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FORMULATION AND IN-VITRO EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF FUROSEMIDE

Km. Pratiksha*, Dr. Vikas Sharma, Lavkush Tiwari and Kris Jain

*Shri Rawatpura Sarkar Institute of Pharmacy (SRI), Datia.

Institute of Pharmacy, Shri Rawatpura Sarkar Institute of Pharmacy (SRI), Datia.

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***Corresponding Author**
Km. Pratiksha
Shri Rawatpura Sarkar Institute of Pharmacy (SRI), Datia.

ABSTRACT

This study is mainly focused on the ability of polymer to polymer to expand the bioavailability of Furosemide and to release the drug in controlled foreordained way. The polymers selected for the study include natural and synthetic polymer like Poly vinyl alcohol, Poly vinyl pyrolidine, Propylene glycol and HPMC 15 based on their physicochemical properties. The mucoadhesive buccal patches were prepared by solvent casting method. The prepared patches were subjected to physical evaluations, in vitro diffusion studies and stability study. All the formulations have shown good adhesive property, tensile strength, folding endurance, thickness, pH and moisture content. The diffusion studies have shown that the percentage drug release is from natural polymer based patches is more than the synthetic polymer with different polymer based mucoadhesive patches. The In vitro drug release, evaluation, stability and accelerated stability studies of the mucoadhesive patches shown that the formulation containing natural polymer has the promising results with 100.71% drug release within 10 hours, folding endurance 301-319, patch thickness 0.21-0.27 mm, surface pH 6.16-6.70, moisture content 1.73 to 2.91, tensile strength 5.18 to 13.64 kg/mm^2.

KEYWORDS: Furosemide, Buccal patches, Mucoadhesive, In-vitro drug release.

INTRODUCTION

Amongst the various routes of administration tried so far for novel drug delivery systems, localized delivery to tissues of the oral cavity has been investigated for a number of applications including the treatment of toothaches[1], periodontal disease[2,3], bacterial and fungal infections[4], aphthous and dental stomatitis[5] and in facilitating tooth movement with

prostaglandins.[6] Over the last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the buccal cavity). Mucoadhesion may be defined as a state in which two materials, one of which is mucus or a mucous membrane, is held together for extended period of time.[7] Recently, Jasti *et al*., Salamat-Miller *et al.,* and Semalty *et al*., has reviewed the use of mucoadhesive polymers in buccal drug delivery and highlighted the use of novel mucoadhesive polymers.[8-10] Various studies have been conducted on buccal delivery of drugs using mucoadhesive polymers. Attempts have been made to formulate various mucoadhesive devices including tablets[11], films[12], patches[13,14], disks[15,16], strips[17], ointments[18] and gels.[19]

Buccal Drug Delivery System[20]

The mucosa of the mouth is very different from the rest of the gastrointestinal tract and morphologically is more similar to skin. Although the permeability of skin is widely regarded as poor, it is not generally appreciated that the oral mucosa lacks the good permeability demonstrated by the intestine. These differences within the gastrointestinal tract can largely be attributed to the organization of the epithelia, which serve very different functions. A simple, single-layered epithelium lines the stomach, small intestine, and colon, which provides for a Minimal transport distance for absorbents. In contrast, a stratified or multilayered epithelium covers the oral cavity and esophagus and, in common with skin, is composed of layers with varying states of differentiation or maturation evident on progression from the basal cell layer to the surface. Drugs have been applied to the oral mucosa for topical applications for many years.

However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Notwithstanding the relatively poor permeability characteristics of the epithelium, a number of advantages are offered by this route of administration. Foremost among these are the avoidance of first-pass metabolism, ease of access to the delivery site, and the opportunity of sustained drug delivery predominantly via the buccal tissues. Delivery can also be terminated relatively easily if required. The robustness of the epithelium necessary to withstand mastication also serves the drug delivery process well as fast cellular recovery follows local stress and damage. Indeed the two most challenging issues to be addressed in the oral mucosal delivery of drugs are undoubtedly

permeability enhancement and dosage form retention at the site of application. The continuous secretion of saliva and its subsequent swallowing can lead to substantial drug depletion from the dosage form and hence low bioavailability.

Advantages[21]

Following buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect.

