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FORMULATION & EVALUATION OF MUCOADHESIVE BUCCAL FILM OF MEFENAMIC ACID

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Abstract

This novel formulation (buccal film) was designed particularly for anti-inflammatory and analgesic therapy in the oral cavity. The advantages reside on the reduction of drug dose because of its localization in the inflammatory process site. One particular problem to drug delivery system, aim to the treatment of the oral cavity disease, is the short residence time at the site of application. This problem may be resolved by using bioadhesive polymer i.e. - polymer that exhibit characteristic adhesive interaction with biological membrane. Recently various bioadhesive mucosal dosage forms including adhesive tablets, gels and recently films have been developed. However, buccal films are preferable over adhesive tablet in terms of flexibility and convenience. In addition they can increase short residence time of oral gels on the mucosa which are easily washed and removed by saliva. Moreover buccal films are also suitable for protecting wound surfaces, thus reducing pain and increasing treatment effectiveness. *In vitro* drug release of this film showed that mefenamic acid was rapidly released during the first 1hrs (35%), and the release was completed after 6 hr and 30 min. % drug release after 6 hr. was found out to be 62% for film code MF1 and for film code MF7, MF8 and MF9 found to be 63%.

Keywords: Buccal film, Bioadhesive polymer, Mefenamic acid.

INTRODUCTION

In recent years, delivery of therapeutic agents through various mucosal routes has gained significant attention owing to their pre-systemic metabolism or instability in the acidic environment associated with oral administration. Absorption of therapeutic agents from the oral cavity provides a direct entry of such agents in to the systemic circulation, thereby avoiding the first pass hepatic metabolism and gastrointestinal degradation. However the sublingual routes of drug delivery has received much more attention because of its unique advantages over other oral transmucosal routes.[1]

New formulation (buccal film) was designed particularly for anti-inflammatory and analgesic therapy in the oral cavity. The advantages reside on the reduction of drug dose because of its localization in the inflammatory process site. One particular problem to drug delivery system, aim to the treatment of the oral cavity disease, is the short residence time at the site of application. This problem may be resolved by using bioadhesive polymer i.e. - polymer that exhibit characteristic adhesive interaction with biological membrane.

Recently various bioadhesive mucosal dosage forms including adhesive tablets, gels and recently films have been developed. However, buccal films are preferable over adhesive tablet in terms of flexibility and convenience. In addition they can increase short residence time of oral gels on the mucosa which are easily washed and removed by saliva. Moreover buccal films are also suitable for protecting wound surfaces, thus reducing pain and increasing treatment effectiveness. [2]

The oral mucosa is composed of an outer most layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia and it has a mitotically active basal cell layer ,advancing through a number of differentiating intermediate layer to the superficial layers, where cells are shed from the surface of the epithelium .The epithelium of

the sublingual epithelium is somewhat about 40-50 cell layers thick. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole .the sublingual mucosal thickness of the mouth measures at about 100-200 um. The mucosa of sublingual is nonkeratinized. Non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramide.

They also contain small amount of neutral but polar lipid, mainly cholesterol sulfate and glucosyl ceramides .These epithelia have been found to be considerably more permeable to water then keratinized epithelia.

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the sublingual mucosa is 4-4000 times greater than that of the skin .In general ,the permeability of the oral mucosa decrease in the order of sublingual mucosa being relative thin and non-keratinized the buccal thicker and non-keratinized and the palatal intermediate in thickness but keratinized.

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called ‘membrane coating granules’ (MCG).

This barrier exists in the outermost 200um of the superficial layer .Permeation studies have been performed using a number of very large molecular weight tracers ,such as horseradish peroxidase and lanthanum nitrate ,The MCG lipids of non-keratinized epithelia ,the major MCG lipid contents are cholesterol asters, cholesterol and glycosphingolipids .Aside from the MCGS the basement membrane may present some resistance to permeation as well ,however the outer epithelium is still considered to be the rate limiting step to mucosal penetration.

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus ,the principle components of mucus are complex made up of proteins and carbohydrates .These complexes may be free of association or some may be attached to certain region on the cell surface. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cell to move relative to one another. Along the same lines the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery system. In the oral mucosa; mucus is secreted by the major and minor salivary glands as part of saliva .At physiological pH the mucus network carries a negative charge (Due to the sialic acid and sulfate residues), Which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer.

