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RESEARCH ARTICLE

Design and Characterization of Buccal Films of Benzocaine for Mouth Ulcer

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ABSTRACT

Mouth ulcer is very common in recent years, which occurs due to the damage of epithelial tissue and/or lamina propria that finally leads to tissue necrosis. Benzocaine has been used to treat the mouth ulcers due to its excellent local anaesthetic effect that relieves the pain associated with mouth ulcer. Hence an attempt was made to develop and characterize the buccal films of Benzocaine to treat mouth ulcers with an aim of prolonging the drug release and improving the patient convenience. The films were fabricated using the mucoadhesive polymer blend of chitosan and HPMC by solvent casting method and the physico-mechanical, *in vitro* drug release and *ex vivo* buccal mucosal permeation characteristics of the films were studied. All fabricated film formulations prepared were smooth and almost opaque, with good flexibility. The weight and thickness of all the formulations were found to be uniform. Drug content in the films ranged from 97–99%, indicating favorable drug loading and uniformity. The inclusion of HPMC, significantly reduced the bioadhesive strength and *in vitro* mucoadhesion time of chitosan films, although the degree of swelling increased. *In vitro* drug release and permeation studies in simulated saliva showed a prolonged release for a period of 6 h for all formulations. The formulation with Chitosan: HPMC ratio 1:1, 10% w/w polysorbate 80 and 10% w/w propylene glycol as plasticizers showed the best results which exhibited the cumulative percentage drug release of 87.9 % and the cumulative amount of drug permeation of 7.62mg/cm^2 across goat buccal mucosa in 6 h. Drug-excipient interaction studies were carried out using DSC and FT-IR technique; films indicated no chemical interaction between drug and polymers used.

Keywords: Keywords: Benzocaine; mouth ulcer; mucoadhesion; buccal film

INTRODUCTION

Mouth ulcers are very common, occurring in association with many diseases and by many different mechanisms. It occurs due to the damage of epithelial tissue and/or lamina propria that finally leads to tissue necrosis. The major causes being the aphthous stomatitis and local trauma, some Viruses (e.g. *Herpex simplex, Varicella Zoster,* HIV), Fungi (e.g. *Candida albicans*) and Bacteria (e.g. *Mycobacterium tuberculosis*) causing infections are also responsible for the ulceration.[1,2] The treatment for the mouth ulcer may be symptomatic or cause related. Maintaining good oral hygiene and use of antiseptic mouthwashes (e.g. Chlorhexidine) are preventive measures while topical anaesthetics (e.g. Benzocaine) and local analgesics (e.g. Benzydamine) may reduce the pain when used in form of topical gels and creams.[1,3] Among all these treatments the use of local anaesthetic is the choice of medication for mouth ulcers.[3]

Local anaesthetics cause reversible loss of sensation by decreasing rate of depolarization and repolarisation of the excited membranes. Benzocaine, a para-amino benzoic acid ester is a local anesthetic used in topical as well as dental surgeries due to its low aqueous solubility. They produce long lasting numbness without systemic toxicity.[4] For this reason, several buccal formulations like gels and mucoadhesive tablets have been developed using polymers that allow the most direct contact with the mucosa and provide a fast and prolonged release of the drug, reducing the need for administration of repeated doses. Mucoadhesive buccal films of benzocaine is novel approach to treat the mouth ulcers and could serve as alternative to the conventional dosage forms like gels, ointments, mouth washes, syrups and injectables.[5]

Buccal film is a type of drug delivery system, which when placed in the buccal cavity; it dissolves and releases the medication for oromucosal and intragastric absorption, without chewing and intake of water. Buccal films show greater accuracy and flexibility in relation to dose and better mechanical resistance when compared to other dosage forms. Besides, they can act as controlled release systems and can be easily removed in emergency cases. Other advantages such as low enzymatic activity, painless administration, easy drug withdrawal, facility to include permeation enhancers/enzyme inhibitors or pH modifiers in the formulation and versatility in designing as multi-directional or unidirectional release systems for local or systemic actions. This type of technology offer a convenient way of dosing medication, not only to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population.[5,6] In the present study, the mucoadhesive buccal films of benzocaine were designed and developed to treat mouth ulcers by incorporating the drug in a suitable polymer system with an aim of improving/enhancing patient convenience and compliance.

