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Research Article

Bilayer Buccal Tablets of Furosemide: Design and Evaluation

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Abstract

Aim: In the present study, mucoadhesive bilayer buccal tablets of furosemide were fabricated with the objective of avoiding first-pass metabolism and enhancing the bioavailability along with reducing the dosing frequency. **Methodology:** Direct compression method was used to prepare bilayer buccal tablets of furosemide, with a combination of polymers such as xanthan gum, karaya gum, and guar gum along with Carbopol 934-P and ethylcellulose as the backing layer. In order to provide a unidirectional drug delivery to the mucosa and for drug loss avoidance that occurs when there is a washout with saliva, the bilayer structure design was used. Physical and biological parameters were measured for the designed tablets. **Results:** FXG1 formulation containing xanthan gum, 1% and 2 % w/w of Carbopol 934p of matrix layer, and mannitol (15% w/w of matrix layer) used as a channeling agent was found to be assuring. This formulation exhibited 82.98% drug release in 8 h along with an acceptable strength of bioadhesion (5.40 g). Short-term stability studies on this formulation showed that no significant changes in drug content and dissolution characteristics existed ($p<0.05$). IR spectroscopic studies showed the absence of any drug-excipient interactions. The drug release was of zero order, whereas the value for release exponent (n) ranged from 0.787 to 1.063 which demonstrated a diffusion control super case II. **Conclusion:** The prepared buccal tablets of furosemide persisted in the buccal cavity longer, indicating that mucoadhesive tablets of furosemide have a good potential for the treatment of edema and hypertension.

Key words: Bioadhesive strength, furosemide, Mucoadhesive buccal tablet, swelling index

Introduction

The oral route of drug delivery is perhaps the most preferred method as compared to other routes, both by clinicians and patients. Among the various routes of drug delivery, drug delivery through transmucosal routes (i.e., the nasal, oral, vaginal and rectal mucosa, and ocular cavities) offers many benefits over per-oral administration in case of systemic effect, but also has drawbacks like degradation caused by gastrointestinal enzymes and first-pass metabolism. Thus, there is rising interest in developing a therapeutic agent utilizing transmucosal pathways to deliver the drug to the right location in the body and in proper quantity, so as to rapidly achieve and sustain the appropriate concentration. As a result, alternative absorptive mucosa is considered for drug administration.[1, 2]

The buccal mucosa is rich in vascularization as the jugular vein receives the blood flow directly. Therefore, drug absorption through the buccal mucosa bypasses the gastrointestinal route and hepatic first-pass metabolism. Buccal cavity is patient-friendly because of its easy accessibility and application, together with the possibility of terminating drug delivery in case of unexpected side-effects and emergency.[3, 4] Buccal tablets can be formulated during the time of application to maintain their position, retain shape, and integrity.

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They are also easily visible when treatment is going on and the dosage can be controlled.[5]

The oral cavity is a potential site for drug delivery because of its unique environment. The advantages of this route are many. The drug is not exposed to the stomach's acidic pH. It is possible to reach therapeutic drug concentration in the serum faster, and without undergoing the first-pass metabolism, the drug goes into the systemic circulation. The mucous membrane forms the lining of the oral cavity and the possibility of using it as a site for drug absorption is very less explored.[6]

The oral mucosal surface contains a thin mucin film, which might serve as a location for mucoadhesive delivery for prolonged contact with the mucosa. Additionally, the drug should be released towards the mucosa in a unidirectional, predictable, and controlled way to cause the necessary therapeutic response. Usage of a bilayer device can provide such a kind of unidirectional release. As a result, for controlled or sustained drug delivery, the mucosal surface of the oral cavity forms a potential site.