2. Materials and methods

2.1. Materials

Mefenamic acid was received as a gift sample from Blue Cross Pharmaceutical ltd. Goa India. PVP- K 30, Sodium CMC,Corbopol-934, Sodium Chloride, HPMC-K15 was purchased from CDH private limited New Delhi .PEG -4000, Potassium di-hydrogen phosphate and di-sodium hydrogen phosphate was purchased from Merck India Ltd, Mumbai , Ethanol and other solvent were of analytical grade.

2.2. Methods

2.2.1. Preparation of buccal film

Initially films were prepared using only film forming polymer i.e. PEG in case of mucoadhesive film MF1, MF2, MF3, MF4, MF9, MF10, MF11, and MF12 , and PVP in case of MF5, MF6, MF7, MF8, MF13, MF14, MF15, and MF16. First film forming polymer dissolved in water (40%) then in various ratio, ethanol was added such that water solon/ dispersion: Ethanol (1:5; 2:4, 4:2, 5:1).

The mixture were prepared with a magnetic stirrer and cast onto petridish. The volume of cast was determined so that 10mm thickness was obtained after casting the mixture. The petridish was stored at 4^0c for 24 hr to remove air bubbles entrapped and dried at 60^0c for 16 hrs. The film were accurately observed and checked for possible imperfection upon the removal from petridish then a water solution of mucoadhesive polymer (1%) was added to the film forming polymer mixture in the ratio specified in the table below, the preparation procedure was repeated as previously described (Table 2).

In case of drug loaded film 1% film forming polymer ethanol mixture and 1% mucoadhesive polymer loaded with 1% drug containing anti inflammatory drug. Mefenamic acid added before stirring so that homogenous mass is formed.

Table 1: preparation of buccal film-

Formulation number	PEG (mg)	PVP (mg)	Sodium CMC (mg)	Carbopol (mg)
MF1	1000	-	700	300
MF2	1000	-	500	500
MF3	1000	-	300	700
MF4	1000	-	400	600
MF5	-	1000	300	700
MF6	-	1000	500	500
MF7	-	1000	700	300
MF8	-	1000	600	400

MF1 mucoadhesive film 1 MF2 mucoadhesive film 2 MF3 mucoadhesive film 3
MF4 mucoadhesive film 4 MF5 mucoadhesive film 5 MF6 mucoadhesive film 6
MF7 mucoadhesive film 7 MF8 mucoadhesive film 8

Table 2: Various Formulation of mucoadhesive film.

Formulation number	PEG (mg)	PVP (mg)	HPMC K-15 (mg)	Carbopol (mg)
MF9	1000	-	700	300
MF10	1000	-	500	500
MF11	1000	-	300	700
MF12	1000	-	400	600
MF13	-	1000	300	700
MF14	-	1000	500	500
MF15	-	1000	700	300
MF16	-	1000	600	400

MF9 mucoadhesive film 9 MF10 mucoadhesive film 10 MF11 mucoadhesive film 11
MF12 mucoadhesive film 12 MF13 mucoadhesive film 13 MF14 mucoadhesive film 14
MF15 mucoadhesive film 15 MF16 mucoadhesive film 16

2.2.2. Evaluation

2.2.2.1. Swelling Index.

Film swelling properties and erosion characteristics were evaluated by determining the percentage of Hydration and Matrix Erosion or Dissolution (DS).

(a) Percentage Hydration: Percentage hydration each film divided in portion of $4cm^2$ and cut, weighted (w_1) and immersed in PBS 6.75 having same composition as simulated saliva fluid for predetermined period of time i.e. (5,15,30,60,120 and 180 minutes) after immersion the films were wiped off from the excess surface solution using filter paper and weighed (W_2) (Table-3)

$$\% \text{ hydration} = \frac{W2-W1}{W1} \times 100$$

W1 – Initial weight; W2 – After PBS treatment

(b) Matrix Erosion: In case of matrix erosion. The swollen film were dried at 60^0c for 24 hrs and kept in desiccators over 48 hr and after drying weighing was reported (W3) (Table 4).

$$\% \text{ erosion} = \frac{W1-W3}{W1} \times 100$$

W3 - Weight of film after drying for 24 hour at 60ºC

2.2.2.2. Ex vivo mucoadhesive time

The ex vivo mucoadhesive time was performed after application of the film mucosa. The goat mucosa was fixed on internal side of beaker; each film was divided in portion of 4 cm^2 & wetted with 50µl of simulated saliva fluid, & pasted to the goat buccal tissue. The beaker filled with simulated saliva fluid kept at 37^0C, 150 rpm stirring rate& film adhesion was monitored during 8 hrs. (Table 5).