Table 1: Composition of Benzocaine buccal films

Sl. No	Ingredients	Qty for 1cm^2 film	Qty for 25cm^2 film	Qty for 20 ml casting solution
1	Benzocaine (mg)	10	250	250
2	Polymer (Chitosan + HPMC) (mg)	35	875	875
3	Polysorbate 80 (mg)	0.35	8.75	8.75
4	Propylene glycol (mg)	0.35	8.75	8.75
5	Citric acid (mg)	2.25	56.25	56.25
6	Mannitol (mg)	2.25	56.25	56.25
7	Peppermint oil (mg)	q.s	q.s	q.s
8	Acetic acid (1 %) (ml)		10	10
9	Ethanol-Water (1:1) mixture (ml)			q.s 20

MATERIALS AND METHODS

Materials

Benzocaine was obtained from Yarrow Chem Products, Mumbai. Hydroxypropyl methyl cellulose (HPMC) and Polysorbate 80 were procured from Loba Chemie Pvt. Ltd., Mumbai. Chitosan (85% deacetylated) and Propylene glycol were procured from Research Lab Fine Chemi Industries, Mumbai. Ethanol and Acetic acid were of analytical grade purchased from Central Drug House Pvt. Ltd., New Delhi.

Formulation of Buccal films

The buccal films were prepared by solvent casting method. Chitosan, the best mucoadhesive polymer with wound healing property was used along with Hydroxypropyl methyl cellulose (HPMC) to provide good film forming property.[7,8] Polysorbate 80 and Propylene glycol were incorporated as plasticizers. The composition of formulation is given in Table 1. A flat square shaped, aluminium foil coated glass molds having surface area 25 cm^2 were fabricated for casting the films.

Preparation of casting solution

Chitosan was dissolved in 10 ml of 1% v / v acetic acid solution, and filtered to remove the debris and undissolved matter. To 5 ml of ethanol-water (1:1) mixture, Polysorbate 80 and Propylene glycol were added as plasticizers, and then the drug and HPMC were dissolved in it. The drug solution was then poured into the Chitosan filtrate and stirred well. The volume was made up to 20 ml with ethanol-water (1:1) mixture and mixed thoroughly using a mechanical stirrer at 100 rpm for 30 min to form a homogeneous mixture. It was left overnight for deaeration and swelling of the polymers.[8,9]

Preparation of buccal films

Casting solution (20 ml) was poured into glass moulds and dried in a hot air oven at 45°C for 6 h for solvent evaporation. The films were removed by peeling and cut into square dims of 4 cm x 4 cm (16 cm^2). These films were kept in desiccator for 2 days for further drying and wrapped in Aluminium foil, and stored in an air tight glass container, to maintain their integrity and elasticity.[8,9] Five types of buccal films were developed with different ratio of Chitosan and HPMC as shown Table 2.

PHYSICO-MECHANICAL CHARACTERIZATION OF BUCCAL FILMS

Physical appearance

All the formulated buccal films were visually inspected for colour, flexibility, homogeneity and smoothness.[10]

Thickness

The thickness of the film was using a screw gauge. The average and standard deviation of six readings was calculated for each batch of the films.[10,11]

Table 2: List of different formulations developed

F. Code	BZ (mg)	CSN (mg)	HPMC (mg)	P-80 (mg)	PG (mg)	CA (mg)	MT (mg)	PO	AS (ml)	E-W (ml)
F1	250	875	-	8.75	8.75	56.25	56.25	q.s	10	q.s 20
F2	250	583.3	291.7	8.75	8.75	56.25	56.25	q.s	10	q.s 20
F3	250	437.5	437.5	8.75	8.75	56.25	56.25	q.s	10	q.s 20
F4	250	291.7	583.3	8.75	8.75	56.25	56.25	q.s	10	q.s 20
F5	250	-	875	8.75	8.75	56.25	56.25	q.s	10	q.s 20

BZ : Benzocaine, CSN: Chitosan, HPMC: Hydroxy propyl methyl cellulose
P-80 : Polysorbate 80, PG: Propylene glycol, CA: Citric acid, MT: Mannitol
PO: Peppermint oil, AS : 1% Acetic acid, E-W: Ethanol-Water(1;1) mixture

Weight uniformity

The films of different batches were dried at 60°C for 4 h before testing. Six films from each batch having area of 1cm^2 were weighed on a digital balance. The average weight and the standard deviation values were calculated from the individual weights. [12]

Folding endurance

Folding endurance was measured manually for the prepared films. A strip of film (2 cm x 2 cm) was cut evenly and repeatedly folded until it broke. The number of times the film could be folded at the same place without breaking was observed. [12,13]

