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BIOADHESIVE BUCCAL FILMS FOR THE DELIVERY OF BENZOCAINE

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ABSTRACT

Bioadhesive films, containing Benzocaine, were formulated to be adhered to the buccal mucosa for a period of time long enough to relieve the usual mouth lesions and pain. To achieve such an objective, formulations A, B, C, and D were developed to make films of different proportions of *Psylium Husk* (*PSH*) in combination with other hydrocolloids using film casting technique. The strength of bioadhesion of selected films to the mucous membrane of the stomach tissues, obtained from a sacrificed *albino rabbit*, was examined. Film D4 which is composed of carboxy-methylcellulose (CMC) and PSH showed the highest force required for detachment from the stomach tissue (83.33 ± 2.31 mN/m), while films composed of PSH and hydroxyethylcellulose (HEC) came second in terms of the tendency of adhering to the rabbit stomach (film A8) . In Vitro drug release from various films in either distilled water or simulated saliva solution was conducted at 37.0 °C. The highest percentage of drug released was noticed when the percentage of PSH was about 41% w/w in the film matrix (film A8) with about 98% drug release after 4 hrs. Benzocaine release from films of different thicknesses, revealed that the release rate constant K was found to be independent of film thickness in full agreement with Higuchi's diffusion controlled mechanism.[1]

KEYWORDS: Bioadhesion, buccal films, *Psylium Husk (PSH)*, carboxymethylcellulose (CMC), hydroxyethyl cellulose (HEC), Stearic acid (SA), Bnzocaine.

1. INTRODUCTION

Many drugs cannot be delivered effectively through the conventional oral route, because of the main obstacle of first-pass effect and the degradation of certain drugs in the GI fluids. Buccal mucosa has an excellent accessibility and relatively immobile mucosa, hence, suitable for the administration of bioadhesive buccal films. Locally, therapy includes the treatment of interoral conditions such as gingivitis, oral candidiasis, oral lesions, dental carries, etc. in addition to local anesthetics which are commonly used to relieve some types of pain. Systemically, as it is well known, buccal and sublingual systemic drug administration is most popular for the treatment of acute cases, such as anginal attacks.

The ability to maintain a delivery system at a particular location for an extended period of time has a great appeal for both local disease treatments as well as systemic drug bioavailability.[2] One of the approaches used to achieve this goal is the concept of Bioadhesion, which is simply formulating certain drug delivery systems using hydrogels. Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids, and retaining a large amount of fluid in the swollen state.[3] Their ability to absorb water is due to the presence of hydrophilic groups such as -OH, -CONH-, -CONH2, -COOH, and –SO3H.[4] Factors such as polymer composition, water content, crosslinking density, and crystallinity, can be used to control the release rate and release mechanism from hydrogels.[5] Chitosan glutamate, a soluble salt of chitosan, was also utilized in hydrogel dosage form for buccal delivery of an anaesthetic drug, lidocaine hydrochloride and found to be effective for symptoms relief of aphthosis and other painful mouth diseases.[6] The main objective of this project is to prepare and evaluate bioadhesive buccal films loaded with Benzocaine, which is a hydrophobic local anesthetic. Prolonging the contact time between benzocaine and the buccal mucosa is expected to lead to an improvement of the amount absorbed and consequently the efficiency of the drug to relieve pain and discomfort of mouth lesions and inflammations. To achieve this goal, several hydrocolloids are suggested to be included in these films for the purpose of adhering to the buccal mucosa and releasing benzocaine at controlled and sufficient rate. PSH, CMC and HEC are examples of the hydrogels suggested to be used in this study. These hydrogels are used internally with perfect safety history. Stearic acid (SA) is going to be introduced to modify the release characteristics in some of these formulations. Sodium Salicylate will be used in some formulations as an example of freely soluble drug.