2.2.2.3. *In vitro* release

A standard basket apparatus was employed to evaluate drug release. A portion of 4 cm^2 (2 cm x 2 cm) of film was used. The film was placed in basket after 2 min, the vessel was filled with phosphate buffer ph 6.75 and maintained at 37 ^{0}C while stirring at 50 rpm. 10 milliliter samples were collected at predetermined time intervals and replaced with an equal volume of phosphate buffer ph 6.75. Mefenamic Acid concentration was determined by a spectrophotometer.

In vitro drug release of this film showed that mefenamic was rapidly released during the first 1hrs (30%), and the release was completed after 6 hr and 30 min. % drug release after 6 hr. was found out to be 62% for film code MF1 and for film code MF7, MF8 and MF9 found to be 63% (Table 6).

2.2.2.4. Measurement of Mechanical Property

(a) Tensile Strength

Tensile strength (T.S.) gives indication of strength and elasticity of the film

Tensile Strength (kg/cm^2) = Force at Break (kg)/ (Initial cross - Sectional area of sample) (cm^2)

(b) Elongation at Break

Elongation at Break ($\%/cm^2$) = Increase in length (cm) x 100 / [Original length (cm) x {Cross – Sectional area} (cm^2)].

Method of analysis as per IS: 2508-1984

Analyzer Make: Deepak Polyplast Pvt. Ltd. Ahmedabad, Gujarat

Load Cell: Max. 50 Kg.

3. Results

3.3.1. Swelling- hydration studies

All the films hydrated very quickly, reaching 80% hydration after just few minutes. Maximum hydration (92–98%) was obtained with formulations containing NaCMC film code MF1, MF7 & MF8.

Films containing HPMC K15M showed a slightly lower hydration of 83-86%. These results inferred that NaCMC films exhibited higher capacity of water uptake than HPMC films as expected capacity of water uptake as HPMC films as expected.