Tensile strength

The tensile strength and percent elongation of the prepared films were performed using the method developed by Alien, et al. [14] A simple apparatus designed at laboratory (Figure 1) was used to carry out the measurement. A strip of 2.5 x 5 mm was selected and attached to a clip on one end of a flat wooden surface. The thread was attached carrying a pan at the other end. The points of attachments were kept 0.5cm from both the sides, so as to get even force distribution and to avoid breaking of film abruptly. The other end of thread carrying the pan was allowed to slide over a pulley opposite to fixed end. Weights were added in the pan in increasing order till the point of break-up. The elongation of the film at the point of break-up was also measured. The tensile strength was calculated as per Alien's formula; Tensile strength = (Break force/a x b) X (1+ΔL/L), where, a is the thickness, b is the width of the strip of film, ΔL is the elongation at the breaking point and L is the length of the test strip (mm). [14,15]

Hardness

The apparatus employed for hardness determination was designed in the laboratory using the literature report (Figure 2). It consists of a wooden stand of 11 cm height and top area of 16 cm × 16 cm. A small pan was fixed horizontally to one end of the 2 mm thick iron rod whose other end is reduced to a sharp point. A hole of 0.2 cm was made at the center of top area of a wooden stand, which was supporting the pan rod. An electric circuit was made with two 1.5-volt battery and a three volt electric bulb in such a way that the bulb lights only when circuit is completed through the contact of a metal plate and sharp end of the rod. The film was placed between the metal plate and sharp end of the rod. The weights were gradually added at an interval of 10 seconds to the surface of wooden plate and when the hardness of the film exceeded, the sharp end penetrates across the film, contact the metal plate and the bulb glows. The average of six such readings was noted at different places of the film and the mean values for the hardness is recorded. [14,15]

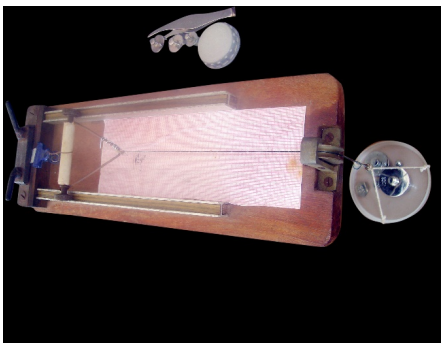

Fig. 1: Instrument for the measurement of tensile strength of films

Fig. 2: Instrument for the measurement of hardness of films

Drug content uniformity

The film of 1cm^2 area was cut into small pieces and transferred in to a graduated glass stoppered flask containing 20 ml of ethanol-water mixture. The flask was shaken continuously for 24 h in a mechanical shaker at 100 rpm. Then the solution was filtered through a 0.45 μm Whatman filter paper to remove the insoluble residue. The filtrate was made up to 100 ml with simulated saliva of pH 6.75. The composition of the salivary fluid, as reported by Peh KK and Wong CF[16], is given in Table 3. The absorbance was measured at 291.4 nm in a double beam UV spectrophotometer (Antech–AN-UV-7000) using the placebo film solution as blank and the drug content was determined. The average and standard deviation of six readings was calculated for each batch of the films.[8,17]

Table 3: Composition of Simulated Salivary Fluid.

Sl. No.	Ingredients	Quantity
1	Disodium hydrogen phosphate	2.382 gm
2	Potassium dihydrogen g phosphate	0.19 gm
3	Sodium chloride	8.00 gm
4	Distilled water	up to 1 lt
5	Phosphoric acid	q.s to pH 6.75

CHARACTERIZATION OF MUCOADHESIVE PROPERTY

Swelling index

This measurement is used to determine the extent of water uptake or the degree of hydration by the hydrophilic polymers used in the fabrication of the films. Most of the mucoadhesive polymers undergo some degree of swelling after hydration, which is necessary to initiate intimate contact of the film with the mucosal surface. The studies for determination of the swelling index of the films were conducted in the simulated salivary fluid of pH 6.75. The film sample having surface area of 1 cm^2 area was weighed and placed in a pre-weighed coverslip. It was then submerged in 50 ml of the simulated salivary medium contained in a petridish. After every 10 min, the coverslip was removed from the petridish and the excess moisture on the surface of film was removed by carefully wiping it off with absorbent tissue, after which it was reweighed. Increase in weight of the film was determined at each time interval until a constant weight was observed.[18] The degree of swelling was calculated using the formula: S.I = (wt -w0) / w0 where S.I is the Swelling Index, wt is the weight of film at time 't' and w0 is the weight of the film at initial time.[8]