- It is richly vascularized and more accessible for administration and removal of dosage forms.
- No hepatic first-pass effect.
- No pre-systemic metabolism in the gastrointestinal tract.
- Ease of administration
- High patient accessibility.
- An expanse of smooth muscle and relatively immobile mucosa, suitable for administration of retentive dosage forms.
- Bypass exposure of the drugs to the gastrointestinal fluids.
- More rapid cellular recovery and achievement of a localized site on smooth surface of buccal mucosa.
- Low enzyme activity, suitability for drugs/ excipients that mildly and reversibly damages or irritates the mucosa.
- The oral mucosa is routinely exposed to a multitude of different foreign compounds. So it has evolved a robust membrane that is less prone to irreversible damage by drug, dosage form or additives used therein.
- Non-invasive method of drug administration.
- Facility to include permeation enhancer or enzyme inhibitor or pH modifier in the formulation.

Disadvantages

- Low permeability of buccal membrane specifically when compared to the sublingual membrane.
- Small surface area (170 cm^2).
- Saliva (0.5–2 L/day) is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane.

- Inconvenience of patient when eating or drinking.

MATERIALS AND METHODS

Furosemide was a gift sample (Aurabindo Pharmaceuticals.), Hydroxypropylmethylcellulose (47 centipoise) (HPMC) Alkem Laboratories, Poly vinyl alcohol, Propylene glycol and Poly vinyl pyrolidine were obtained from SD Fine Chemicals Ltd.., (India) Concentrations of Furosemide were measured with a UV VIS spectrometer (UV-1700, Shimadzu Corporation, Tokyo, Japan). Interaction between Furosemide and polymers was verified using FTIR and UV-VIS spectrometric methods.

Compatibility Studies of Furosemide and Polymers

FT-IR spectrum of drug and physical mixture of drug with polymers were obtained. The samples were mixed with KBr and the spectrum was obtained by scanning over the wave number range of 4000-400 cm^{-1}. IR helps to confirm the identity of the drug and to detect the interaction of the drug with the excipients.

Calibration Curve

a. Scanning of drug

Accurately weighed 100 mg of Furosemide and dissolved in 10ml of methanol and make up the volume to 100 ml with distilled water. Take one ml from the above solution and make up the volume to 100 ml with distilled water having concentration of 10 mcg/ml. The absorption maxima of the above standard solution was scanned between 200-400nm in UV spectrophotometer against blank. The absorption maxima were found to be 276nm.

b. Preparation of Calibration Curve of Furosemide

From the above standard solution aliquots of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ml was withdrawn and the volume make up to 10 ml with distilled water to get the concentration of 1-10 mcg/ml respectively. Absorbances of these solutions were measured against blank at 276 nm.

Preparation of Buccal Patches

Patches containing Furosemide and HPMC E15, PVP, PVA different proportions was prepared by the solvent casting method. The drug was dissolved in 5ml of methanol and the polymers were dissolved in separate container with 20ml of distilled water under continuous stirring for 4 hours. After stirring, mix the drug and polymer solution. Propylene glycol was added into the solution as a plasticizer under constant stirring. The viscous solution was left

over night to ensure a clear, bubble free solution. The solution was poured into a glass petridish and allowed to dry at 40 ºC temperature till a flexible patch was formed. Dried patch was removed carefully, checked any imperfections or air bubbles and cut into pieces of 1mm^2 area. The patches were packed in aluminum foil and stored in desiccators to maintain the integrity and elasticity of the patches. Table no.1 shows the composition of different buccal patches.[22]

Table 1: Composition of Buccal Patches of Furosemide.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Furosemide	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
HPMC E15	750 mg	----	250 mg	375 mg	500 mg	750 mg	----	250 mg	375 mg	500 mg
PVP	125 mg	125 mg	125 mg	125 mg	125 mg	----	----	----	----	----
PVA	----	----	----	----	----	125 mg	125 mg	125 mg	125 mg	125 mg
Ethanol	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
Propylene glycol	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7ml	0.7 ml	0.7 ml	0.7 ml
Distilled water	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml

Evaluation of Muccoadhesive Buccal Patches of Furosemide[23-27]

A) Physical Parameters

Thickness of Patch

Thickness of patch was measured at 5 different randomly selected spots using screw gauge. The mean and standard were calculated.

Folding Endurance

Folding endurance of the buccal patches was determined by taking 20mm diameter of patch was repeatedly folding at the same place till it broke. The no of times of patch could be folded at the same place without breaking gave the value of the folding endurance. The test was done three times and calculates the mean and standard.