Furosemide is a broadly used "high-ceiling" loop diuretics drug, used for chronic renal failure, congestive heart failure, and hepatic cirrhosis. Furosemide is weakly acidic (pKa 3.93), and therefore its absorption occurs typically in the stomach and upper portion of the small intestine. After oral ingestion/administration, it is absorbed incompletely, rapidly undergoes first-pass metabolism, giving a narrow absorption window and low bioavailability (43-50%). Furosemide has a biological half-life of 1-2 hours. The physiochemical properties of furosemides and their low half-life and molecular weight (330.7g/mol), make it an ideal drug of choice for administration through the buccal route. Hence, the aim of the present study is to prepare and evaluate buccal tablets of furosemide by the use of various bioadhesive polymers. This will increase bioavailability and decrease the side effects caused due to dosage and frequency of administration. Such a dosage form is expected to be retained for a longer time in the oral cavity and provide sustained release, prolonging the absorption phase and causing an increase in drug effect.[7]

In the present study, efficacious and prolonged release mucoadhesive tablets of furosemide using various polymers to surpass the first-pass metabolism were designed in order to reduce dosing frequency and to improve patient compliance with improved bioavailability.

Table 1: Composition of buccal tablets of furosemide

Ingredients* (mg/tablet)	Formulation code														
	FXG_0	FXG_1	FXG_2	FXG_3	FXG_4	FKG_0	FKG_1	FKG_2	FKG_3	FKG_4	FGG_0	FGG_1	FGG_2	FGG_3	FGG_4
Furosemide	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Carbopol934P	---	2	2	2	2	---	2	2	2	2	2	2	2	2	2
Xanthan Gum	5	1	2	3	5	---	---	---	---	---	---	---	---	---	---
Karaya Gum	---	---	---	---	---	5	1	2	3	5	---	---	---	---	---
Gaurgum	---	---	---	---	---	---	---	---	---	---	5	1	2	3	5
Mannitol	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Aspartane	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Flavour	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
MCC	63	65	64	63	61	63	65	64	63	61	63	65	64	63	61
Ethyl cellulose	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Total weight	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

*Weights expressed as mg per tablet;
FKG - formulation containing karaya gum as polymer
FGG - formulation containing guar gum as polymer FXG - formulation containing xanthan gum as polymer

Materials

Furosemide was gifted by Geno Pharmaceuticals Ltd, Mapusa, Goa. Ethyl cellulose was obtained as a gift from Loba Chemie Pvt Ltd, Mumbai, India; karaya gum and guar gum was gifted by Nutriroma Pvt Ltd, Hyderabad; xanthan gum was obtained as a gift from Panchi Chemicals Pvt Ltd, Mumbai; and Carbopol 934p was gifted by Alkem Labs Pvt, Ltd, Mumbai. All other materials used were of analytical or pharmacopoeial grade.

Methods

Preparation of the buccal tablets [8-9]

Preparation method: Direct compression method was used for the preparation of buccal tablets of furosemide by using xanthan gum, karaya gum, guar gum, and Carbopol 934p as polymers.

Procedure for preparation: The constituents for the formulation, namely furosemide, polymer, and other excipients were weighed accurately (Table 1). Furosemide was mixed with mannitol thoroughly on butter paper. Next, the rest of the ingredients, apart from the lubricant, were mixed from low to high weights in order and blended in an inflated polyethylene pouch for 10 min. Next, after the addition of lubricant, mixing was carried on for another two minutes. The blend thus formed (100 mg) was pre-compressed in a 10-station rotary tablet punching machine (Clit, Ahmedabad) at a pressure of 0.5 ton and turret speed of 2 rpm in order to form a flat-faced tablet of a single layer of 7 mm diameter. Then, a pressure of 3.5 tons and turret speed of 2 rpm, after the addition of 50 mg of ethyl cellulose powder, was carried out for the final compression to form the bilayer tablet.

Evaluation of buccal tablets

Evaluation of the tablets was carried out by measurement of the following: variation in weight, hardness, friability, drug content uniformity, swelling index, surface pH, ex vivo mucoadhesive strength, in-vitro drug release, short-term stability (IR spectroscopy), and drug-excipient interaction.

