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Effect of Quaternary Ammonium Surfactant on Buccal Permeation of Budesonide Film Formulation: *In Silico* Docking Studies

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Budesonide, an immunosuppressant glucocorticosteroid generally used to ameliorate chronic inflammation. Low bioavailability due to first pass metabolism decreases its therapeutic activity. The present study focuses on the formulation of a biodegradable buccoadhesive film for improvement of buccalpermeation. Transparent buccoadhesive films were prepared by incorporating budesonide in HPMC matrix with triethalonamine as a plasticizer and a number of surfactants. Absence of the characteristic drug melting peak at 252°C in Differential Scanning Calorimetry (DSC) thermogram study confirmed almost complete amorphization of the drug to a homogenous solid-solid mixture in the film. The characteristic Fourier-Transform Infrared Spectroscopy (FTIR) peak of pure drug showed the carbonyl stretching in between 1600–1900 cm^{-1} and C–O stretching at 1095 cm^{-1}. Broadening of C–O stretching and masking of carbonyl stretching confirmed the drug polymer interaction. *In vitro* dissolution and *ex-vivo* buccal tissue permeation revealed upto 72% and more than 58% respectively using surfactants upto 6 hour of study. Enhanced buccal permeability and flux were found in presence of surfactant compared to its absence. New film formulation could be developed including surfactant for improved buccal permeation with expected increased bioavailability. The *in silico* study confirmed about a stable interaction between drug and polymer (−3.1 kcal/mol).

Keywords: Buccoadhesive film, Buccal permeation, *Ex vivo* permeation, Glucocorticosteroid, Immunosuppressant, Quaternary ammonium compounds

Introduction

Budesonide is an immunosuppressant glucocorti costeroid drug. One of the main indications of the drug is to ameliorate chronic inflammation. Enzymatic degradation and acid hydrolysis in the Gastrointestinal (GI) tract also a major obstacle for absorption process.[1] Budesonide is available in the market in the form of the Dry Powder Inhaler (DPI), tablets and as capsules. Due to its high hepatic first pass metabolism, it shows low oral bioavailability of 6–11% and very short elimination half-life of 2 to 3 hours. As per available report, bioavailability of the drug in the case of nebulization and inhalation is in the range of 6%.(2) It is a Biopharmaceutical Classification (BCS) class system II drug having low aqueous solubility and high permeability, with $logP$ value of 3.2. Inflammatory Bowel Disease (IBD) is of two kinds, for example, Ulcerative Colitis (UC) and Chron's Disease (CD). In UC, the proximal region of the colon part is mostly affected and in Chron's disease the distal part of the ileum is affected.[3] Development of drug delivery is required to target both the sites at a time and sustaining the release.

Nasal, rectal, vaginal, buccal are the more advantageous routes for increasing the bioavailability of the drug. In DPI formulation the flow property of the formulation and compatible device play a crucial role. Irregularity in the above mentioned parameters may cause problems like upper airway deposition, segregation and agglomeration.[4] These problems can also be avoided by administering the drug through buccal delivery. But buccal mucosal delivery system holds a position of greater importance for its higher patient acceptability. Buccal mucosal tissue is more vascularised and easily administrable for any kind of patient. The buccal route also allows patients to discontinue the medication once the intended action is exerted and to side step from overdosing. Buccal tissue recovery rate is also higher than other transmucosal routes and could be explored for better drug delivery.[5,6] Thus, buccal drug delivery is the more promising and potential delivery system rather

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than other delivery routes because buccal mucosa is 4–4000 times more permeable than that of the skin.[6]

In a previous study, budesonide mouthwash in multiple dosing showed improvement in drug transport comparing to oral administration.[7] In another very recent report of *in-vitro* experiment mucoadhesive formulation of budesonide has not shown any additional improvement in tissue penetration.[8]

Mucoadhesive polymers in film type buccal drug delivery have more advantageous factors like increased residence time of polymer, site-specific adhesion, penetration enhancement, and avoiding enzymatic attack on drug.[1] Hydrogels are used in many drug delivery.[9] Being the quaternary ammonium surfactants Benzalkonium Chloride (BZK) and Cetrimide (CET) can overcome problems associated drug absorption in many formulations.[10] CET was used as a preservative in the study of rheological properties of *Leucaena leucocephala* seed gum.[11] Triethanolamine was used as a plasticizer in film formulation to increase flexibility and patient compliance.[12,13]

In widespread literature survey, sustained buccoadhesive formulation of budesonide with the incorporation of quaternary surfactants for permeation enhancement was rarely found. Which lead this study towards the buccal film formulation of budesonide incorporating BZK and CET as quaternary surfactants to find any increase in buccal permeation which in turn supposed to improve bioavailability of the drug.