Mechanical Strength

Mechanical properties of patches were evaluated by using the microprocessor based advanced force gauze equipped with a motorized test stand equipped with cell. Patch with diameter 60×10mm and without any visual defects were cut and positioned between two

clamps separated by a distance 3cm. clamps were designed to secure the patch without crushing it during test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate 2mm/sec until the patch broke. The force and elongation of the film at the point when the patch broke was recorded. The tensile strength and elongation at break values were calculated using the formula.

$$\text{Tensile strength } (kg.mm^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample } (mm^2)}$$

$$\text{Elongation at break } (\%.mm^{-2}) = \frac{\text{Increase in length (mm)}}{\text{Original length}} \times \frac{100}{\text{Cross sectional area } (mm^2)}$$

Water Uptake Study

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. This test was carried out by dissolving 5% w/v agar in hot water. It was transferred into petriplates and it was allowed to solidify. Six drug free patches from each formulation were selected and weighed. They were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37 ºC for one hour, removed and reweighed. The percentage moisture absorption was calculated by using the formula.

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

This test was performed in triplicate.

Surface pH

For determination of surface pH three films of each formulation were allowed to swell for 2 h on the surface of an agar plate. The surface PH was measured by using a PH paper placed on the surface of the swollen patch. A mean of three readings was recorded.

B. Performance Parameters

Drug Content Uniformity

Drug content uniformity was calculated by taking three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of PH 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyzed at 276nm in a UV spectrophotometer (Sysronic). The average of drug contents of three films was taken as final reading.

Measurement of Bioadhesive Strength

The force required to detach the bioadhesive films from the mucosal surface was applied as a measure of the bioadhesive performance. Bioadhesive strength of the patches was examined by the slightly modified procedure using the porcine gastric mucosa as the model membrane. The instrument is broadly composed of a modified two arm physical balance in which the right pan had been replaced by a formulation holding glass plate and counter balanced by a water collecting pan suspended to the left arm. The pan received a siphon tube from a 10 L bottle, which was kept at a high place in such a way that water head in the bottle, always remains above the water collecting pan. The siphon tube bears a flow regulating device. Nylon thread was used to suspend both the glass plate and the pan. An acrylate tissue mounting stage was attached to the center of a glass beaker. Glass beaker was filled with phosphate buffer (PH 6.8) to simulate in-vivo saliva conditions. A magnetic stirrer provided with temperature control was used to maintain the temperature of phosphate buffer (PH 6.8) in glass dish at 37±0.5 °C. A piece of porcine gastric mucosa, 3 cm long, was tightly secured on the upper surface of the acrylate tissue mounting stage with thread. Films were fixed on the centre of the formulation holding glass plate with an adhesive. The exposed film surface was moistened with phosphate buffer (PH 6.8) and left for some time for initial hydration and swelling. Then glass plate (with the film) was kept on the mucosal tissue secured on the tissue mounting stage in such a way that films completely remained in contact with mucosa.

The whole assembly was kept undisturbed for few minutes (preload time) to establish the adhesion between the film and mucosal tissue. The glass plate (weight 50 g) itself acted as a preload. After the preload time, water collecting pan was suspended to the left arm and water was added in it, by the siphon tube, at a constant rate of 200 drops per minute until detachment of the film from mucosal surface took place. A support was kept under the water collecting pan to hold it at the time of detachment. Weight of water collected in the pan at the time of detachment was measured. The experiment was performed in triplicate.

Measurement of in vitro Residence Time

The in vitro residence time was determined by using modified USP disintegration apparatus. The disintegration medium was 800 ml of isotonic Phosphate buffer solution (PH 6.8) taken and maintained at temperature 37±20C. The segments of porcine buccal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three muccoadhesive films of each formulation were hydrated on one surface

using isotonic Phosphate buffer solution (PH 6.8) and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded.

C. In-vitro Release Study by Dissolution[21]

The US pharmacopoeia XXIII rotating paddle method was used to study and calculate the drug release from the buccal patches, 500 ml of phosphate buffer used as the dissolution medium at 37±0.50c and a rotation speed 50RPM was used. Patches of 1cm2 area were cutted and sandwiching the patch in dialysis membrane. A piece of glass slide was placed as support to prevent the assembly from floating. The dialysis membrane tubing with patch inside was secured from both ends using closure clips, then it was placed in the bottom of the vessel containing phosphate buffer having Ph 6.8. Samples 5 ml were withdrawn at a specific time interval and replaced with fresh buffer medium. The samples were filtered using Whatmann filter paper and analyzed by using UV spectrophotometer at 276 nm. The experiments were performed triplicate and average values were calculated and reported.

