characteristic sharp peaks at 3450 cm^{-1}, 2896.5 cm^{-1}, 1448.9 cm^{-1}, 1371.2 cm^{-1}, 1054.20 cm^{-1} and 942.68 cm^{-1} that were attributed to O-H stretching vibration, C-H stretching vibration, CH_2 scissoring, asymmetric carbon bending vibration, C-O-C stretching vibration and ring asymmetric stretching, respectively (25). FTIR spectrum of sodium alginate displayed peak at 3359.10 cm^{-1} due to -OH stretching vibration and another peak at 2879.7 cm^{-1} that corresponds to -CH stretching vibration. Observed band at 1590.6 cm^{-1} was attributed to asymmetric COO- group stretching vibrations. The peak at 1027 cm^{-1} was assigned to C-C stretching vibrations (26). FTIR spectrum of chitosan showed a strong peak around 3312.86 cm^{-1} that corresponds to O-H stretching vibration, suggesting intermolecular H-bonding of chitosan, overlapping N-H extension vibration in the same region i.e. 3300-3500 cm^{-1}. The peak at 2914 cm^{-1} was assigned to C-H stretching vibration in methylene group. Additionally, the small sharp peaks at 1649 cm^{-1} and 1570 cm^{-1} correspond to carbonyl stretching of amide group and N-H bending of primary amine. The absorption band at 1189 cm^{-1} was attributed to C-N stretching of third amide

group. Chitosan also presented sharp peak at 1020 cm^{-1} that corresponds to C=O stretching vibration (27,28).

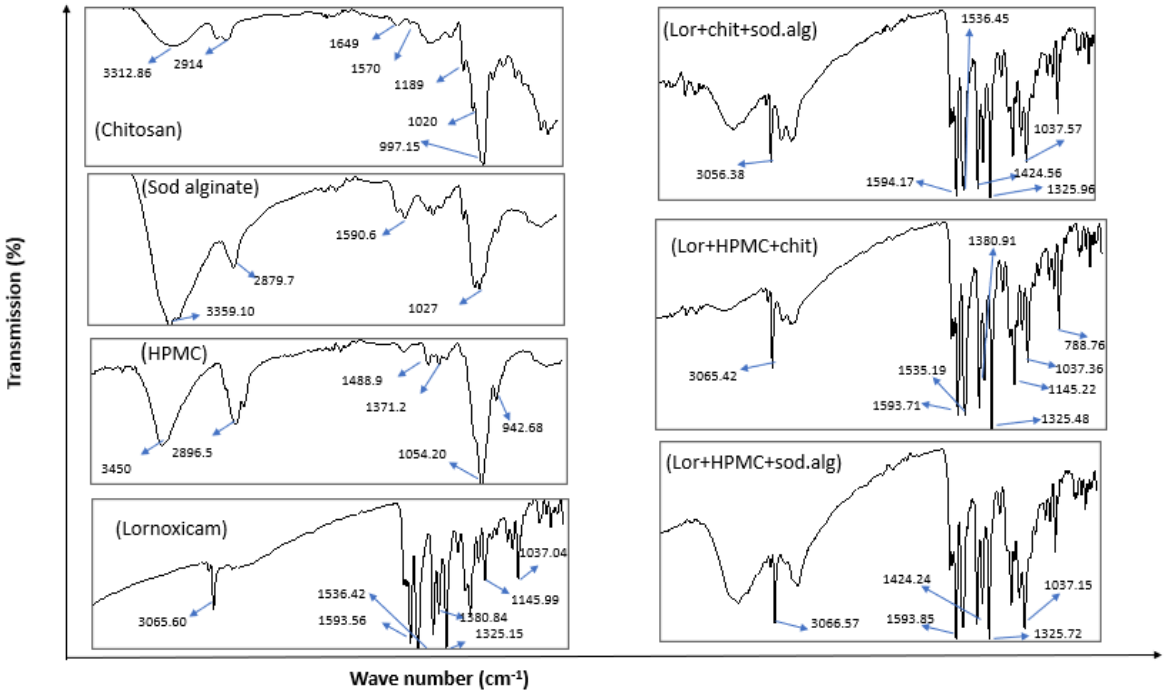

Figure 1. FTIR spectra of pure drug, polymers and drug polymers physical admixtures.