Materials & Methods

Materials

Buesonide was a gift sample from Cipla Labrotories; HPMC K15M and triethalonamine were purchased from SRL labrotories. Benzalkonium chloride (solution 50%) was obtained from MERCK labrotories India and Cetrimide (Cetyl Trimethyl Ammonium) was purchased from Burgoyne Burbidges & Co. Labrotories Mumbai (India).

Preparation of Budesonide Films

For the preparation of budesonide film required amount of polymer (HPMC K 15 M) was weighed accurately. Then in one 100 ml beaker the polymer was transferred and 40 ml distilled water was poured. Afterwards, the beaker was placed in cooling condition for 24 h in a refrigerator for soaking of water. Then other excipients like plasticizer, surfactant were weighed and added to the swelled polymer. Required amount of drug was dissolved in small amount of methanol and added. After complete mixing the viscous mixture was transferred to a Tarson Petri disc and drying was carried out at 40–50°C for 30–48 h. After complete drying, the films were collected and kept in a cool place.[14] Film formulation has been presented in Table 1.

Determination of Thickness

Every formulated film was taken and thickness of the different area was measured by using Mitutoyo Digimatic Micrometer and the mean value was calculated to obtain the uniformity of thickness.

Moisture Content

Uniformed films were placed into an airtight desiccator containing activated silica gel for 24 h. Moisture content was calculated from the decreasing film weight from the initial weight.

Moisture Uptake

Moisture absorption study was carried out in the laboratory under a humidity condition. By using a supersaturated solution of sodium chloride, 75% RH (Relative Humidity) condition was maintained in dessicator. Films were placed in the desicator for 24 h and moisture uptake was calculated from the increasing film weight after the initial.[15]

Swelling and Erosion Study

A (≈1 cm × 1 cm) size matrix film was placed over a glass side in a Petri dish having 40 ml of simulated buccal fluid (phosphate buffer 6.8). At regular interval of time the weight gain of the films were noted after wiping out the excess liquid from the film surface. After complete hydration upto 6 h swollen films were placed in the incubator at 60°C for 24 h for drying. Weight of the dried films was noted and percent swelling and percent matrix erosion were found out by using the following expressions.[12,15]

Table 1 — Budesonide polymeric matrix film formulation for buccal delivery

Film code	Budesonide (mg)	HPMC k15M (mg)	Triethlonamine (%)	Surfactant (0.1 %)
BHT_1	50	1000	15	—
BHT_2	40	900	20	—
BHT_b	40	900	20	Benzalkonium
BHT_c	40	900	20	Cetrimide

$$Dynamic\ hydration = \frac{Weight\ after\ hydration - Initial\ dry\ weight\ before\ hydration}{hydrated\ weight} \times 100$$

$$Matrix\ erosion = \frac{(Initial\ dry\ weight - Final\ dry\ weight\ after\ swelling)}{Initial\ dry\ weight} \times 100$$

Determination of Folding Endurance

Folding endurance test was performed to recognize fragility of films. This test was carried out by folding and opening the film at a particular place repeatedly until it breaks. Folding endurance value of the film was estimated by the number of times it has taken to break.

FTIR

Bruker alpha (Ettlingen, Germany) Fourier transform infrared (FTIR) spectrophotometry was used to obtain the Infrared (IR) characteristic peaks within the 4000–400 cm^{-1}. For the IR analysis samples were placed on the ZnSe (Zinc-Selenide) crystal and pressed over the Attenuated Total Reflectance (ATR) crystal by the help of integrated pressure devices and FTIR spectra were recorded.