D. Kinetic Study: (Clark 2004 and Higuchi 1963)

The matrix systems were reported to follow the zero order release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into, Zero order, First order, Higuchi matrix and peppa's model. In this by comparing the r- values obtained, the best fit model was selected.

RESULTS AND DISCUSSION

Drug –Excipients Compatibility Studies

From IR spectra of pure drug and the combination of pure drug with polymers, shows that all the characteristic peaks of Furosemide were present in the combination spectrum thus indicating compatibility of the drug and polymer. IR spectra of pure drug and in combination with the polymers are shown in spectrum.

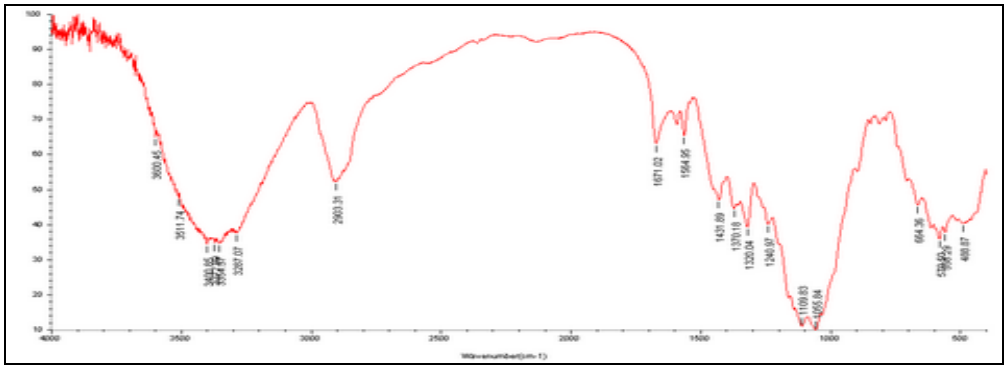

Figure 1: FTIR of Drug with Excipients.

Calibration Curve of Furosemide in Distilled Water

Absorbance of Furosemide standard solution containing 1-10 mcg/ml of drug in distilled water. Graph no shows a representative calibration curve with slope and regression coefficient, 0.019 and 0.998 respectively. The curve was found to be linear in the range of 1-10 mcg/ml at absorbance maxima 276.5 nm.

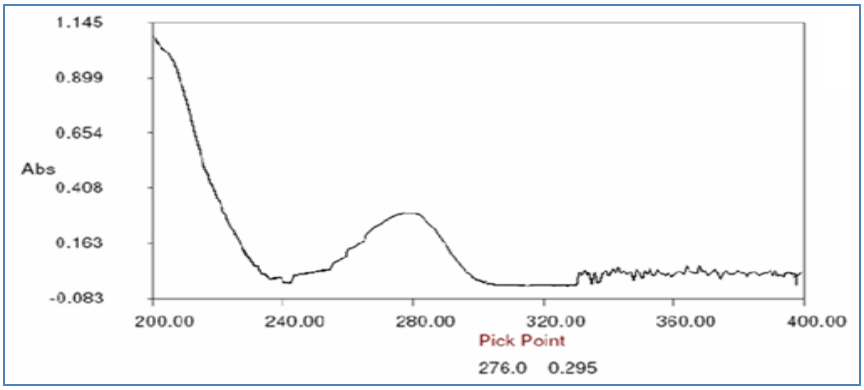

Figure 2: Absorption maxima scanning of Furosemide.

Preparation of Buccal Patches

In the present work efforts have been made to develop the controlled release Muccoadhesive buccal patches of Furosemide prepared by solvent casting technique using HPMC E15, PVA and PVP in different ratios to produce the therapeutic dose is needed to be maintained for long time.

Evaluation Parameters

A) Physical Properties

Thickness of Patch

The thickness of the prepared buccal patches of each formulation was determined with in the range of 0.21- 0.27 mm.

Folding Endurance

The folding endurance of each formulation was determined within the range of 301 to 319.

Mechanical Strength

Three patches of each formulation were evaluated and mean values are recorded in table 2. The values were found to be in the range of 5.18 to 13.64 kg/mm^2. The values revealed that the patches were having good mechanical strength.