3.2. Preliminary Study Protocol

In the current study, both polymers (sodium alginate and HPMC) were mixed with chitosan in two concentrations i.e. 2.5 % and 5 % in all possible combinations, as is evident in Table 1. As a result, total eight formulations were fabricated (F1-F8). In preliminary study, the dose of lornoxicam was decreased to half because drug release was determined to be approximately 3-4 h. Likewise, polyvinyl pyrrolidone K30 (PVP) as binder, sucralose as sweetener and magnesium stearate as lubricant were added in fixed amounts (29), as shown in Table 1.

Table 1. Composition of various mucoadhesive buccal tablets in preliminary study (F1-F8)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
LRX	4	4	4	4	4	4	4	4
Chitosan	5	7.5	5	7.5	5	7.5	5	7.5
HPMC	2.5	2.5	5	5	-	-	-	-
Na-alginate	-	-	-	-	2.5	2.5	5	5
PVP	5	5	5	5	5	5	5	5
Sucralose	5	5	5	5	5	5	5	5
Mg stearate	5	5	5	5	5	5	5	5
Lactose	73.5	71	71	68.5	73.5	71	71	68.5

3.3. Physical Evaluation

Results showed that none of the formulations changed their color. On the surface of the tablets, there were no pitted markings, cracks, stains, or abrasions. The tablet's surface had a near-off-white tint with flat surface and rounded corners. According to the results of the current investigation, the thickness of formulations ranged from 2.47 mm to 2.68 mm. The formulations F2 and F7 showed the least amount of variation, i.e. 0.05 and 0.04, respectively. Tablets diameter ranged from 8.02 mm to 8.17 mm, with the formulation F8 having the highest concentration of sodium alginate and chitosan, showing the greatest variation from the mean diameter value. All of the tablets friability values fell inside the specified USP limit of < 1 %. However, F5 and F7 exhibited maximum and minimum

friability values, which were 0.714 % and 0.389 %, respectively. The tablets had a 100 mg predetermined weight. The United States Pharmacopeia (USP) states that this weight is within the allowed deviation range of ± 10 % (30). The mean weight of all the formulations, however, varied from 91.12 mg to 104.21 mg. After conducting tests on the tablet's hardness, a final hardness value of 5 - 7 kg/cm^2 was set (31). Results indicated that all formulations' hardness values fell within this range. Table 2 provides detailed results of all physical characterization tests of mucoadhesive buccal tablets.

Table 2. Physical characteristics of lornoxicam loaded mucoadhesive buccal tablets (mean ± SD, n=3)

Formulations	Thickness (mm)	Diameter (mm)	Friability (%)	Weight Variation (mg)	Hardness (kg/cm^2)
F1	2.47 ± 0.13	8.02 ± 0.04	0.592	93.65 ± 1.63	5.32 ± 1.22
F2	2.53 ± 0.05	8.09 ± 0.03	0.643	91.12 ± 1.48	5.65 ± 0.56
F3	2.58 ± 0.19	8.11 ± 0.04	0.501	103.43 ± 2.89	6.23 ± 1.36
F4	2.61 ± 0.13	8.13 ± 0.04	0.643	90.29 ± 2.23	5.97 ± 0.99
F5	2.53 ± 0.09	8.15 ± 0.03	0.714	98.13 ± 4.89	5.88 ± 0.89
F6	2.63 ± 0.20	8.07 ± 0.06	0.512	93.78 ± 1.23	7.13 ± 1.24
F7	2.60 ± 0.04	8.17 ± 0.05	0.389	89.18 ± 3.02	6.59 ± 1.66
F8	2.68 ± 0.18	8.15 ± 0.07	0.619	104.21 ± 0.41	6.73 ± 1.58

3.4. Physico-chemical Evaluation

3.4.1. Swelling Index

The figure 2 showes the swelling index results of various formulations. The formulation, F8, composed of chitosan (7.5 %) and sodium alginate (5 %) exhibited greatest swelling tendency. Additionally, it was noted that after 6 h, a decrease in swelling index was observed for all formulations (F1-F8). Even though chitosan had little effect on swelling behavior (32), more research is needed to compare the effects of the polymeric combination to those of the individual polymers.