DSC (Thermal Analysis)

Differential Scanning Calorimetry (DSC) study was carried out for thermal analysis of drug and films by using DSC-1 (Mettler Toledo, Switzerland). Thermal analysis study was performed under a dynamic nitrogen atmosphere (20.0 ml/min) at a constant heating rate of 10 °C/min and temperature range from 30–300°C.

X-ray Diffractometry (XRD)

The pure drug and films were analyzed by powder ray diffraction (Instrument: Rigakuultima IV). Samples were scanned from 5–70° at 2θ. The anode material for X- ray source Cu was used.

Scanning Electron Microscopy

Morphology of the pure budesonide crystal and surface texture of the prepared films were analyzed by using scanning electron microscopy (JEOL JSM-6510). Morphological analysis of samples carried out after coating one side of the sample by using plantinium coating. Then the samples were analyzed at 3,000X to 10,000X magnification.

***In vitro* Drug Release**

Pre-weighed cut piece of the film was fixed on glass slide by using cyanoacrylate adhesive and theslide was placed in the dissolution vessel at the bottom in horizontal manner to the surface of vessel. Phosphate buffer (pH 6.8) was used as dissolution media. The test was carried out in USP Type-II dissolution apparatus (Electrolab, Dissolution Tester USP, TDT06L, India) having 50 rpm rotation speed of paddle. The temperature maintained at 34 ± 0.2°C and the study was carried out for 6 h. The absorbance was observed at 247 nm using UV-visible spectrophotometer.[16]

***Ex vivo* Buccal Permeation**

Buccal permeation study was done by collecting buccal skin of chicken from chicken butcher house within 30 min of its sacrifice. Buccal mucosal lining was properly rinsed with deionized water and dipped into pH 6.8 phosphate buffer. After 30 min mucosal tissue was attached with the diffusion tube and buccal permeation study was started using phosphate buffer of pH 6.8, 200 ml as diffusion media. The diffusion was carried for 6 h at 50 rpm speed and temperature maintained at 34 ± 0.2°C. To calculate the percentage of drug permeated absorbance was observed at 247 nm using UV-visible spectrophotometer.[17,18] Flux was calculated from the initial linear slope of the amount permeated per unit area vs time plot.

Molecular Docking Study

Molecular docking study was carried out to check the interaction between ligand and macromolecule. Budesonide was taken as ligand against the receptor HPMC K15M as macromolecule. By using marvin-sketch software the 3-D structure of macromolecule (HPMC K15M) and 3-D structure of ligand (budesonide) have been drawn. AutoDock Tools of MGL Tools were used to convert it to PDBQT (Protein Data Bank, Partial Charge (Q), & Atom Type (T)) format. Using Auto Dockvina software molecular docking was performed and binding constant and interaction energy were measured. Interaction of budesonide with HPMC K15M was studied using molecular docking method.

Results and Discussion

Properties of Film Formulation

Thickness of the formulated films was in between 166–189 μm which was convenient thickness for buccal films.[19] Folding endurance (183–196) confirmed the robust nature of the film and was not easily breakable. Presence of a minimum moisture level is required to improve the plasticizing ability of

Table 2 — Physical and swelling properties of the budesonide buccal film

Film Code	Moisture uptake (%)	Moisture content (%)	Thickness (μm)	Folding endurance	Swelling Rate (K_s) (t^{-1})	Erosion (%)
BHT_1	5.89 ± 0.58	4.51 ± 0.98	189.6 ± 3.6	183	3.6 ± 0.2	70.9 ± 12
BHT_2	5.67 ± 0.26	2.41 ± 0.66	166.0 ± 3.3	192	2.4 ± 0.4	72.1 ± 2.8
BHT_b	5.68 ± 0.17	1.42 ± 0.44	174.8 ± 7.1	196	3.5 ± 0.1	69.7 ± 9.5
BHT_c	5.66 ± 0.27	1.19 ± 0.25	172.8 ± 6.0	194	2.0 ± 0.04	80.7 ± 1.8

the added plasticizer in the film. Low moisture may not be sufficient enough for molecular mobility for crystal transformation and maintaining film stability, whereas high moisture can lead to crystal transformation, chemical instability and mold formation. So a level of moisture content (1.19 to 4.51%) and not fully dried could help the films to stay stable. Moisture uptake was found in 5–6% even after the exposure at 75% RH as per International Council for Harmonisation (ICH) guideline. Physical properties and hydration behavior of the budesonide buccal film formulations were shown in Table 2.