Fifteen tablets were randomly selected and each was weighed separately. The weight of each tablet was compared with the average weight in order to determine the weight variation. Monsanto hardness tester was used to determine hardness and the friability was determined using Roche friabilator. In order to carry out the drug content uniformity test, five tablets were weighed and powdered. A powder equivalent to 10 mg of drug was extracted in methanol, filtered using 1.5 µm membrane filter disc (Whatsman No 1 filter paper), and analyzed by measuring the absorbance at 233.6 nm against solvent blank after appropriate dilutions were prepared. Using the standard calibration curve, the amount of furosemide present was found out. The % drug content was determined as a mean of three measurements.

For the determination of the surface pH of the buccal tablets, a combined glass electrode was used. Swelling of the tablet was carried out for 2 h at room temperature by keeping it in contact with 6 ml of distilled water (pH 6.8±0.05). The pH was measured by placing the electrode onto the surface of the tablet and equilibrating for 1 min.[10] (Fig.1).

The swelling index[11,12] of the buccal tablet was calculated using phosphate buffer pH 6.8. The initial weight of the tablet was measured (w1). Then, it was placed in a petri-dish containing pH 6.8 phosphate buffer (6 ml) kept at 37±1°C in an incubator, The tablet was taken out at different time points (0.5, 1.0 to 9.0 h), and weighed again (w2) (Fig.2). Then, the swelling index was calculated by using the formula below:

$$\text{Swelling index} = 100\,(w2-w1)/w1.$$

Fig 1: pH examination of buccal tablets using glass electrode

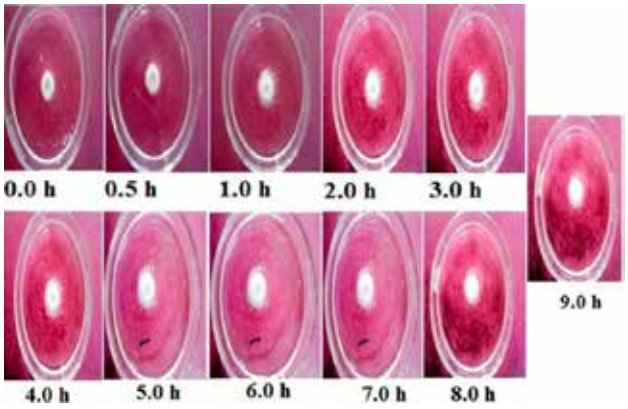

Fig 2: Swelling index study of formulation FXG_1

Mucoadhesion strength[13-16]

In the laboratory, the instrument used for measuring bioadhesion was assembled. Mucoadhesion strength of the tablet was calculated by a modified physical balance by the procedure reported by Gupta et al.15 whereas, a mucosal model, bovine cheek pouch was used (Buccal mucosa was collected from the local slaughterhouse).(Fig.3).

Fig 3: Bioadhesion testing apparatus

In vitro drug release study[17-18]

For the study, USP XXIII tablet dissolution test apparatus-II (Electrolab TDT-06N) was used, with 50 rpm paddle and for dissolution medium 200 ml of pH 6.8 phosphate buffer was used. The release study was performed at a temperature of 37±0.5°C. The tablet's backing layer is attached to a glass disk having cyanoacrylate adhesive. The disk is kept in the dissolution vessel at the bottom. Samples (5 ml each) are taken at fixed time intervals and are replaced with an equal volume of fresh medium. The samples were filtered through 0.45 µm membrane filter disc (Millipore Corporation) and analyzed for furosemide after appropriate dilution and measured at 274.50 nm.

Stability studies

To perform the accelerated stability studies, the following criteria were maintained: 40±2°C temperature / 75±5% relative humidity for a duration of 90 days. An adequate number of tablets (formulations FXG1, 15 nos.) were kept in vials of amber colour with rubber stoppers. These were then placed in a stability chamber which was maintained at 40±2°C/75± 5% RH. Samples were taken at one-month interval and analyzed for the drug content. After 90 days, the drug release profile was determined by dissolution test.