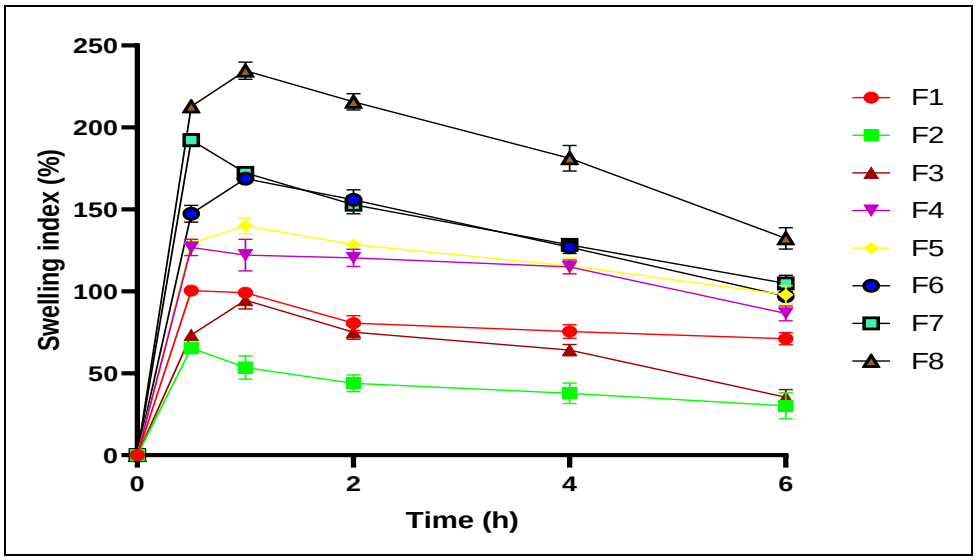

Figure 2. Swelling indices of mucoadhesive buccal tablet formulations (F1-F8) in preliminary study (mean ± SD, n=3)

3.4.2. Surface pH

Table 3 illustrates the results of surface pH of mucoadhesive buccal tablets. The lower and higher limits for pH values ranged from 6.38 – 7.14 for F5 and F2, respectively. These readings fall within the range of normal pH of saliva. It follows that the mucoadhesive formulation's pH was determined to be imitating physiological pH.

3.4.3. Matrix Erosion

Table 3 demonstrates matrix erosion values that fall between 35.22 to 80.59 %.The significant hydration loss in the mucoadhesive buccal tablets may be explained by the polymers' lower concentration (33). The formulation, F4, composed of greater concentrations of chitosan (7.5 %) and HPMC (5 %) exhibited lowest matrix erosion. Formulations containing sodium alginate, on the other hand, were likewise exposed to significantly higher matrix erosion values.

3.4.4. *Ex-vivo* Mucoadhesive Strength

According to the results, as HPMC concentration increased from F2 to F4, an increased trend in mucoadhesive force was observed (34). As opposed to formulations containing HPMC, those containing sodium alginate gave lower values of mucoadhesive strength (35). The greater concentration of sodium alginate (5% in F7 and F8) did not significantly affect the mucoadhesion values, which were low compared to formulations containing similar concentration of HPMC (5 % in F3 and F4). The formulation, F7, which contained chitosan and sodium alginate in 5 % concentration each, had the lowest value of mucoadhesive strength. On the contrary, greater force of mucoadhesion i.e. 9.55 g, was obtained for formulation F4, composed of 7.5 % chitosan and 5 % HPMC, as shown in Table 3.