Water Uptake Study

Water uptake of all buccal patches containing Furosemide is given in table 2. These values represent the mean of three replicate determinations. The values were found to be within the range of 1.73 to 2.91. The percentage water absorption of the respective patches was determined at Third hour.

Table 2: Evaluation of Physical Parameters of Different Mucoadhesive Buccal Patches of Furosemide.

Formulation code	Physical parameters			
	Thickness (mm) ±S.D (n=3)	Folding endurance ±S.D (n=3)	Mechanical strength ± S.D (n=3) (kg/mm^2)	Water uptake ± S.D (n=3)
F1	0.24 ± 0.005	308± 4.04	5.18± 0.076	2.14± 0.64
F2	0.23 ± 0.014	306± 4.72	6.14± 0.056	2.07± 0.52
F3	0.25 ± 0.002	312± 2.51	11.94± 0.098	2.91± 0.102
F4	0.27 ± 0.0023	319± 2.51	13.64± 0.124	2.43± 0.23
F5	0.21 ± 0.001	301± 1.00	11.96± 0.132	1.85± 0.051
F6	0.27 ± 0.003	311± 2.51	7.84± 0.079	1.73± 0.153
F7	0.26 ± 0.023	319± 2.52	8.22± 0.32	2.17± 0.354
F8	0.25 ± 0.01	311± 5.50	9.45± 0.054	2.68± 0.243
F9	0.24 ± 0.034	308± 5.51	11.15± 0.045	2.96± 0.109
F10	0.26 ± 0.023	303± 4.50	12.96± 0.091	2.08± 0.63

B) Performance Parameters

Measurement of Bioadhesive Strength

An effective buccal mucosal device must maintain an intimate contact with mucus layer overlying the epithelial tissue. This parameter very important to successful utilization of these dosage forms. Hence in-vitro evaluation of buccal patches was carried out using porcine gastric mucosa. This gives the indirect measurement of bioadhesive strength in grams.

Table 3: Evaluation of Performance Parameters of Different Mucoadhesive Buccal Patches of Furosemide.

Formulation code	Performance parameters(Bio adhesive)		
	Bioadhesive strength (gms) ± S.D (n=3)	Force of adhesion(N) ±S.D (n=3)	Bond strength ±S.D (n=3) (kg/mm^2)
F1	144.3± 2.64	1.40± 0.03	453.02± 5.34
F2	149.34± 2.13	1.44± 0.02	432.12± 3.65
F3	187.67± 0.78	1.82± 0.05	586.09± 5.23
F4	176.28± 0.98	1.62± 0.01	543.63± 1.86
F5	167.33± 1.34	1.75± 0.01	513.78± 4.33
F6	132.64± 3.67	1.62± 0.06	421.12± 6.98
F7	134.23± 2.87	1.42± 0.04	435.47± 5.32
F8	167.35± 1.74	1.47± 0.03	564.65± 6.90
F9	168.23± 1.53	1.76± 0.01	523.34± 3.23
F10	159.46± 1.13	1.12± 0.01	498.21± 4.98

Content Uniformity of Active Ingredient

Table 4 shows the result of drug content uniformity in each formulation. Three replicates of each test were carried out. The mean drug content was found to be in the range of 3.68 to 3.96 for (each patch size 10 mm diameter) the prepared buccal patch formulations.

Measurement of Surface pH

Table 4 shows the result of surface ph values for each formulation. These values represent the mean of three replicate determinations. They were found to be within the range of 6.1 to 6.7 for all formulations and were almost within the range of salivary pH i.e. 6.2 to 7.4. It represents the better patient acceptability.

Table 4: Evaluation of Performance parameters of Different Mucoadhesive Buccal Patches of Furosemide.

Formulation code	Performance parameters(Bio adhesive)		
	Drug content (mgs) ±S.D (n=3)	Surface pH ± S.D (n=3)	*In-vitro* residence time (min)±S.D (n=3) (kg/mm^2)
F1	3.68± 0.23	6.32± 0.54	321±10
F2	3.78± 0.13	6.42± 0.43	352±5
F3	3.81± 0.011	6.16± 0.57	495± 15
F4	3.90± 0.54	6.54± 0.43	429± 5
F5	3.85± 0.36	6.45± 0.57	453±10
F6	3.79± 0.45	6.4± 0.57	312±10
F7	3.58± 0.98	6.67± 0.23	304± 10
F8	3.96± 0.21	6.10± 0.45	429± 15
F9	3.03± 0.11	6.68± 0.34	482± 5
F10	3.68± 0.78	6.70± 0.23	437± 10

In-vitro Release Study

The in-vitro dissolution was studied in phosphate buffer pH 6.8. The *In-vitro* dissolution studies were carried out in triplicate and the results shown in the tables are mean of the replicate values. The *in-vitro* released data obtained for patches F1 to F10 are tabulated in table 5 respectively.