Drug-excipient interaction studies

Drug-excipient interactions were ruled out by IR spectroscopy studies on the samples (FSA_3, FXG_3, FKG_3, FGG_3) stored for three months at 40±2°C / 75±5% RH. The IR spectrum of the pure drug furosemide displayed characteristic peaks at 3120-3400cm^{-1}, 1593cm^{-1}, 1323cm^{-1}, 580cm^{-1}, 1408cm^{-1} due to C-H (aromatic), C-H (aliphatic), C-H bending (in plane), C-H bending (out of plane), C-CL and S=O groups, respectively. All the above characteristic peaks of the pure drug were also found in the IR spectrum of the formulation FSA_3 (peaks at 3123.00 cm^{-1}, 1670.41 cm^{-1}, 1593.25 cm^{-1}, 1321.28 cm^{-1}, 580 cm^{-1} and 1402.00 cm^{-1}, FXG_3 (peaks at 3126.00 cm^{-1}, 1672.34 cm^{-1}, 1593.25 cm^{-1}, 1323.21 cm^{-1}, 583 cm^{-1} and 1402.00 cm^{-1}) FKG_3 (peaks at 3122.00 cm^{-1}, 1672.34 cm^{-1}, 1593.25 cm^{-1}, 1323.21 cm^{-1}, 582 cm^{-1} and 1402.00 cm^{-1}) and FGG_3 (peaks at 3124.00 cm^{-1}, 1672.34 cm^{-1}, 1593.25 cm^{-1}, 1323.21 cm^{-1}, 580.59 cm^{-1} and 1402.00 cm^{-1}) due to C-H (aromatic), C-H (aliphatic), C-H bending (in plane), C-H bending (out of plane), C-CL and S=O groups respectively. The presence of the above peaks indicates the undisturbed structure of the drug in the above formulation. Hence, there are no drug-excipient interactions. IR spectra of furosemide (pure drug), FSA_3, FXG_3 FKG_3, FGG_3 along with other excipients are shown in figure 8 to 12.

Results and discussion

The main objective of the present work was to produce buccoadhesive bilayer tablets of furosemide,

an antidiuretic (Na-K-2Cl symporter), comprising of a non-adhesive protective layer that is free of drug. The double-layered structure was expected to - i) provide unidirectional drug delivery, ii) prevent drug loss due to saliva washout, iii) immediately release the drug to produce a rapid pharmacological effect and iv) provide sustained drug release over a prolonged period of time. A total of fifteen formulations of buccoadhesive bilayer tablets of furosemide were prepared and their evaluations were carried out for physical, biological, and mechanical parameters. According to the work plan, the tablets were evaluated for their thickness, hardness, friability, weight variation, swelling index, surface pH, drug content, and mucoadhesive strength. The buccoadhesive tablets were uniform and smooth in appearance on physical examination. The hardness was found to be 3.76 to 4.67 kg/cm2; hardness increases with increasing Carbopol 934p proportion in the formulation. As shown by the minimum value of standard deviation, the variance in the thickness and weight were found to be uniform (3.21 to 3.37 mm and 148.49 to 150.46 mg respectively). In order to withstand the rigours of handling and transport, friability values below 1% imply strong mechanical strength, the results of which are given in Table 2. It shows that the drug content of tablets was quite uniform, and on an average, the drug content was within 98.56% to 100.97 %. The standard deviation and coefficient of variation were found to be low (<1, not shown in the table) which shows that there was a uniform distribution of furosemide within the buccoadhesive tablets. The surface pH of all the tablets was within a range of 5.88 to 6.94 (Table 2) which was close to neutral pH. Hence, it can be understood that the prepared tablets will be non-irritant in the mouth. The swelling profile of the prepared formulations is shown in Table 2. It has been previously reported that the polymer's swelling state is critical for its bioadhesive behaviour. Adhesion takes place soon after swelling begins, although there is not a very tight bond between the mucosal layer and the polymer. With the amount of hydration, the adhesion can increase to a point where over-hydration leads to an unexpected decrease in adhesive strength due to disentanglement at the interface between polymer and tissue. The obtained results indicate that with increase in the Carbopol 934P concentration, the swelling index increases. The highest mucoadhesive strength was obtained for FXG4, i.e., 7.88 gm. The reason for this might be a strong electrostatic interaction between opposite charges on the surface of Carbopol 934P and mucous membrane which are positive and negative, respectively.