Fig 1 : Percentage Hydration for film MF1

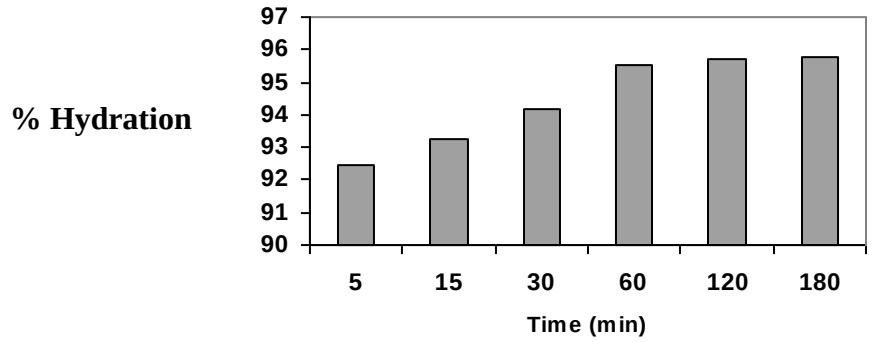


Fig 2: Percentage Hydration for film MF7

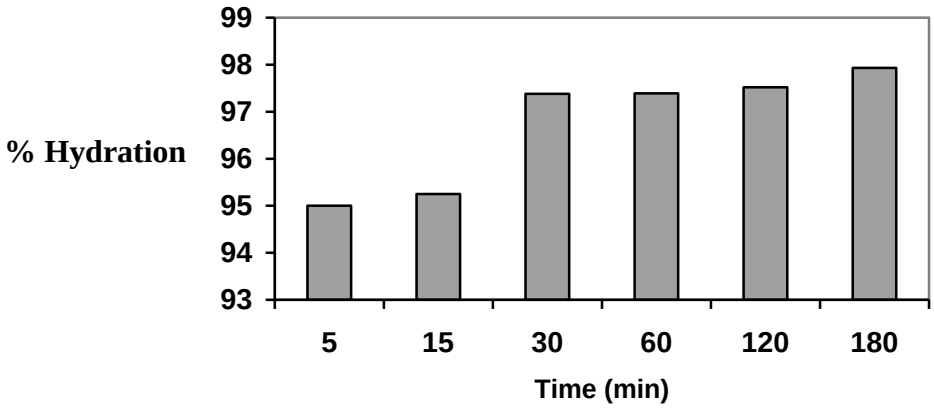


Fig 3: Percentage Hydration for film MF8

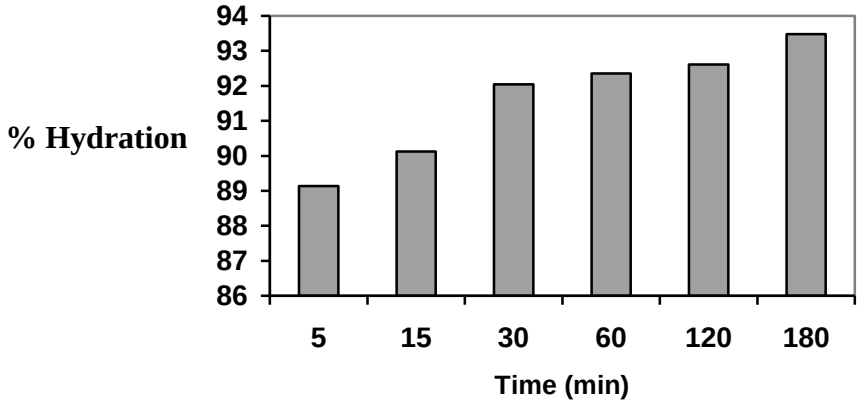


Fig 4: Percentage Hydration for film MF9

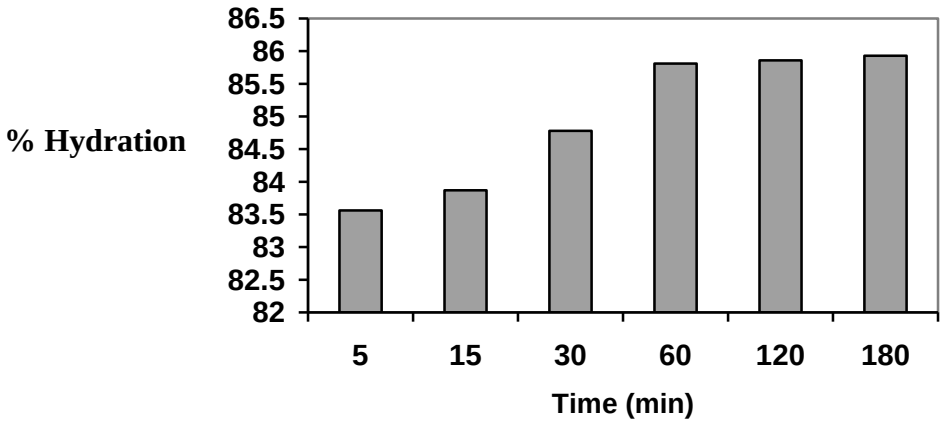


Fig 5: Percentage Matrix Erosion for film MF1

Fragmentation was already evident at 100 min when HPMC instead of NaCMC was employed. The highest losses were observed for films containing HPMC as mucoadhesive polymer; for some of these films fragmentation was so high that it was not possible to recover and handle the film from the 6.75PBS, even immediately after the beginning of the experiment (MF15 & MF16). This higher fragility of the HPMC films could be due to the larger swelling in water of this polymer with respect to NaCMC. The consequence could be the formation of empty spaces within the film matrix that could make this structure less resistant to mechanical stresses.