3.4.5. *Ex-vivo* Mucoadhesive Time

The values of mucoadhesive time were observed to rise from approximately 3 h to > 4 h with increasing concentration of HPMC from 2.5 % to 5 %, as depicted in Table 3. The values of mucoadhesive time for all formulations (F1-F8) ranged from 0.68 to 5.82 h. Formulation F4, containing chitosan and HPMC in concentrations of 7.5 % and 5 %, respectively, showed maximum mucoadhesive time of 5.82 h. The values of mucoadhesive time for formulations containing sodium alginate (F5-F8) ranged from 0.68 to 2.61 h. There was slight increase in mucoadhesive time values for these formulations due to increase in concentration of chitosan from 5-7.5 % and sodium alginate from 2.5-5 %.

3.4.6. *In-vivo* Residence Time

Table 3 presents the findings of *in-vivo* residence time for all formulations which was found to be approximately 2 h. Upon administration into buccal mucosa, mucoadhesive tablets gradually disappeared from their site of administration. Moreover, 5 % HPMC containing formulations i.e. F3 and F4, were able to persist in the buccal mucosa for more than 1 h as compared to the rest of formulations. On the contrary, formulations composed of sodium alginate (F5-F8) disintegrated in less than 1 h and shed off in the form of particulate gel at the administration site (36).

Table 3. Physico-chemical characterization tests of mucoadhesive formulations (F1-F8) (mean ± SD, n=3)

F.Codes	Surface pH	Matrix Erosion (%)	*Ex-vivo* Mucoadhesive Strength (g)	*Ex-vivo* Mucoadhesive Time (h)	*In-vivo* Residence Time (h)
F1	6.99 ± 1.22	65.69	6.44 ± 1.56	3.65 ± 0.58	0.20 ± 0.04
F2	7.14 ± 1.56	69.23	6.12 ± 1.89	3.74 ± 0.43	0.48 ± 0.10
F3	6.89 ± 1.04	59.14	8.23 ± 2.11	4.81 ± 1.20	1.75 ± 0.36
F4	6.41 ± 0.59	35.22	9.55 ± 1.84	5.82 ± 1.11	2.01 ± 0.85
F5	6.38 ± 0.88	70.18	6.08 ± 1.51	1.87 ± 0.62	0.32 ± 0.06
F6	6.78 ± 1.36	73.94	6.19 ± 2.03	0.68 ± 0.08	0.25 ± 0.09
F7	7.13 ± 1.47	80.59	5.23 ± 0.66	1.98 ± 0.43	0.41 ± 0.11
F8	6.84 ± 0.56	55.63	6.01 ± 1.25	2.61 ± 1.09	0.13 ± 0.01

3.4.7. *In-vitro* Drug Dissolution Studies

Results demonstrated that, with the exception of F8, all other formulations containing sodium alginate released LRX before 2 h, as depicted in Figure 3. The formulations composed of 5 % HPMC (F3 and F4) sustained LRX release for 4 h, while with 2.5 % HPMC, complete LRX release was accomplished in approximately 2 h. As a result, it implies that more HPMC must be incorporated for sustained action if the formulation is intended to release the drug over a longer duration. The sustained release action of HPMC is well-defined (37). Compared to HPMC, chitosan exhibits negligible sustained drug release in powdered state (38).