Table 2: Evaluation parameters of buccal tablets of furosemide

Formulation code	Mean Hardness* (kg/cm²± SD)	Mean Thickness* (mm± SD)	Mean Weight Variation* (mg± SD)	Friability (%±SD)	Drug Content* (Mean±SD)	Surface PH* (Mean ±SD)	Swelling Index after 8 h* (Mean ±SD)	Mucoadhesive Strength* (gm) (Mean±SD)
FXG_0	3.76±0.02	3.30±0.015	149.37±0.57	0.96±0.015	98.70±1.05	6.17±0.05	28.17±5.43	4.19±0.16
FXG_1	4.13± 0.15	3.25±0.030	150.28±0.10	0.94±0.05	99.29±0.75	6.53±0.05	59.59±4.95	5.40±0.13
FXG_2	4.29±0.01	3.28±0.02	149.28±0.13	0.49±0.03	100.26±0.75	6.67±0.05	73.08±4.28	6.59±0.42
FXG_3	4.32±0.02	3.37±0.11	150.18±0.07	0.27±0.05	98.60±0.92	6.74±0.7	85.24±4.08	7.35±0.19
FXG_4	4.38±0.02	3.30±0.015	150.46±0.20	0.59±0.05	99.28±1.10	6.94±0.10	99.65±4.77	7.88±0.105
FKG_0	3.87±0.02	3.24±0.015	148.49 ±0.52	0.84±0.04	98.56 ±0.96	5.88± 0.09	38.80±5.38	4.22±0.12
FKG_1	4.17± 0.01	3.28±0.015	150.28 ±0.15	0.72±0.04	98.58 ±1.14	6.19±0.05	59.67± 4.61	5.57±0.10
FKG_2	4.28±0.02	3.29±0.01	148.51 ±1.01	0.62±0.045	100.03±0.56	6.27± 0.05	76.83± 5.06	6.63±0.13
FKG_3	4.40±0.02	3.28±0.02	150.25 ±0.10	0.62±0.045	99.64 ±1.30	5.94±0.04	83.24± 4.89	7.34±0.13
FKG_4	4.65±0.01	3.32±0.032	150.07±0.05	0.60±0.05	100.10±0.46	6.63±0.05	98.81±5.49	7.74±0.16

Formulation code	Mean Hardness* (kg/cm²± SD)	Mean Thickness* (mm± SD)	Mean Weight Variation* (mg± SD)	Friability (%±SD)	Drug Content* (Mean±SD)	Surface PH* (Mean ±SD)	Swelling Index after 8 h* (Mean ±SD)	Mucoadhesive Strength* (gm) (Mean±SD)
FGG_0	3.86±0.01	3.21±0.01	149.47±0.47	0.82±0.05	99.56±0.83	6.41±0.05	39.19±5.00	3.79±0.22
FGG_1	4.15±0.01	3.24±0.04	150.16±0.076	0.75±0.06	100.25±0.24	5.96±0.04	68.5±5.55	5.60±0.43
FGG_2	4.20±0.01	3.25±0.03	150.18±0.070	0.60±0.03	100.56±0.64	6.20±0.04	83.54±3.39	6.28±0.14
FGG_3	4.39±0.01	3.24±0.015	149.63±0.38	0.69±0.04	100.97±0.025	5.96±0.06	96.31±2.69	7.29±0.12
FGG_4	4.67±0.10	3.29±0.01	149.18±0.07	0.63±0.05	100.96±0.04	6.26±0.06	123.16±3.99	7.79±0.14

*Average of three determinations

In vitro drug release: It can be well understood from the dissolution data that the developed formulations have released more than 82.98% drug in 8 h. The formulation FXG1 (containing xanthan gum 1% and 2% w/w of Carbopol 934p), and mannitol (15% w/w of matrix layer) was assuring, having t25%, t50% and t70% values of 2.1, 4.1 and 6.25 h, respectively and released 82.98% drug within 8 h. Results are tabulated (Table 3) and the drug release profiles have been shown in figures 4, 5, and 6. A comparison of the release parameters is shown in figure 7.