Swelling and Erosion Study

Budesonide film formulations were hydrogel forming films which swelled when came in contact with water. Estimated values of swelling index, rate of swelling and % of erosion are reported in Table 2. Films containing benzalkonium chloride remarkably increased swelling index upto a period of 360 min. Formulation BHT_b showed the highest sustained swelling rather than other formulations as shown in Fig. 1. BHT_1 formulation showed second highest swelling with sustained action due to presence of highest content of Hydroxypropyl methylcellulose (HPMC) in the film and in absence of surfactant. Whereas, film BHT_2 and BHT_C showed a similar and reduced swelling pattern. That means presence of benzalkonium in the film sustained the swelling action more than the cetrimide containing formulation. As compared to other formulation having same polymer, BHT_b showed highest swelling rate of 3.5 min^{-1} with least erosion of 69% compared to other films (Table 2).

FTIR Study

The FTIR analysis is given in Fig. 2(a). Budesonide showed characteristic peaks at 3490.56, 2956.84, 1723.14, 1666.56, and 888.61 cm^{-1}. The main characteristic peak at 1666.56 has been shifted slightly and intensity also decreased. In 1100–1000 regions the peaks were broader than the parent peaks. These shifting, masking, and changing intensity of parent peak gave indication about interaction of drug with polymer and surfactants (penetration enhancer).[20]

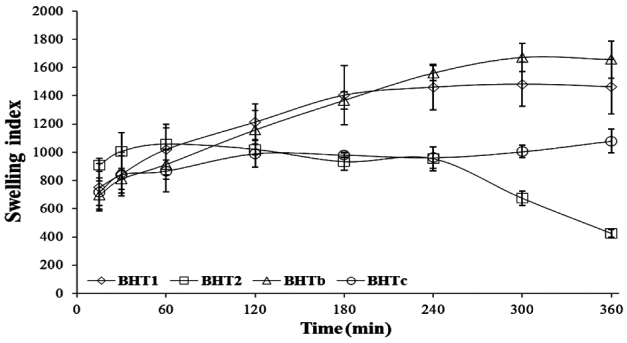

Fig. 1 — Swelling profile of the prepared budesonide films

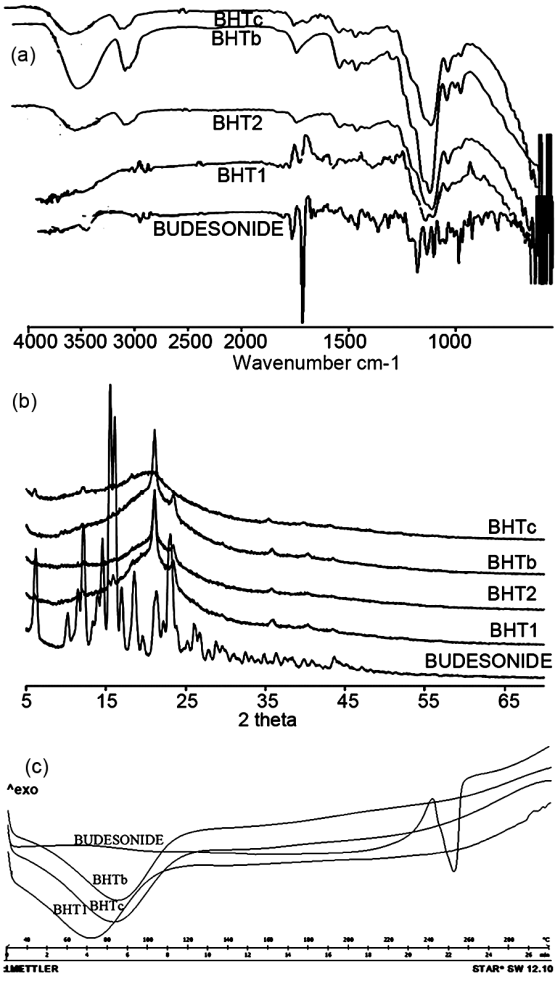

Fig. 2 — Characterization studies of budesonide and the film formulations: (a) FTIR study, (b) DSC study, and (c) XRD study