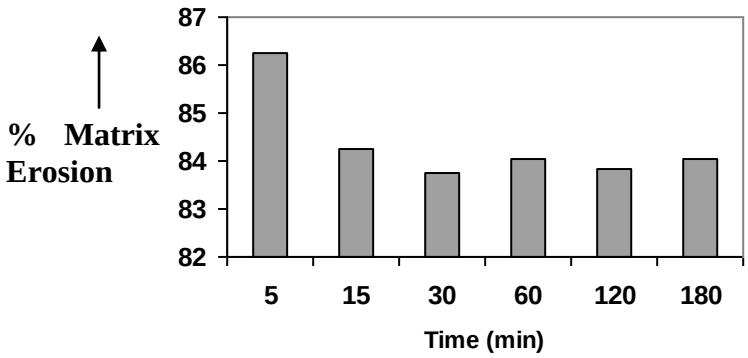


Fig 6: Percentage Matrix Erosion for film MF7

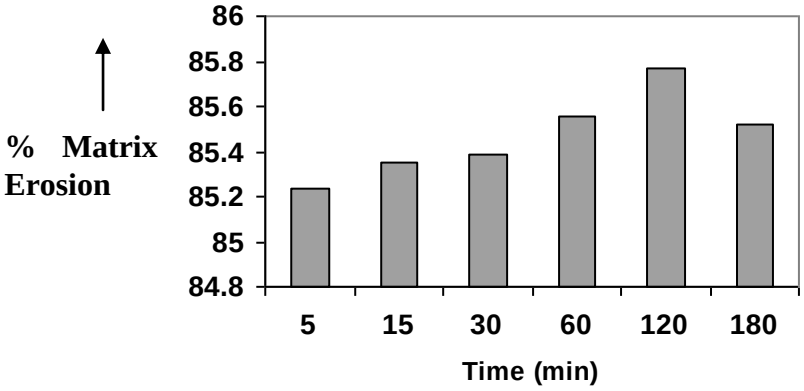


Fig 7: Percentage Matrix Erosion for film MF8

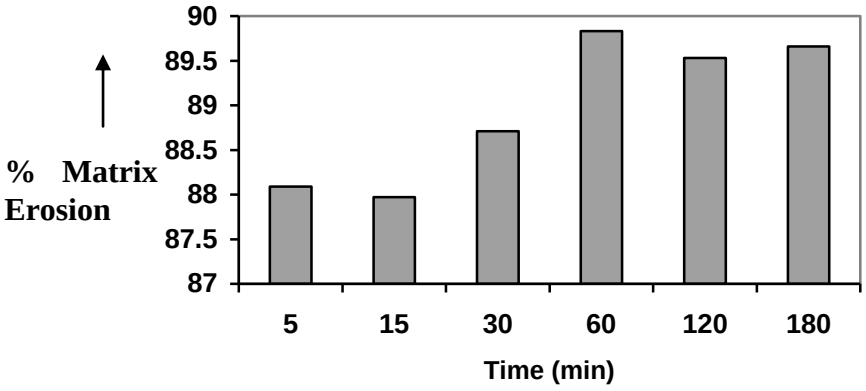
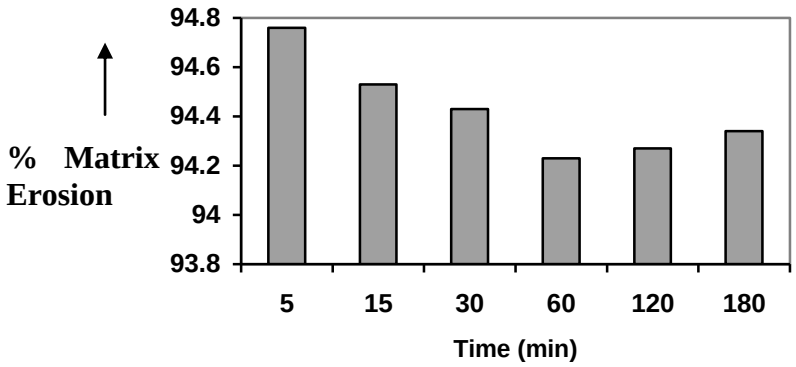


Fig 8: Percentage Matrix Erosion for film MF9



It was highlighted that swelling properties are probably more important when film integrity is evaluated. In fact, as already said, since HPMC have an increased swelling capacity with respect to NaCMC; it is able of conditioning, to a larger extent than PVP do, the mechanical and physical properties of the films.

3.3.2. Ex vivo mucoadhesion times of free drug Film

Film mucoadhesion times varied from 3 to 6.5hr MF15 showed the highest adhesion time whereas the films from MF1 showed the lowest mucoadhesion time.

This difference depends upon several factors that affect the effectiveness of such a formulation. First of all, the employment of NaCMC favors hydration and the outward diffusion of the drug from the film matrix. Moreover, NaCMC, due to its solubility in water, results less effective as mucoadhesive polymer and it was demonstrated by the

already cited lower mucoadhesion times of MF1. In fact, when using HPMC, mucoadhesion time always resulted high, because the polymer although manifesting decisively higher swelling is less water affined and hence tends to retain its structure better than NaCMC that, in turn, is better dissolved. Another important factor to be considered is the kind of film forming polymer used for the film preparation and the goodness and homogeneity of the polymer solution mixtures.