Drug release kinetics: The data obtained from in vitro drug release from buccoadhesive tablets of furosemide was analyzed by linear regression for the goodness of fit test according to zero and first kinetics and according to Higuchi's and Peppas models to understand the drug release mechanism. It is evident from the results that all the tablets showed drug release through zero order kinetics (having 'r' values from 0.987 to 0.999). Data from the Higuchi and Peppas models reveal that the drug release occurred through diffusion control super case II transport mechanism (having 'n' values from 0.787 to 1.063).

Pure Furosemide in its IR spectrum showed characteristic peaks at 3400 cm-1 and 1664 cm-1 due to C-NH (aromatic) and C-H (aliphatic) groups, respectively. The spectra also showed peaks of 1593 cm-1 and 1323 cm-1 which were characteristic of -NH2 and -SO2 groups, peaks at 580 cm-1 and 1408cm-1 are due to –Cl and S=O, respectively. All of these characteristics appeared in the IR spectrum of FXG3 (3122 cm-1 and 1672.34 cm-1 due to -NH and C-H stretching respectively and peaks at 1593.25 cm-1 and 1323.21 cm-1 are due to –NH2 bending and SO2 groups, peaks at 583 cm-1 and 1402 cm-1 are due to –Cl and S=O, respectively). From the IR data, we can say that the structure of furosemide was undisturbed in the prepared formulation.

The stability studies indicate that the drug content of FXG1 did not show any significant alteration at 40±2 0C / 75±5% RH after it was stored for 90 days. The value of 't' was found to be 1.978 ($p < 0.05$).

Table 3: Dissolution parameters of the formulations

Sl. No.	Formulation code	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{70\%}$ (h)	Cumulative % drug release in 8 h
1	FXG_0	2.90	5.8	7.55	71.53
2	FXG_1	2.1	4.1	6.25	82.98
3	FXG_2	2.25	4.80	6.45	77.35
4	FXG_3	3.25	6.2	>8	68.27
5	FXG_4	4.25	7.7	>8	57.60
6	FKG_0	3.25	6.3	>8	68.27
7	FKG_1	2.4	4.2	6.4	81.33
8	FKG_2	2.3	5.4	7.25	75.01
9	FKG_3	3.25	6.3	>8	63.88

Sl. No.	Formulation code	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{70\%}$ (h)	Cumulative % drug release in 8 h
10	FKG_4	4.2	7.59	>8	52.66
11	FGG_0	3.3	6.6	>8	63.88
12	FGG_1	2.65	4.6	6.9	81.11
13	FGG_2	2.55	4.7	7.5	74.64
14	FGG_3	2.8	5.45	>8	63.88
15	FGG_4	3.95	7.9	>8	51.33

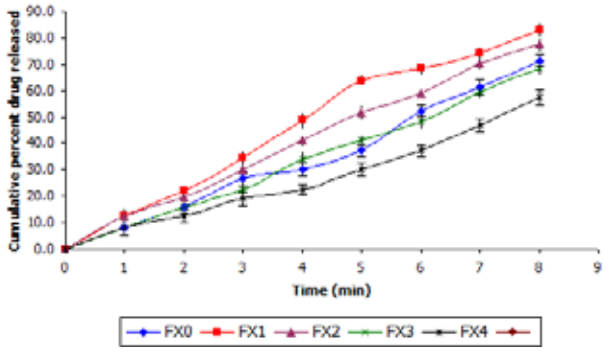

Fig 4: Cumulative percent drug released Vs time plots (zero order) of formulations FXG_0, FXG_1, FXG_2, FXG_3 and FXG_4

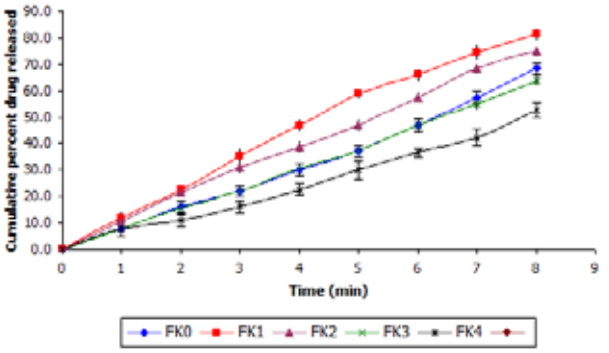

Fig 5: Cumulative percent drug released Vs time plots (zero order) of formulations FKG_0, FKG_1, FKG_2, FKG_3 and FKG_4