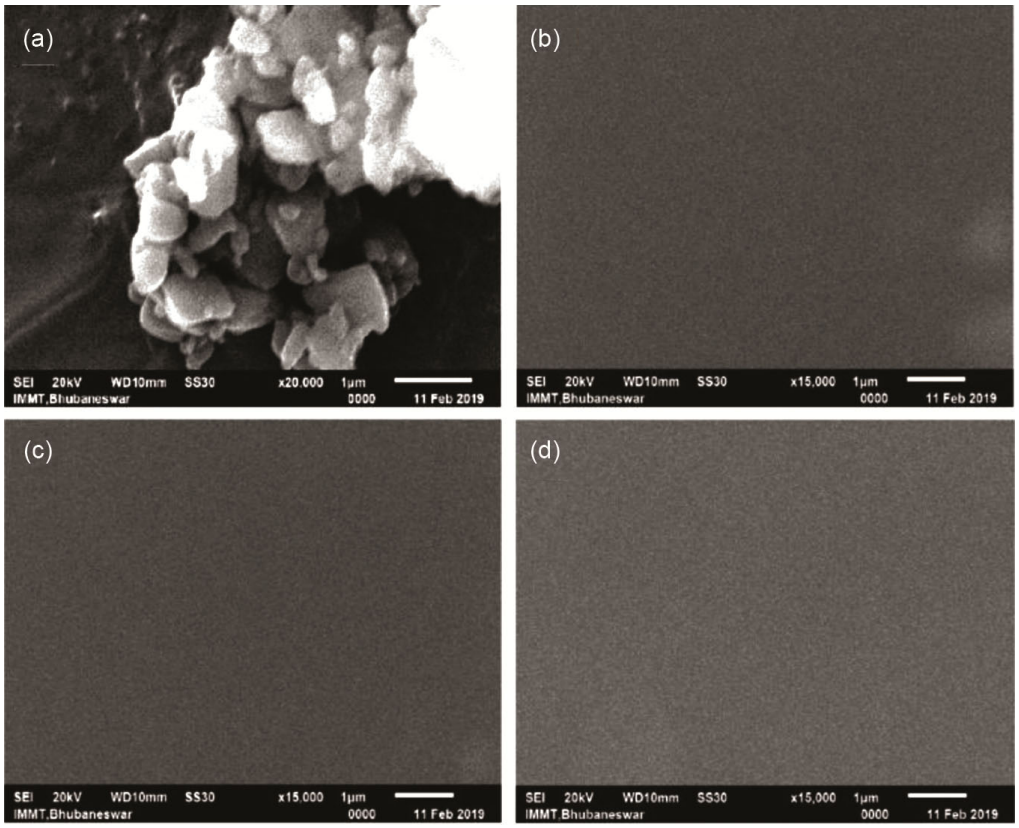

Fig. 3 — Scanning electron microscopy images of Budesonide, BHT_1, BHT_b, BHT_c

A DSC Study

Differential Scanning Calorimetry analysis study was done to characterize the peak (endothermic) of pure drug to know the crystal degradation if any and the behavior in the course of rising temperature. Budesonide showed a sharp endothermic peak at 252.5°C (Fig. 2(b)) indicating crystalline nature of the drug. Thermogram of films exhibited broad endothermic shouldering in the 50–100°C range due to the water evaporation from the HPMC polymeric matrix. But the endothermic peak at and around 252.5°C was absent in the polymeric films. Completely masking of the endothermic peak (Fig. 2) gave the evidence about the almost complete amorphaization of drug in the films.[21]

XRD Analysis

Under X-ray Diffraction (XRD) study, pure budesonide showed high intensity peaks at angle 6.21, 10.18, 11.49, 12.17, 15.53, 16.10, and 22.16° 2θ (Fig. 2(c)). These peaks suggested about the properties of crystallinity of the pure drug. Almost complete absence of characteristic peak in XRD of film formulation suggested about complete complexation and solubilization of drug with polymer. Possibly no crystal structure was practically present in the films.[22]