2. EXPERIMENTAL

2. 1. Materials

Benzocaine hydrochloride, Chemcenter 5580 La Jolla Blv, (Ste 413), La Jolla, CA 92037.Psyllium Husk powder, Now foods, 3955. Glen Ellyn Rd, Lot 5975. Hydroxyethylcellulose, RIEDEL-DE HAËN AG SEEIZE-HANNOVER, 500g, Lot 64624. Carboxy methyl cellulose sodium salt, BDH chemicals Ltd poole England, Lot 27929.Stearic acid, MERCK, E. Merck, Darmastadt. Lactose, MERCK, E.Merck, Darmastadt. Glycerol, BDH chemicals Ltd poole England, Lot 28454. Lactic acid,, BDH Limited Ltd poole England, Lot 29001. Ethanol 99.6%, RIEDEL-DE HAËN, Lot 83370.Sodium Salicylate, RIEDEL-DE HAËN AG SEEIZE-HANNOVER, chem.,rein,ph,Eur, Lot 13475. Potassium Chloride,BDH Laboratory supplies pool, BH 15 1TD,England,Lot TA817937. Urea Cryst, MERCK, E.Merck, D-6100 Darmastadt, F.R.Germany. lot 8486. Ammoniumacetate, MERCK, E.Merck, Darmastadt, lot 130322. Sodium Sulphate, Northampton, U.K,lot P480H. Sodium Hydroxide solution N/1,FARM ITALIA CAPLO ERBA, Milano, lot 1085N100. Polyethylene Glycol 3350 and 400, Northampton, U.K,lot P535H.

2. 2. Equipment

Spectrophotometer,JEN WAY, Model 6305. Force Tensiometer,KRüSS GmbH, Model K6, Germany. USP Dissolution Apparatus,PHARMA TEST DT 70, Germany. pH-meter handy Lab,Schott Glaswerke Mainz,Made in Germany Ser- Nr-99350390/9935. Balance SARTORIUS AG GőTTINGEN,Germany,12704989. MEBRANE FILTERS, Schlricher and Schuell,0.45 µm, Germany,Lot-No CF0323-1. Elcometer 456 Coating Thickness Gauge, Standard Model Bluetooth SIG Inc, and Licensed to Elcometer Ltd, Edge Lane,Manchester England-U.K.

2.3. Preparation of films

The method used for preparing the films was developed in our laboratories as follows.

An amount equal to 0.4g of Psyllium husk and 0.6 g of the other film constituents were mixed into a 50ml beaker. Five mls of glycerol were transferred into a 100-ml volumetric flask, and the volume was then adjusted to the 100-ml mark with distilled water. The already prepared aqueous solution of glycerol was added to a beaker containing the dry polymers mixture which was stirred gently till it became homogenous. A known amount of the drug (benzocaine) was dissolved in about 2.5 ml of ethanol with the aid of gentle stirring. The benzocaine ethanolic solution was added slowly to the beaker containing the solution of polymers while stirring gently over a magnetic stirrer till a homogenous colloidal solution was formed. Five mls of the colloidal solution were poured into glass Petri dishes (surface area 19.63 cm^2) using a graduated glass pipette. The dishes were kept on a level surface to ensure uniform distribution of the solution. The solution was left to evaporate over 48 hours leaving thin and transparent films deposited on the bottom of these dishes. The Petri dishes with dried films were kept in a dry place for further release studies.

2.4. Bioadhesion study

An Albino rabbit weighing about 2 kg was sacrificed. The stomach was selected as a model membrane since the stomach provided a flat and uniform surface. A piece of stomach mucosa of about 2 cm long and 0.5 cm width was mounted on the platform of the tension-compression stand of the tensiometer as follows: The piece of stomach mucosa was stapled to a Scotch tape which was fixed to the bottom of a glass Petri dish, and the mucosal surface was hydrated by placing simulated saliva solution on the tissue surface. The selected film was mounted using Scotch tape around the circumference of the bottom face of a stainless steel disk attached to the force gauge. The film and the mucosal surfaces were brought into contact for 5 minutes. The film was then slowly pulled off the tissue surface following the application of force, using the knob of the instrument scale. The value for the force of detachment was measured in mN/m by lowering the platform of the tensiometer compression stand.

2.5. Swelling study

The films A9, C5, and D4 were selected to conduct this study. These films have been chosen on the basis of their composition and have been tested for their ability to swell using simulated saliva solution. Each film sample was weighed and placed in a pre-weighed stainless steel wire mesh. The mesh containing the film sample was submerged into 60 ml of distilled water or simulated saliva solution in a beaker. After 24 hours and 48 hours, the wire mish was pulled out of the beaker and the excess water was gently wiped off using a piece of clean paper towel. The increase in the weight of the whole assembly was determined at preset time intervals until a constant weight was observed. The swelling index was calculated according to the following equation:

Swelling index = $(W_t - W_1) / W_1$ …… Eq. (4)

Where: W_1 is the original weight of the dry film, and W_t is the weight of the film at the end of the swelling study at time t.