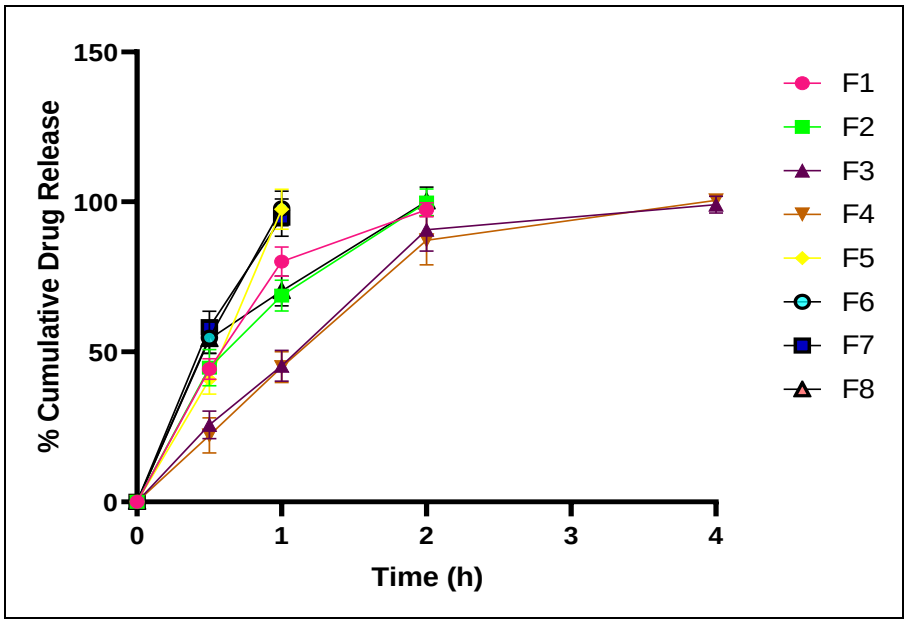

Figure 3. *In-vitro* drug release from mucoadhesive buccal formulations (F1-F8) in preliminary study (mean ± SD, n=3)

4. Discussion

This preliminary trial was carried out to optimize the strength of the constituents based on the dosage form performance for the local drug release. The mucoadhesive buccal tablets were fabricated in which the optimization of quantities of various formulation constituents was performed. The FTIR spectra of physical mixtures of drug and polymers was done to investigate the presence of any new peak. The characteristic peaks of drug and polymers were still present, and no new or unusual bands appeared in the physical mixtures of drug and polymers, suggesting the absence of any chemical reaction between lornoxicam and polymers. In case of mucoadhesive buccal tablets, preliminary study consisted of preparing either mono polymer formulations or formulations composed of polymers blended with chitosan. The selection of chitosan was based on its anti-microbial and pharmaceutical attributes (39). Its properties were, however, more prominent in gel and film dosage forms. Therefore, initially chitosan was employed at less than 10 % concentration with HPMC and sodium alginate. In the beginning, mannitol, as diluent, was incorporated into the formulations which was later replaced by lactose because of poor friability and compression problems. Lactose helped in improving physical attributes and making the tablet weight to 100 mg (40).

Lornoxicam loaded mucoadhesive buccal tablets' surface and degree of smoothness were evaluated on the basis of their physical appearance. Although, the formulation F8 having the highest concentration of sodium alginate and chitosan, showing the greatest variation from the mean diameter value, however, this deviation was regarded as insignificant because it was less than 5 %. The friability parameter is a crucial factor in determining the formulation's physical resistance to mechanical stress during transportation (41). The significance of the weight variation test lies in the fact that if this value falls beyond the compendial limits, it indicates that there is considerable fluctuation in the amount of

the active ingredient present in the unit dosage form (42). All formulations weight variation values fell within Pharmacopeial guidelines, and none of the weight variation value exceeded the compendial deviation limit. The formulation F8 showed the least amount of variance.

The physicochemical characteristics of a dosage form are crucial because they greatly influence swellibility, irritation extent, mucoadhesion and drug release from the dosage form (43). Swellibility, also termed as swelling index, is a measurement of water absorption by the formulation with respect to time. It is crucial because as water enters the formulation, the active moiety might travel out of mucoadhesive system (44). The values of swelling index of all the formulations have been recorded for 6 h and presented in Figure 2. It was observed that all formulations tend to swell with the passage of time, but swelling was lowered till 6 h. Additionally, it was noted that swelling index values were greater for formulations containing sodium alginate (F5-F8) as compared to formulations containing HPMC (F1-F4). This was attributed to the greater swelling capability of sodium alginate as compared to HPMC (45). As the concentration of sodium alginate increased in the formulations, swelling index also increased correspondingly, as shown in Figure 2.