SEM Analysis

To verify the surface nature and morphology of drug and films SEM technique was used and presented in Fig. 3. Budesonide crystals were of regular geometric structure partly spherical and become visible to have a smooth particle surface (Fig. 3A). But in the polymeric film there was no evidence about crystal structure in the films as shown in Fig 3B, 3C and 3D. Films with and without surfactant showed clear surface due to the complete solubilization of drug in HPMC matrix and seen as empty. DSC, XRD, and SEM analysis also confirmed about the absence of crystal properties in the film.[13,22,23]

***In vitro* Drug Release**

In vitro release profile indicated a clear evidence about the amount of drug released from polymeric matrix film into the dissolution media in the time period of 6 h (Fig. 4). The use of HPMC polymer in the film protected the drug from recrystallization[24] and controlled the release rate. Presence of surfactant

Table 3 — Kinetics of in-vitro drug release and buccal permeation of budesonide film formulation

Code	Drug release					Drug permeation					
	First order	Higuchi		Peppas		Flux (J_s)	First order	Higuchi		Peppas	
	r^2	k	r^2	n	r^2	(μg/min)	r^2	k	r^2	n	r^2
BHT_1	0.95	2.17	0.99	0.47	0.99	0.76 ± 0.25	0.89	1.82	0.98	0.37	0.99
BHT_2	0.97	3.37	0.99	0.56	0.82	0.82 ± 0.15	0.97	2.29	0.98	0.70	0.98
BHT_b	0.92	3.66	0.97	0.48	0.96	0.85 ± 0.02	0.95	2.89	0.99	0.41	0.99
BHT_c	0.885	3.24	0.95	0.34	0.98	0.63 ± 0.20	0.98	1.90	0.98	0.56	0.99

in the formulation (BHT_b and BHT_c) improved the drug release significantly compared to its absence. Benzalkonium in the film (BHT_b) enhanced the drug release even better than the film containing cetrimide (BHTc). Korsmeyer-Peppas equation clarifies the drug release kinetics.[15,25] (Table 3)

$$\frac{M_t}{M_\infty} = Kt^n$$

Here, $\frac{M_t}{M_\infty}$ is the fraction of drug release at time'*t*', *K* is the constant related to system structure and geometry and *n* is the drug release exponent. Budesonide film formulation exhibited the fickian type diffusion controlled release (*n* values 0.34 to 0.56; r^2 values 0.82 to 0.99).[25–27]

Ex vivo Buccal Permeation

Permeation study was carried out to observe the amount of drug transport through the buccal mucosal lining within the 6 h study (Fig. 4) (Table 3).[28] Only the benzalkonium surfactant containing film (BHT_b) enhanced the permeation (57%) to the noteworthy extent than the others. Film BHT_1 and BHT_2 showed permeation up to 35 and 40% respectively. Cetrimide formulation (BHT_c) did not show any remarkable changes compared with BHT_1 and BHT_2. Benzalkonium chloride proved earlier also the penetration enhancing effect by breaking the physiological diffusion barrier layer in ocular delivery of diclofenac.[12] The permeation rate or flux (J_s) also augmented after adding benzalkonium chloride. According to Korsmeyer-Peppas equation kinetics of drug permeation '*n*' value of BHT_1, BHT_b and BHT_c is found as 0.37, 0.41 and 0.56 demonstrating almost fickian type of tissue diffusion ('n' value below or closer to 0.5). Only the cetrimide containing film, BHT_2 followed anomalous or non fickian type of diffusion ('*n*' value was 0.7 i.e., well more than 0.5) indicating partially diffusion controlled and partially erosion controlled process.