2.6. Folding endurance study

Folding endurance of the films was determined by manually folding one film, repeatedly at the same place till it broke or folded for at least 300 times, which is considered satisfactory to reveal good film elasticity and strength. The number of times at which the film could be folded at the same place without breaking, gave the value of the folding endurance.

2.7. Film surface pH study

The surface pH of the films was checked to ensure that the presence of these films in the buccal area would not irritate the buccal mucosa in any way. The pH was determined by the use of a portable pH meter. Films were left in Petri dishes each containing 5 mls of simulated saliva and allowed to swell for a while. The

pH was measured by bringing the pH meter electrode near to the surface of the wet swollen film.

2.8. Determination of film thickness

Films of different thicknesses were prepared by the film casting technique. 5 mls, 7 mls, and 9 mls of the film forming solution were poured on the surface of a disc of wax paper placed at the bottom of glass Petri dishes. The film forming solution was left to dry for about 48 hours. The dry films were carefully removed from the dishes and were individually stored between sheets of wax paper in a dry place. Film's thickness were measured using " elcometer 456 film thickness Gauge Probe". The instrument was calibrated using a standard metal provided with the instrument. The readings were recorded at different points of the film surface. An average of ten readings on two films of the same composition, and the standard deviation was calculated.

2.9. In Vitro drug release Studies

The release studies were carried out using a USP dissolution apparatus. Five hundred mls of distilled water or simulated saliva solution were added to each beaker, followed by careful immersion of glass Petri dishes with test films adhered to the bottom of these dishes. The agitation speed was maintained at 30 rpm throughout each experiment and water bath temperature was kept at 37ºC. Five mls samples were withdrawn at appropriate time intervals over 4 hours, and analyzed for Benzocaine content spectrophotometrically at 278 nm wave length. Each sample (5 mls) was replaced by an equal volume of fresh bathing fluid (distilled water or simulated saliva solution) to keep the total volume constant.

3. RESULTS AND DISCUSSION

3.1. Film Thickness study

Three volumes of the film former solution which were 5 mls, 7 mls and 9 mls have resulted in the formation of films with thicknesses of 51.48 ± 2.58, 103.98 ± 4.51 and 197.30 ± 13.36 µm ± S.D. (n = 5), respectively.

3.2. Swelling study

By reviewing table (1), it is clear that formulations D4 and A8 showed higher swelling indices respectively, due to the presence of the hydrocolloids CMC, PSH and HEC. Formulation C3 showed the lowest swelling index probably because of the presence of high percentage of the freely water soluble lactose.

Table (1): The calculated swelling indices for films of selected formulations A8, C3 and D4 in distilled water and simulated saliva.

Formulation	*Swelling index in Distilled water ± S.D.	*Swelling index in Simulated saliva± S.D.
A8 PSH 40.3% w/w HEC 57 % w/w	8.04 ± 0.77	8.07 ± 0.11
C3 PSH 55.6% w/w Lactose 41.7% w/w	3.65 ± 0.19	4.59± 0.13
D4 PSH 55.6% w/w CMC 41.7% w/w	9.69 ± 0.85	6.88 ± 0.50

* The study was carried out in triplicate

3.3. Bioadhesion studies

Table (2) reveals that films composed of combinations of PSH and HEC have shown somewhat lower tendency to adhere to the rabbit stomach (formulation A8). Films of formulation D4 composed of lower percentage of PSH showed significantly higher force of attachment to the rabbit stomach compared to the other formulations ($p < 0.05$), probably due to the presence of CMC. The superiority of CMC as a bioadhesive polymer compared to other hydrocolloids studied is well documented in the literature.[7-9] Very close results was reported in the literature in another study using Chitosan[10] where almost every primary amino group of chitosan could be modified by EDTA resulting in increased bioadhesive strength (81.7 ± 9.9 mN).

Table 2: The observed force of detachment for films of selected formulations A8, C3 and D4.

Study	Film A8	Film C3	Film D4	ANOVA	Tukey's allowable difference
Force of detachment mN/m ± S.D.*	59.33±1.15 PSH 57% HEC 40%	47.00±5.57 PSH 55.6% Lctose42%	83.33±2.31 PSH 55.6% CMC 42%	P < 0.05	A8&C3 A8&D4 C3&D4 P<0.05 p<0.05 p<0.01

* The study was carried out in triplicate

3.4. Film folding endurance

The mechanical strength and the flexibility of the prepared films was confirmed. All prepared films have shown high degree of elasticity after their repeated folding for more than 300 times without showing any signs of breaking down. This finding suggests that all

films can be applied very easily to the buccal area with perfect physical coherence.