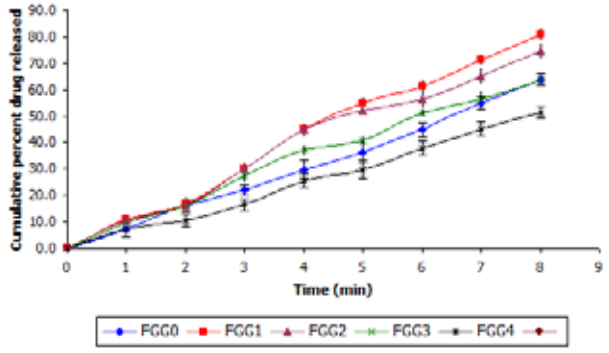

Fig 6: Cumulative percent drug released Vs time plots (zero order) of formulations FGG_0, FGG_1, FGG_2, FGG3 and FGG_4

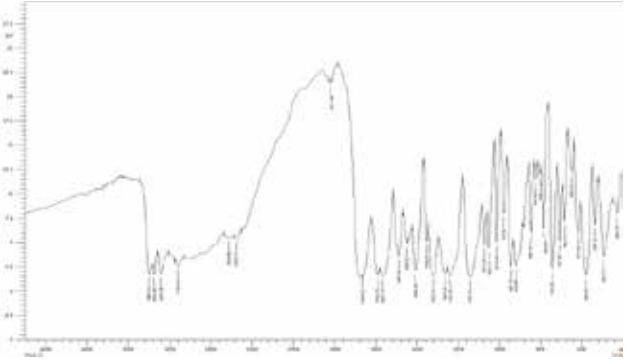

Fig 8: IR spectrum of furosemide

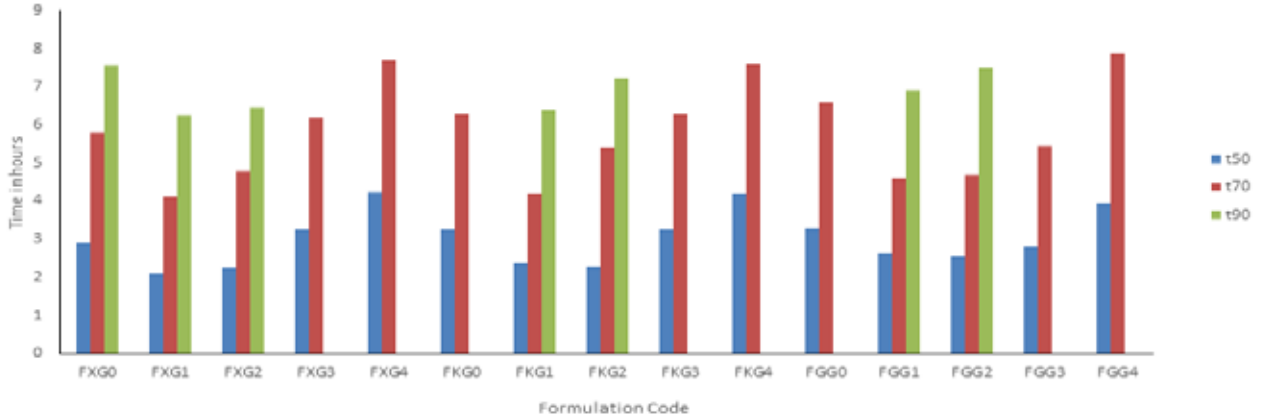

Fig 7: Comparison of dissolution parameters (t25%, t50% and t70%) of buccal tablets of furosemide