Table 5: Drug Release Kinetics.

Batch	Zero order r^2 values	First order r^2 values	Higuchi r^2 values	Korsmeyer-Peppas r^2 values	'n' value
F1	0.982	0.722	0.986	0.995	0.795
F2	0.951	0.814	0.969	0.986	0.665
F3	0.981	0.831	0.948	0.999	0.799
F4	0.982	0.878	0.954	0.983	0.767
F5	0.992	0.784	0.954	0.983	0.894
F6	0.973	0.931	0.955	0.989	0.822
F7	0.995	0.823	0.934	0.984	0.826
F8	0.989	0.776	0.880	0.942	0.899
F9	0.981	0.784	0.952	0.975	0.746
F10	0.987	0.875	0.951	0.988	0.751

Table 6: Cumulative % Drug release of Formulation F1 to F10.

Time Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	18.67	31.25	15.85	23.86	13.21	17.96	19.73	13.58	17.97	21.14
2	33.36	45.83	33.58	34.91	22.13	37.78	23.25	18.01	25.96	23.49
3	43.85	61.98	48.74	43.15	38.75	42.61	38.46	22.36	41.14	30.21
4	63.68	74.44	53.20	54.30	55.84	63.19	57.27	32.49	58.49	54.32
5	76.89	83.18	62.93	67.33	68.03	75.37	68.83	48.62	65.03	71.88
6	82.59	98.39	73.31	82.91	72.14	85.64	82.44	63.90	80.89	82.30
7	91.37	98.58	86.23	91.53	83.93	91.87	93.78	72.59	89.48	89.10
8	98.78		91.42	98.8	92.09	99.55	98.94	86.50	96.13	94.11
9			97.66	100.1	99.18			94.52	99.33	100.21
10			99.19					100.75		

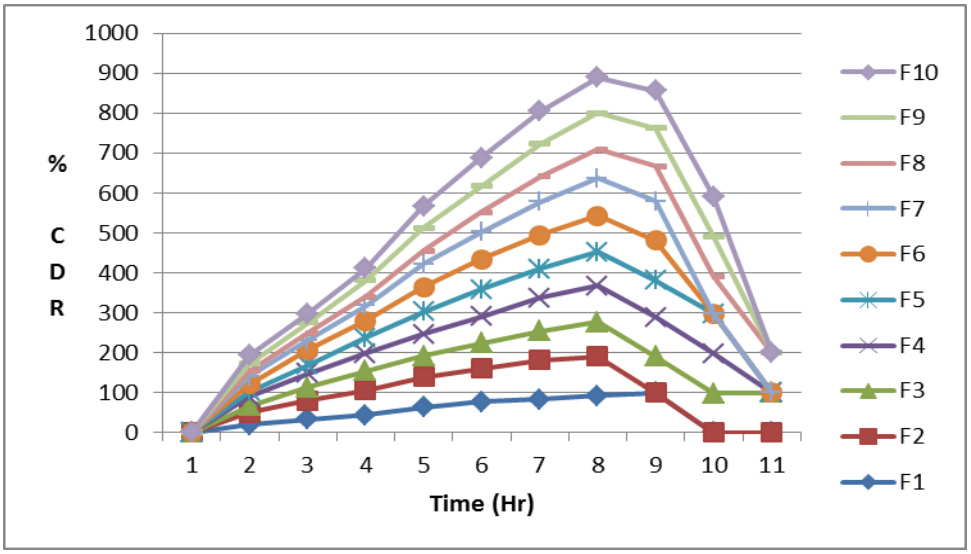

Fig 3: Cumulative % Drug release of Formulation F1 to F10.

CONCLUSION

Good results were obtained both in vitro conditions for Furosemide mucoadhesive buccal patches. It was revealed that polymer ratios had significant influence on drug release. Thus conclusion can be made that stable dosage form can be developed for Furosemide for controlled release by buccal patches.

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CONFLICT OF INTEREST: Nil.

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