3.5. Film surface pH study

The pH of the surface environment of selected films was found to be in the range of 6.1 – 6.2 which is within the tolerance of the buccal mucosa which tolerates up to pH 6.8. This conclusion indicates that the surface pH of these films, when swollen, would not irritate the buccal mucosa.

3. 6. In Vitro release studies:

In previous work in our laboratories, formulations containing psylium husk granules as a potential DDS were prepared.[11] M. Yasir et al. found out that PSH took about 6-8 hours to complete swell.[12] Figures 1, depicts the drug release pattern from films of formulations A1-A9 at different concentrations of Benzocaine which were introduced in formulations containing combinations of PSH and HEC. The highest percentage of drug released, after four hours, was noticed when the ratio of PSH to HEC, in the formulations, was 1:1.

3.6.1 Formulation A (PSH and HEC)

Figure 1 reveals the following: Three different concentrations of benzocaine were used (2.7%, 16.7% and 33.3% w/w) in formulations A1 – A9. At 2.7% drug concentration, the highest percentage of drug released was (87% and 98%) for formulations A8 and A9. At drug concentration 16.7%, the highest percentage of drug released was noticed when the ratio of PSH to HEC, in these formulations, was 1:1 (formulation A5). At drug concentration of 33.3% w/w, a lower percentage of drug released was noticed for all formulations studied The highest percentage of drug released from these formulations at different drug loadings are noticed when the percentage of PSH was about 40.0 – 41.7% (formulations A3, A5 and A8).

3.6.2. Formulation B (PSH and Stearic acid SA)

The same loadings of benzocaine were used in formulations B1 – B8, using SA in combination with PSH. By reviewing figure 2, it is possible to notice that despite the fact that the percentage of drug released over 4 hours was low (18.8% - 21.7%) from films of formulations B1-B3, the maximum drug released was observed when the ratio of PSH to SA was about 1.3:1. It is also noticeable that when higher percentage of SA in formulation B4 was introduced, about 92% of the drug was released after 4 hours compared to only 63% of the drug released from formulation B5. At drug concentration of 2.7% w/w (formulations B6-B8), a high percentage of drug released from film B6 was observed, probably attributed to the high concentration of the solubilizing agent SA in the formulation (41.7% w/w). Films B7 and B8 showed lower percentage of drug released most likely due to the lower percentage of SA and higher percentage of PSH (62.3% w/w) in these formulations. This finding is consistent with that reported earlier by Hernandez and coworkers where Metronidazole release was found to be increasing with the increase of the concentration of SA in floating matrices.[13] The authors of this article concluded that besides the effect of SA as a solubilizing agent, it has contributed significantly to the relaxation and expansion of these matrices leading to a higher drug release.