Ex vivo mucoadhesive strength

The force required to detach the mucoadhesive film from the mucosal surface was applied as a measure of the mucoadhesive performance. Several techniques have been reported in literature for the measurement of bioadhesive strength. In the present study mucoadhesive strength was measured by Wihelmy's method[8] using buccal mucosa of Goat as the model surface. After the buccal mucosa was freshly cut and trimmed evenly, it was then washed in simulated salivary fluid and then used immediately. A Teflon block, 1.5 inches in height and 1.5 inches in diameter was hung with a nylon thread and goat mucosa was adhered to this. The film under test was fixed to the surface another Teflon block with cyanoacrylate glue. Provision was given to raise the weight from the other end of this Teflon block. Finally both the Teflon blocks were bought in intimate contact, so that the film was adhered to the goat buccal mucosa. Few drops of simulated salivary fluid were applied on the mucosal surface to keep it moist. Slowly weights were added, starting from 500 mg, at 30-second time intervals. The total weight at which detachment of the film from the mucosal surface took place was noted and the mucoadhesion force was calculated per unit area of the film, as follows: F = (w×g)/A, where F is the mucoadhesion force (kg/m/s^2), w is the mass applied (g), g is the acceleration due to gravity (cm / s^2) and A is the surface area of the patch (cm^2).[19,20]

Ex vivo residence time

The residence time for the formulation, that is, the time taken for the film to detach or erode completely from the mucosa was measured *ex vivo*, by application of the film on freshly excised buccal mucosa of Goat. The buccal mucosa was cut to an appropriate size of a 3 cm × 3 cm square patch and fixed on the internal side of a beaker with cyanoacrylate glue. The film was first wetted with few drops of simulated saliva fluid and attached to the buccal tissue by applying light pressure with a fingertip for 20 sec. The beaker was filled with 200 ml simulated saliva fluid and kept at 37°C on a magnetic stirrer. After two minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and during the test, the time taken for the film to completely erode or detach from the mucosa was observed as the *ex vivo* mucoadhesion time.[8,19]

In vitro drug release studies

In vitro release studies were carried out by a slight modification of the method suggested by Perioli L, et al.[21] and Ilango et al.[22] The buccal film sample having surface area of 1cm^2 area was attached to the wall of the dissolution vessel of the USP Dissolution Test Apparatus, midway from the bottom, with cyanoacrylate glue. After two minutes, the vessel was filled with 500 ml of simulated saliva. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C and stirred at 50 rpm. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with a fresh medium. The samples were filtered and drug

concentrations were determined at 291.4 nm using UV - visible spectrophotometer (Antech –AN-UV-7000) after suitable dilution with dissolution media. [8,17]

Ex vivo drug permeation studies

The *ex vivo* permeation study of mucoadhesive film of benzocaine was carried out using Keshery - Chein diffusion cell with buccal mucosa of goat as the model surface. After the buccal mucosa was freshly cut and trimmed evenly, it was then washed in simulated salivary fluid and then used immediately. The buccal tissue was mounted between donor and receptor compartment of the diffusion cell with mucosal surface facing towards the donor compartment. The receptor compartment was filled with 30 ml of simulated saliva as diffusion media. The prepared mucoadhesive film of benzocaine having surface area of 1 cm^2 was placed in the donor compartment. The whole assembly was fixed on a hot plate magnetic stirrer and the solution in the receptor compartment was continuously stirred at 100rpm using magnetic beads and the temperature was maintained at 37 ± 1°C. Specific volume of the sample (3ml) of the receptor fluid were withdrawn at predetermined intervals and replaced immediately with same volume of fresh diffusion media. [9,23] The samples were analyzed for drug content at 291.4 nm in a double beam UV spectrophotometer (Antech –AN-UV-7000). [17]

Compatibility studies

The DSC and FT-IR studies were performed to check the compatibility of drug and polymers. Spectra of the pure benzocaine, and the optimized film (F3) were taken individually the peaks were compared for any significant deviation. [24,25]

Stability study

The stability studies of the formulated films were carried out on optimized formulation (F3) as per ICH guidelines. The films were wrapped in Aluminium foil and placed in glass petridish and were stored in stability chamber (Thermolabs, india TH90 S/G) at 40 ± 0.5 ^{0}C and 75 ± 5% RH for 90 days. The sample patches were withdrawn at 0, 30, 60 and 90 days and examined for the changes in appearance, texture, physico-mechanical characteristics and drug content. The *in vitro* drug release studies and *ex vivo* drug permeation studies were also conducted. [25,26]

RESULTS AND DISCUSSION

Physico-mechanical characterization

In the present study, totally five films were prepared for the optimization of formulation. In all these formulations a constant amount of drug (250 mg) was maintained. 20 ml of the casting solution was spread in to 25 cm^2 so that each cm^2 contains approximately 10.0 mg of the drug. The prepared films were smooth and almost opaque with homogeneous appearance and possessed uniform surface (Figure 3). Drug was uniformly distributed through the matrix film. There were no observable particles of drug in the matrix film. The physico-mechanical valuation data of the films was presented in Table 4.