The mucoadhesive buccal tablets come into contact with the buccal mucosal membrane directly, therefore, surface pH is a crucial parameter. Pathological irritation can result from very acidic or basic pH levels. Theoretically, it is better to accept a value that is close to the normal range (46). Saliva's pH typically ranges between 6.2 to 7.6 and is roughly 6.7 (47). The evaluation of matrix erosion was performed for the estimation of disrupted matrix of swelled tablets at the end of 6 h. This parameter also indicated the extent of swelling loss by polymers in dosage form when exposed to high temperatures in an unsaturated oven (48). . The greater matrix erosion values of sodium alginate containing formulations might be due to the fact that formulations with higher swelling capacities show higher values of matrix erosion (49).

The magnitude of force needed to attach and separate the mucoadhesive formulation from mucosal surface is estimated using the mucoadhesive strength (50). A modified balance was employed for *ex-vivo* mucoadhesion experiment in a laboratory setting with ambient conditions. Fresh rabbit buccal mucosa was isolated and attached to glass slides surface. In the present investigation, chitosan has been employed as mucoadhesive polymer owing to its biocompatibility and biodegradability. However, it exhibits somewhat weaker mucoadhesion characteristics and needs certain conditions for effective swelling (51). Thus, poor results of polymer mucoadhesion were obtained. Therefore, it is necessary to include greater polymer concentrations for the adjustment of constituents desirability that could ultimately result in achieving more suitable outcomes for mucoadhesive strength. The evaluation of mucoadhesive time is significant because it corresponds to the length of time needed for drug release into buccal mucosa (52). An increasing trend has been reported in mucoadhesion time upon incremental rise in the HPMC concentration that could be attributed to the water soluble nature of HPMC due to OH^- groups availability to for the formation of hydrogen bonds and electrostatic association with mucin (53). According to the results of mucoadhesive strength, the mucoadhesion was correlated with concentration of HPMC and formulations comprising sodium alginate had lower values than those containing HPMC. Similar display was found with formulations containing sodium alginate and the possible reason for increased mucoadhesive time of formulations could be greater swelling capability of sodium alginate along with its disintegrant effect between 2.5 to 10 % . Much higher values of time may be possible if the concentration of polymer is raised beyond the above-mentioned range (54).

In-vivo residence time was determined for all mucoadhesive formulations lacking active ingredient fabricated at preliminary stage. An approval was taken from committee to conduct experiment in volunteers for calculation of *in-vivo* residence time by evaluation of polymers safety. Thus, it could be inferred that greater HPMC concentrations are required to demonstrate *in-vivo* effects, owing to the fact that HPMC is sustained release polymer (55).

All mucoadhesive buccal formulations were subjected to *in-vitro* drug dissolution studies for determination of percent drug release from the dosage form. The predetermined criteria for drug release were set up to 6 h or if the quantitative result was greater than 95 %, the sampling was halted for that formulation. Samples of the dissolution medium elutes were taken out in order to quantitatively measure LRX using UV-spectrophotometric technique. It is recommended to employ greater polymer concentrations for more sustainability of dosage form. Out of the developed formulations, formulations F3 and F4 were chosen as optimum formulations based on drug release data. However, both these formulations were further evaluated on the basis of highest swelling behavior and greater mucoadhesive characteristics for the selection of optimized formulation. F4 formulation outperformed F3 formulation in terms of mucoadhesive strength as well as time, thus chosen as optimized formulation.

Conclusion

This preliminary study explored LRX optimization as mucoadhesive buccal drug delivery system for local sustained action. Various concentrations of polymers in mucoadhesive tablet formulations were tested. The results of swellibility showed direct relationship with sodium alginate concentration; greater polymeric concentration gave higher values of swelling index. The *ex-vivo* mucoadhesive strength as well as time were linked to greater HPMC concentration. Thus, the outcomes of the study conclude that mucoadhesive buccal formulation F4 was chosen as an optimized formulation and could be subjected to main study.

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