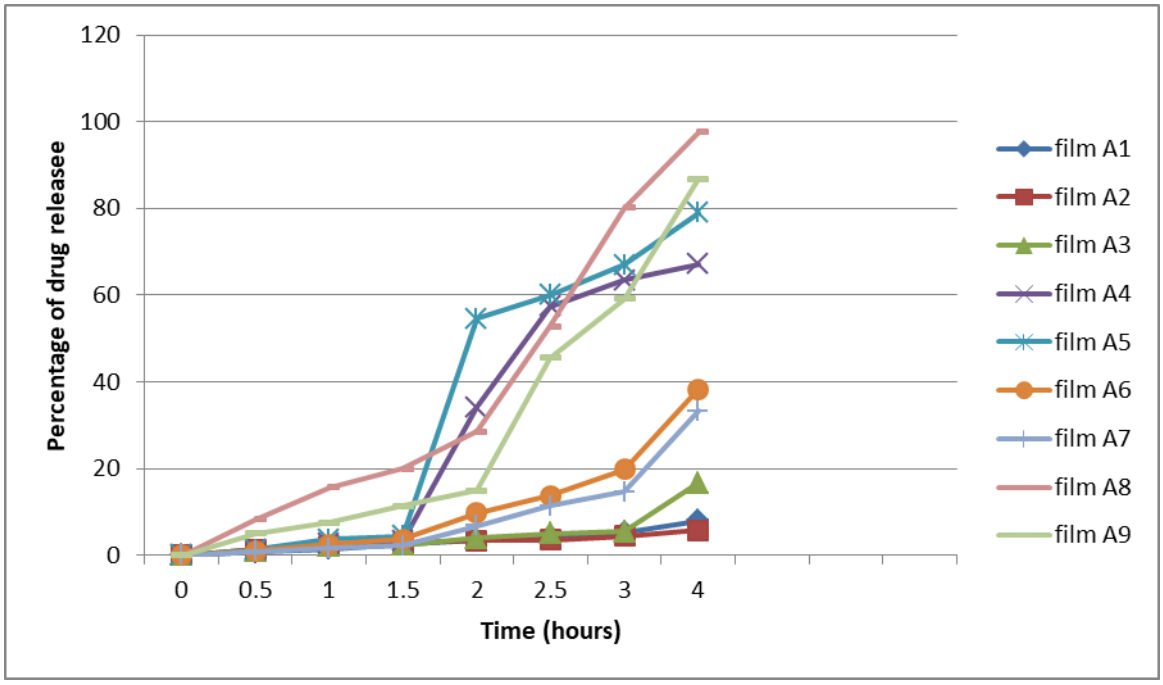

Figure 1.

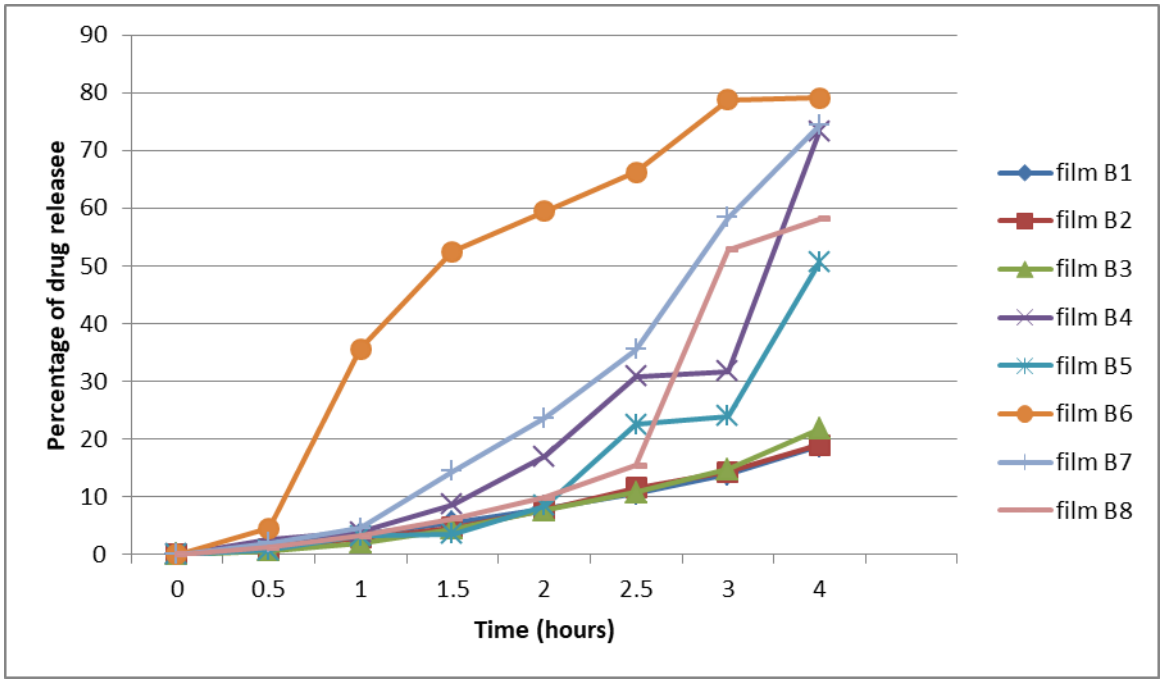

Figure 2.

3.6.3. Formulation D (PSH and CMC)

Two drug loadings of 2.7% and 33.3% were used in this formulation. The presence of CMC in these formulations played a major role in the release of the drug from these films. Formulations D1 and D2 have shown a considerable reduction in the percentage of drug released (< 5.5%) when the ratio of PSH to CMC was 1:1 or less (figure 3), which is consistent with the findings reported earlier in our laboratory.[12] When the drug loading was 2.7%, the percentage of drug released was the highest when the ratio PSH to CMC was 1.3:1 (formulation D4). This finding has been found to be in agreement with similar finding observed with previous formulations.