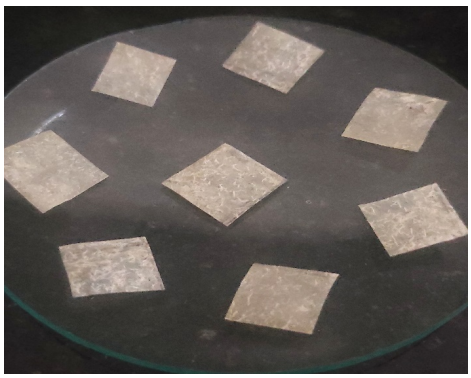

Fig. 3: Fabricatedmucoadhesive buccal films containing Benzocaine

The films were evaluated for the film thickness at various points. It was found that the thickness at the edges was a bit higher and uneven compared to the rest of the parts of the film. It may be due to the curvature of the viscous slurry at the edges of the foil due to surface tension. After removing these edges, films were re measured for thickness and it was observed to have uniform thickness and low standard deviation. It indicates the uniformity of the films prepared by the solvent casting method. The thickness was found to be high with films prepared with HPMC. As the proportion of this hydrophilic polymer increased, the thickness was also increased (Table 4). No significant difference in the average weight among each group indicating that the patches are uniform throughout. However the average weight of the films was slightly increased with hydrophilic polymer HPMC. The increase in the weight may be due to the hydrophilic nature of the adjuvants which may absorb moisture from the atmosphere resulting in increase in weight. It was also found that, with the incorporation of hydrophilic polymer (HPMC) increased the tensile strength and the percentage elongation whereas the hardness of the film decreased.

The folding endurance was measured manually and it is found that Chitosan / HPMC films without adjuvants were hard and fragile with low folding endurance. To enhance the flexibility and permeability of the matrix, Polylobate 80 and Propylene glycol (10% w/w in respect of the dry weight of the polymer) as plasticizers, was added, which can diffuse into and soften the polymer matrix. Folding endurance value were 210 ± 16 for formulation F1 and 298 ± 16 for formulation F5, other formulations were within

Table 4: Physico-mechanical characters of formulated buccal films

F. Code	Thickness* (mm)	Weight* (mg)	Folding Endurance*	% Elongation at break*	Tensile strength* (Kg/cm^2)	Hardness* (Kg)
F1	0.62 ± 0.05	50.8 ± 1.86	210 ± 16	17.9 ± 1.91	0.422 ± 0.06	0.387 ± 0.05
F2	0.64 ± 0.07	51.2 ± 1.58	240 ± 10	19.5 ± 2.43	0.476 ± 0.04	0.384±0.06
F3	0.64 ± 0.06	51.5 ± 1.53	264 ± 14	21.9 ± 2.24	0.527 ± 0.05	0.376 ± 0.04
F4	0.65 ± 0.09	51.9 ± 1.67	272 ± 13	22.4 ± 2.11	0.543 ± 0.04	0.367 ± 0.04
F5	0.66 ± 0.13	52.4 ± 2.86	298 ± 17	23.3 ± 2.56	0.564 ± 0.07	0.362 ± 0.08

* Mean ± Standard deviation (SD), n = 6

these ranges, which shows that the presence of HPMC can provide higher folding endurance and good flexibility. The results also suggested that the films would not break and would maintain their integrity with general buccal mucosa folding when applied.

Drug content uniformity

Good uniformity of the drug content among the patches was observed for all the formulations which ranged from 97.56±0.564% to 99.17±0.538% (Table 5). Based on the initial drug loading, all the formulations were containing above 9.75mg of drug, which proves that the process employed to prepare the films in this study was capable of producing films with uniform drug content and minimum batch variability.