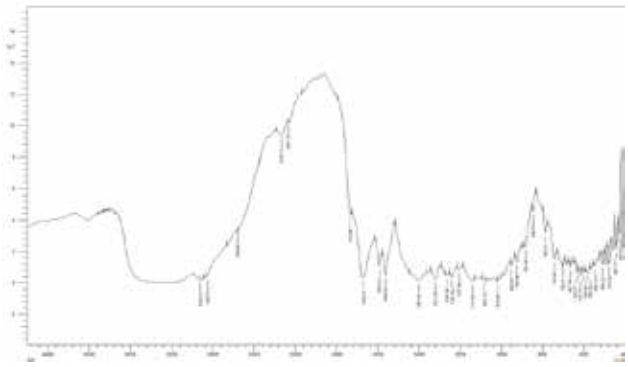

Fig 9: IR spectrum of promising formulation FSA3

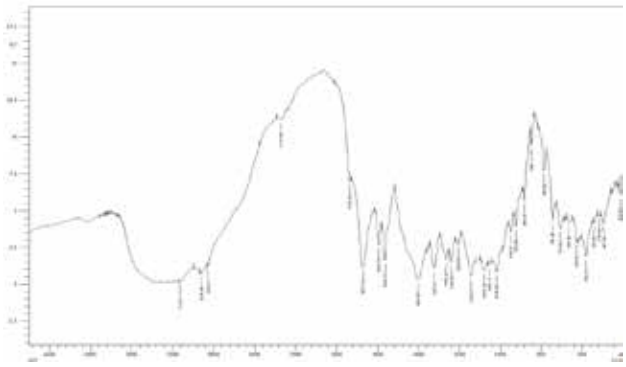

Fig 10: IR spectrum of promising formulation FXG3

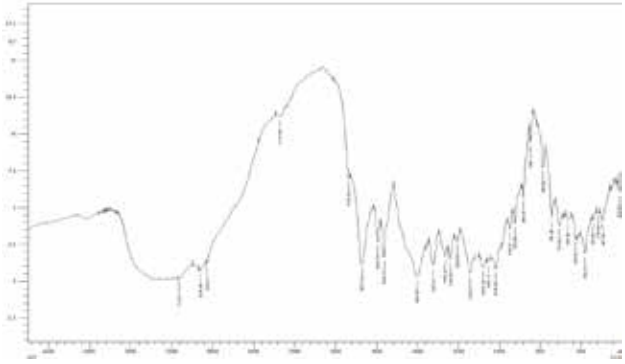

Fig 11: IR spectrum of promising formulation KKG3

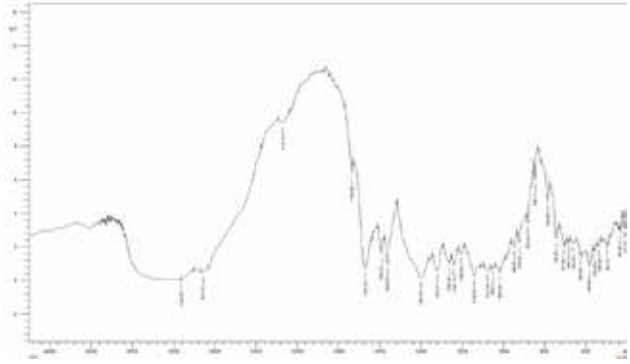

Fig 12: IR spectrum of promising formulation FGG3

Conclusion

The outcomes of this study indicate that buccoadhesive bilayer tablets of furosemide with controlled drug release can be successfully prepared by direct compression method using xanthan gum, karaya gum, guar gum, and Carbopol 934p as mucoadhesive polymers and ethyl cellulose as a backing layer. It exhibited well-controlled and delayed release pattern. This study concludes that the addition of Carbopol 934p increases the viscosity and swelling of tablets which in turn controls the drug release and improves its mucoadhesive properties. The formulation FXG1 (containing xanthan gum 1% and 2% w/w of Carbopol 934p of matrix layer), Carbopol 934p (2% w/w of matrix layer), and mannitol (channeling agent, 15% w/w of matrix layer) were promising. It showed an in vitro drug release of 82.98% in 8 h and an acceptable bioadhesion strength (5.40 g).

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