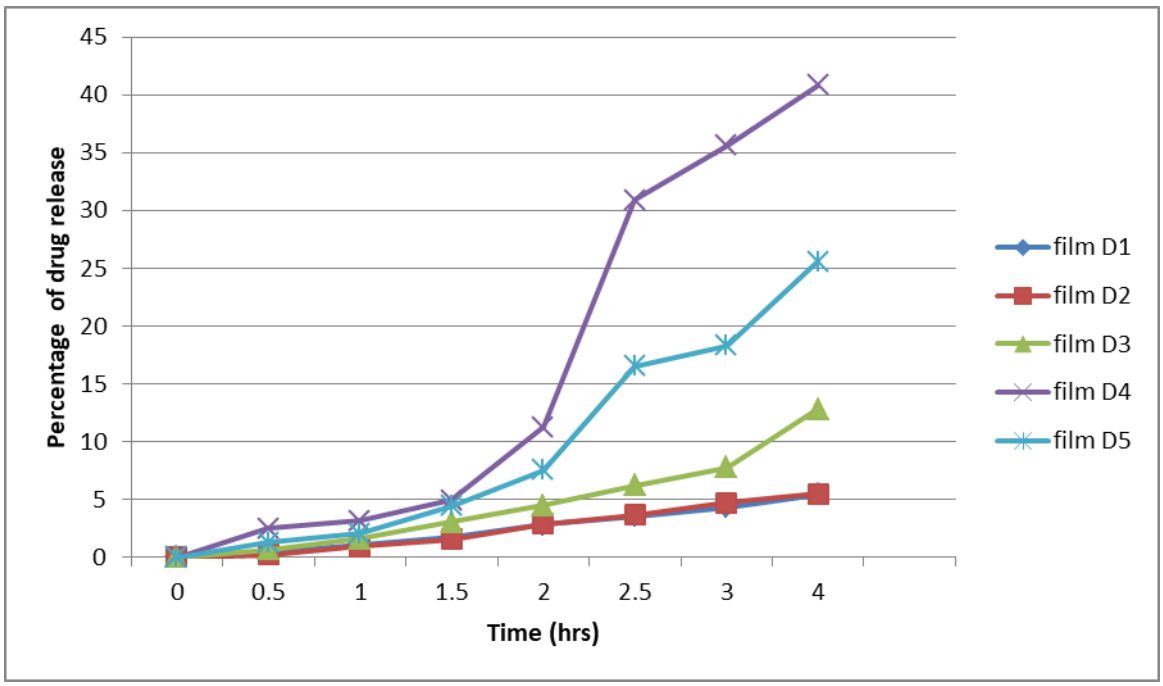

Figure 3.

3.6.4. Effect of film thickness

Series of films (formulation A1) of different thicknesses were investigated for drug release. According to Higuchi's diffusion controlled mechanism of drug release, the release rate constant should be independent of film thickness. The approximate constancy of K with varied film thicknesses is shown in table (3). It was reported[14,15] that the film thickness does affect the

duration of drug release. The time required for the release of half of the amount of the drug present in the film, the product half-life ($t_{½}$), was shown to be related to the film thickness by the following relationship.

$$t_{½} = \left(\frac{Ah}{2k}\right)^2 \quad \text{..... Eq. 2}$$

where:
A: initial amount of the drug in the film matrix
h: film thickness
K: release rate constant (Higuchi)

Table 3 and figure 4 show drug release profile and the $t_{½}$ values calculated by first-order relationship.

$$t_{½} = \frac{0.693}{k} \quad \text{..... Eq. 3}$$

where k : first-order rate constant

This data reveal the fact, that first-order rate constant k is dependent on film thickness (table III).