Table 5: Drug content andmucoadhesive properties of formulated buccal film

F. Code	Drug content* (%)	Mucoadhesive strength* (Kg/m/s^2)	Residence Time* (min)
F1	97.56 ± 0.564	16.24 ± 0.17	430 ± 6
F2	98.15 ± 0.266	13.61 ± 0.27	385 ± 8
F3	98.67 ± 0.443	12.87 ± 0.31	376 ± 4
F4	99.17 ± 0.538	10.37 ± 0.22	338 ± 2
F5	97.72 ± 0.403	8.45 ± 0.37	294 ± 3

* Mean ± Standard deviation (SD), n = 6

Swelling index

The swelling character of the polymer affects its mucoadhesive behaviour. The adhesion increases with the degree of hydration up to a point where excess hydration leads to a rapid drop in adhesive strength, due to disentanglement at the polymer tissue interface. The rate and the extent of swelling of film also influence the drug release from film.[8] The poor solubility of Chitosan limits the swelling of the films and hence the film with Chitosan polymer alone (F1) showed the lowest rate of swelling (SI value of 1.87).[2] The presence of HPMC, a hydrophilic polymer, increases the extent of swelling.[27] Swelling is more pronounced in formulation F5, which contains only HPMC (SI value of 3.5).

The swelling profile of the formulated buccal films is shown in Figure 4.

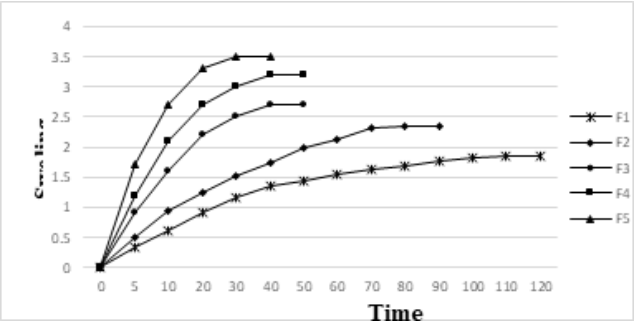

Fig. 4: Swelling profile of fabricated buccal films in simulated saliva

Ex vivo mucoadhesive strength

Buccal mucosa of goat was used as the model membrane for this study, since a larger expanse of the mucosa was available for performing several concurrent experiments which diminishes individual biological variation. Satisfactory mucoadhesion is essential for the successful application of mucoadhesive film in order to increase the residence time at the site of application, and hence, provide prolonged release of the drug. The mucoadhesive strength was observed within the range of 8.45±0.37 to 16.24 ± 0.17 Kg/m/s^2. Formulations F5 and F1 showed the highest and the lowest mucoadhesive strength respectively. The results illustrate that Chitosan is an excellent mucoadhesive polymer, but the incorporation of HPMC, a hydrophilic polymer, decreased the mucoadhesive strength of the film, and hence, the mucoadhesive strength among the Chitosan films decreased with the increasing content of HPMC.[27] The results are tabulated in Table 5 for all films.

Ex vivo residence time

It was observed that with increasing content of HPMC in the formulations, the mucoadhesion time decreased. Thus, F1 and F5 formulations showed the longest and the least adhesion time, respectively, as HPMC tended to decrease the mucoadhesive strength of chitosan. The residence time was found within the range of 294±3 to 430±6 min. The

results of *ex vivo* mucoadhesion time of all the formulations demonstrated in Table 5, revealed that the formulations F3, F4 and F5 are providing residence time more than 6 h and are suitable for overnight application.

In vitro drug release studies

In vitro drug release studies were carried out to indicate the influence of polymer concentration on the release of the drug. The rate and amount of drug released over 6 h were determined and the drug release profile of all the formulations are shown in Figure 5. After 6 h the drug release was found to be in the range of 65.74 to 95.36%. The rank order of drug release after 6 h was found to be 65.74, 78.34, 87.93, 94.28 and 95.72% for formulations F1, F2, F3, F4 and F5 respectively It was observed that, the drug release increased with the increasing content of HPMC, with respect to both rate and extent. The film F5 showed a burst release of drug within first 2 h and gradually increased afterwards. This higher release is attributed to the higher rate and extent of water uptake, with an increase in the amount of the water soluble polymer HPMC, resulting in increased wetting and penetration of water into the film matrices, and hence, increased diffusion of the drug.[9] Comparatively the drug release profile from F3 and F4 appeared to be more prolonged for a period of 6 h, with an extent of 87.93±3.41 and 94.28±3.85% respectively.