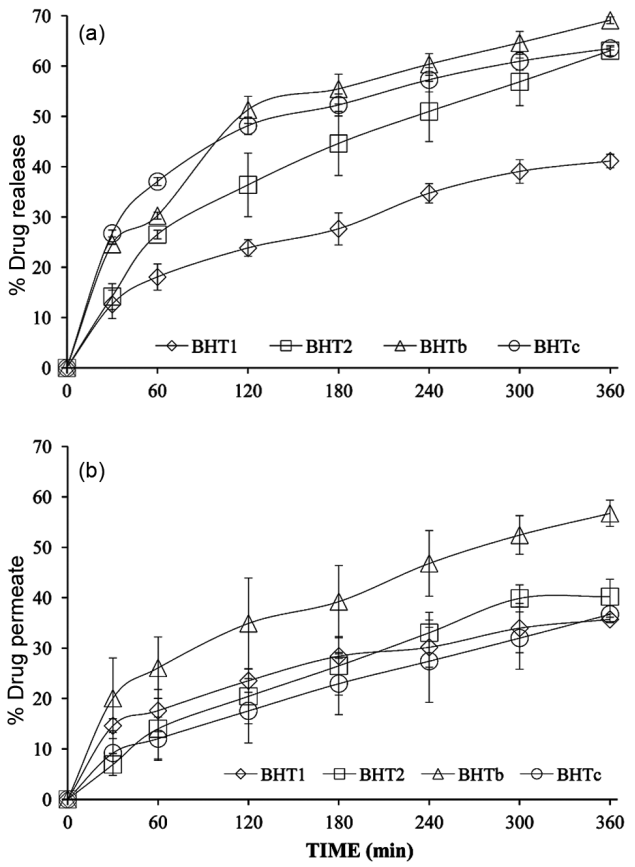

Fig. 4 — *In vitro* and *ex vivo* evaluation of budesonide buccal delivery

Molecular Docking Study

The theoretical molecular docking study indicates a possible complex formation and physical interaction between the drug and carrier, and is related in controlling diffusion of drug.[29] Docking score showing molecular interaction between budesonide and HPMC as the carrier has been presented in Table 4 (Fig. 5). The binding energy value found as −3.1 kcal/mol between the HPMC and budesonide indicates a fairly stable interaction. The shifting of functional group in the FTIR attributed to the formation of hydrogen bonding in between budesonide and HPMC. The higher negative binding

Table 4 — Docking score showing molecular interaction between drug and HPMC as carrier

Mode	Affinity (kcal/mol)	Distance from best mode	
		Rmsdl.b	Rmsdu.b
1	−3.1	0.000	0.000
2	−2.8	5.367	7.780
3	−2.8	6.386	10.486
4	−2.7	2.331	3.587
5	−2.7	2.942	6.020
6	−2.5	5.755	9.713
7	−2.5	2.617	7.556
8	−2.5	3.412	5.156

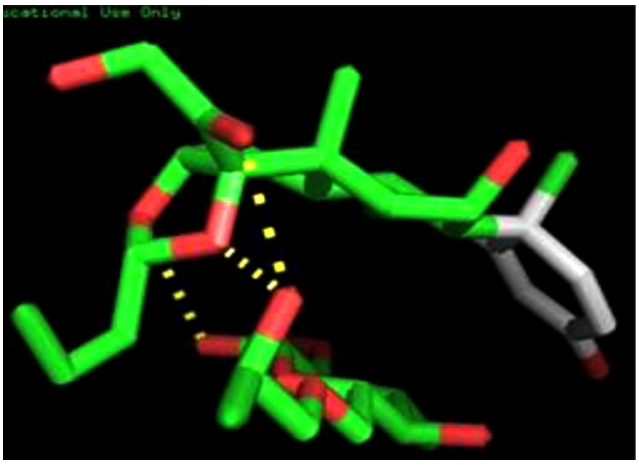

Fig. 5 — Docking interaction between Budesonide and HPMC

energy values indicate stable interactions than that of lower negative values. Lower negative value of molecular docking is the indication of destabilizing interactions.

Conclusions

Budesonide buccal films were prepared using BEZ and CET as quaternary ammonium surfactant in HPMC K15M matrix polymer. Films were found sturdy enough and flexible for buccal administration. Presence of benzalkonium chloride remarkably increased sustained swelling upto a period of 360 min with least erosion. Both the quaternary ammonium surfactant increased remarkably *in vitro* release and buccal permeation. The film containing BZK (BHT_b) has shown both the release and permeation to the highest extent. Molecular docking study also revealed greater (−3.1 kcal/mol) negative binding energy indicating a stable interactions between budesonide and HPMC compared to others. Effect of other quaternary ammonium compounds could only be confirmed after performing the experiment. Many other quaternary ammonium compounds having not only antibacterial, but also antifungal activity such as methacryloyloxy dodecyl pyridinium bromide, dimethylamino dodecyl methacrylate, methacryloyl oxydecyl pyridinium bromide etc. could be attempted for studying the effect on buccal permeation of budesonide in future.

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