Table 3: Mucoadhesive time for various formulations

S. No	Muco-adhesive Film Code	Muco-adhesive time(Hour)
1	MF1	3
2	MF3	4:40
3	MF5	5
4	MF7	4
5	MF9	6
6	MF10	5.5
7	MF11	5
8	MF13	5:30
9	MF15	6.5
10	MF16	6:15

In fact, PVP is water soluble and these characteristics influenced miscibility with the mucoadhesive polymer, the uniformity of the film as well as permeability to water of the film matrix. In spite of these differences, ex vivo mucoadhesion times were not drastically influenced by the polymer chemical and physical characteristics.

Table 4 *In vitro* Release for MF1

S. No	Time Interval (hours)	Concentration (µg/ml)	Percentage Release (%)
1	1	16± 1.2	32
2	2	19± 1.1	39
3	3	26± 1.3	52
4	4	27± 1.5	55
5	5	28± 1.4	57
6	6	31± 1.6	62

Table 5: *In vitro* release for MF7

S. No	Time Interval (hours)	Concentration (µg/ml)	Percentage Release (%)
1	1	15± 1.5	30
2	2	19± 1.1	39
3	3	25± 1.2	51
4	4	28± 1.6	57
5	5	28± 1.3	57
6	6	32± 1.4	63

Table 6 : *In vitro* release for MF8

S. No	Time Interval (hours)	Concentration (µg/ml)	Percentage Release (%)
1	1	15± 1.3	30
2	2	20± 1.4	40
3	3	26± 1.7	52
4	4	27± 1.6	55
5	5	28± 1.5	57
6	6	32± 1.4	63

Table 7 : *In vitro* release for MF9

S. No	Time Interval (hours)	Concentration (µg/ml)	Percentage Release (%)
1	1	13± 1.4	28
2	2	17± 1.1	34
3	3	26± 1.5	52
4	4	27± 1.3	55
5	5	28± 1.6	57
6	6	32± 1.4	63

4. Discussions

On the basis of the results obtained in terms of hydration, mucoadhesion time and % matrix erosion, the film containing PVP and NaCMC (MF7) was selected for its characteristics that resulted suit formulations. Hence, this film was loaded with a reference anti-inflammatory drug, such as mefenamic acid to test its behavior as carrier for mefenamic acid sustained release in the oral cavity. For this purpose, an mefenamic acid containing film (1% of the mixture before mixing) was prepared and tested for *In vitro* drug release. *In vitro* release profile showed a burst effect of the drug during the first 1 hrs (30%), followed by a more sustained pattern. The mefenamic acid concentration in the film was resulted 11.11 mg/cm^2 (sodium salt). *In vitro* drug release of this film showed that mefenamic was rapidly released during the first 1hrs (30%), and the release was completed after 6 hr and 30 min. % drug

release after 6 hr. was found out to be 62% for film code MF1 and for film code MF7, MF8 and MF9 found to be 63%.

Optimized batch MF7 was selected as best batch and loaded with model anti inflammatory drug mefenamic acid, it showed % hydration between, 95% and 97.93% and matrix erosion between 85.24% and 85.52% this indicated that NaCMC films exhibited higher capacity of water uptake then HPMC films.

The employment of NaCMC films flavor hydration and outward diffusion of the drug from the film matrix. Measurement of mechanical property of MF7 film resulted in high T.S. tensile strength of 95.3 kg/cm^2 and Elongation at break of 16% which indicated presence of hard and tough polymer which is acceptable for delivery of mucoadhesive formulation.

Mucoadhesive time for film MF7 of 4 hr. indicate moderate mucoadhesive time and *in vitro* release of 63% is suitable parameter for development of mucoadhesive buccal film of mefenamic acid.

The main advantage of this formulation is that it contain a lower drug dose i.e. 11.11mg/cm^2 sufficient for therapeutic effect as it is located directly on the site of inflammation, if compared to traditional systemic therapies. Moreover this buccal film is very tolerable and comfortable because it is non irritant and may be preferred over adhesive tablet in terms of elasticity, flexibility and capability to protect the wounded or inflamed surface.

Acknowledgement

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