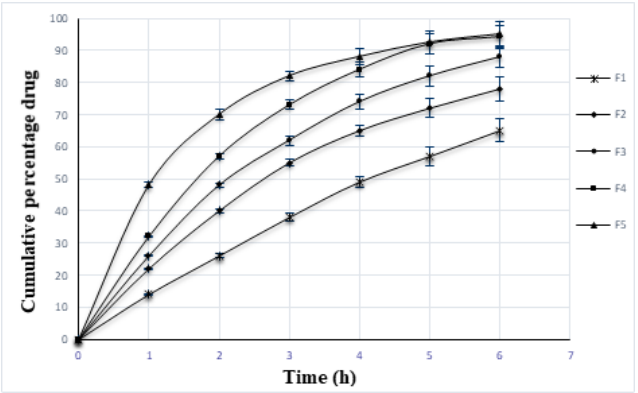

Fig. 5: *In vitro* release profile of Benzocaine from fabricated buccal films in simulated saliva

Drug release kinetics

Data of *in vitro* drug release were fitted into different kinetic equations to explain the release kinetics and the correlation coefficient values were calculated and compared. The kinetic models used were zero order equation, first order equation and Higuchi model.[25] For all the formulations, when the cumulative amount of drug released from the buccal films was plotted against time, the release profiles of drug appeared to follow the Higuchi model as indicated by regression coefficients (R^2 = 0.938 to 0.997) better than first order (R^2 = 0.803 to 0.912) and zero order (R^2 = 0.789 to 0.991) (Table 6). Further to determine the mechanism of release of drug from the formulations, the data was applied to Korsmeyer–Peppas equation. The release exponent 'n' was calculated and is reported in Table 5. Based on the 'n' value, it can be explained that in drug release, anomalous (non-Fickian) type of diffusion predominate in all formulations, as it is evident by the slope values of more than 0.5 but less than 1 for Korsmeyer – Peppas plot: the plot of log cumulative amount of drug released versus log time. This shows that the drug is released by diffusion based and swelling based mechanism simultaneously.[8]

Ex vivo Drug Permeation Studies

The cumulative amount of drug permeated through goat buccal mucosa for a period of 6h from each formulation is shown in Figure 6. It is observed that, the rate and extent of penetration of Benzocaine through buccal mucosa is less than its release from the films. However, an increase in the drug release from the films tends to increase its mucosal permeation. Availability of large amount of drug at the site of absorption can increase the concentration gradient. According to the Fick's first law of diffusion, higher concentration gradient across the membrane can enhance the rate of permeation of drug by diffusion.[8] It is exhibited from the results that, as the HPMC content of the films increased, the drug permeation at the end of 6 h increased from 5.72±0.35 mg for film F1 to 8.26±0.43 mg for film F5. Polysorbate 80 and propylene glycol, which are incorporated as plasticizers in film are also responsible for drug permeation.

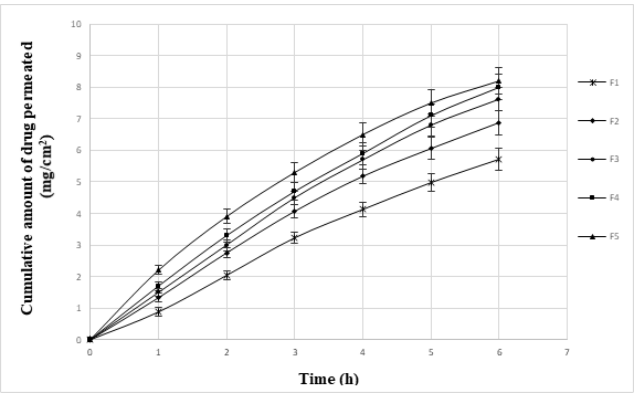

Fig. 6: *Ex vivo* permeation profile of Benzocaine from fabricated buccal films

Choice of best formulation

The results of physico-mechanical characterization, mucoadhesive strength, residence time, drug release and buccal permeation studies of formulated films shows that the combined use of chitosan, HPMC and plasticizers

Table 6: Kinetic values obtained from *in vitro* release profile of formulated buccal film

F. Code	Regression Constant (R^2) Value			Korsemeyer – Peppas Model Diffusion exponent value (n)
	Zero Order	First Order	Higuchi's Model	
F1	0.991	0.912	0.997	0.659
F2	0.948	0.862	0.991	0.733
F3	0.939	0.856	0.993	0.806
F4	0.902	0.821	0.967	0.829
F5	0.789	0.803	0.938	0.611

(polysorbate 80 and propylene glycol) are essential for the effective mucoadhesive buccal films of benzocaine. Among the five formulations, the film F3 was found to be the best formulation which exhibited the buccal residence for a period of 6h with the cumulative percentage of drug release of 87.93±3.41% and the cumulative amount of drug permeation of 7.62 ± 0.374 mg/cm^2 across goat buccal mucosa within 6 h.