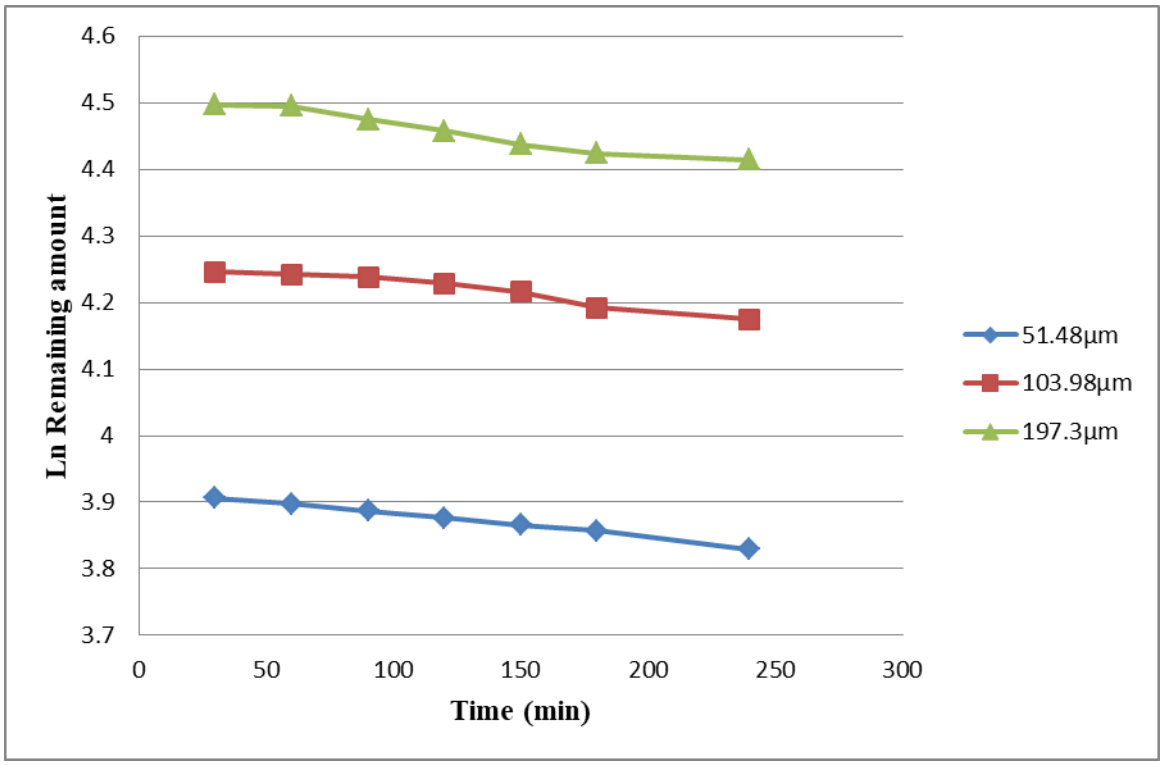

Figure 4.

Table 3: Higuchi and first-order treatment of data for the release of Benzocaine from film A1 as a function of film thickness.

Film thickness µm ± SD	Higuchi K * (mg/cm² min.½)	Higuchi $t_{½}$ (min)	First-order $t_{½}$ (min)	First-order K (min .⁻¹)
51.48 ± 2.58	5.8	27225	1.888	0.367
103.98 ± 4.51	5.3	471556.9	5.210	0.133
197.30 ± 13.36	5.3	2806295.1	10.34	0.067

* p > 0.05

4. Statistical Analysis

Spss statistics software package (version 20) was used for logical batched and non-batched statistical analysis. ANOVA test for significance or lack of significance among treatments, at 95% and 99% confidence limit was adopted. Tukey's allowable difference was calculated to find out the difference between treatments "formulations".

5. SUMMARY AND CONCLUSIONS

Films of different proportions of PSH and other hydrocolloids were prepared with good physical appearance, integrity and elasticity. The bioadhesion studies revealed the superiority of the formulation containing PSH and CMC (formulation D) in terms of bioadhesion to the rabbit stomach (force of detachment was 83 mN/m). However, the percentage of benzocaine released from these films was not satisfactory (about 40% released over 4 hours). The formulation that showed higher percentage of drug released over 4 hours was

formulation A8 (PSH and HEC) which has released about 97% of drug content from these films over 4 hours with reasonable bioadhesion strength (force of detachment was about 60 mN/m). This later finding suggests that the most reasonable film was formulation A8, which is expected to adhere to the buccal mucosa for at least 4 hours and releasing at least 97% of its drug content.

Future work is warranted to improve the drug loading to at least 5%.

6. List of Figures

Figure (1): Percentage of drug released vs time, from films of formulations A1-A9

Figure (2): Percentage of drug released vs time, from films of formulations B1 - B8.

Figure (3): Percentage of drug released vs time, from films of formulations D1 - D5.

Figure (4):): First-order plots of Benzocaine release from film A1 at thickness of 51.48µm, 103.98µm, 197.30µm.

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