Compatibility studies

DSC analysis and FT-IR studies were performed to verify the compatibility between the drug and polymers used to fabricate the films. DSC thermograms of pure drug (Benzocaine) and the optimized buccal film (F3) were recorded and are reported in Figure 7. DSC analysis of pure drug, Benzocaine showed a sharp melting endothermal peak at 90.32°C, which correspondence to its melting point (88-90°C). The comparison of melting point endothermal peak value of the formulated film with the pure drug revealed that, there is not much difference in the values. FT-IR spectra of the pure drug (Benzocaine) and the optimized buccal film (F3) are recorded and reported in Figure 8. The IR spectra of the buccal film indicate that the characteristic peaks for the drug (Benzocaine) are identifiable and there is no shift when combined with polymers and other components in the film. This indicates that the drug is intact in the film and it is not reacted with the polymers and other components. Thus the results of DSC and FT-IR studies revealed that the drugs and polymers used to fabricate the buccal films are compatible.

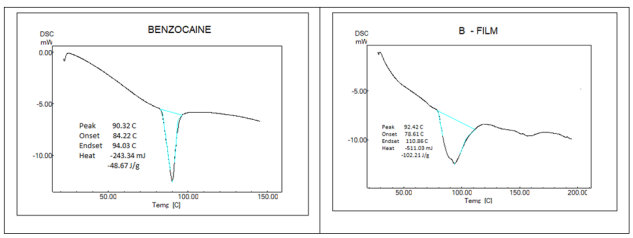

Fig. 7: DSCthermogram of pure drug (Benzocaine) and formulated buccal film (F3)

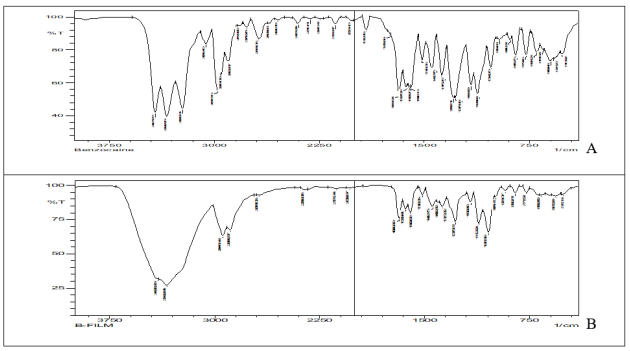

Fig. 8: FT-IR spectra of pure drug Benzocaine (A) and formulated buccal film F3 (B)

Stability study

The stability studies were carried out on the optimized formulation (F3) in a stability chamber for a period of 90 days. Six samples of each formulation were withdrawn at 0, 30, 60 and 90 days and analysed for the physical appearance, texture, physico-mechanical characteristics and drug content, *in vitro* drug release and *ex vivo* drug permeation characteristics.

The films remained flexible, smooth, non-sticky and no visual differences in colour or texture was observed. It was found that, there is no significant change in thickness, weight, folding endurance, tensile strength and hardness. The results of stability studies are encouraging as the variation in drug content is less than 2%. The drug release profile and drug permeation pattern were also not altered significantly even after the storage of 90 days. These results revealed that the formulated buccal film of benzocaine is found to be stable during the entire period of storage.

CONCLUSION

The choice of appropriate polymer blend and concentration of plasticizer and permeation enhancer are critical issues in mucoadhesive buccal drug delivery system. In the present study, the mucoadhesive buccal films of Benzocaine were successfully prepared by solvent casting method using mucoadhesive polymers Chitosan and HPMC. Based on the physico-mechanical, mucoadhesive, drug release and permeation characteristics, the present study concludes

that the formulation with Chitosan: HPMC ratio 1:1, 10% w/w Polysorbate 80 and 10% w/w Propylene glycol as plasticizers showed the best results which exhibited the cumulative percentage of drug release of 87.93±3.41% and the cumulative amount of drug permeation of 7.62 mg/cm^2 across goat buccal mucosa in 6 h. Thus this fabricated mucoadhesive buccal films containing Benzocaine is one of the best controlled drug delivery systems in the effective therapy of mouth ulcer, where the drug is made available for a period of 6 h, so most suitable for night time application. The findings of this result revealed that mucoadhesive buccal films of Benzocaine can improve patient convenience and compliance.

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