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Research Article

DESIGN, *IN VITRO,* AND *EX VIVO* EVALUATION OF BUDESONIDE BUCCAL PATCH USING XANTHAN GUM AS A NATURAL POLYMER MATRIX

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ABSTRACT

Objectives: The present study aimed to formulate sustained-release mucoadhesive buccal patches of bio-pharmaceutical classification class II drug budesonide (BUD) using the mucoadhesive polymer xanthan gum (XG) and the film-forming agent hydroxypropyl methylcellulose (HPMC) E-15.

Methods: To enhance the solubility of BUD, a solid dispersion of BUD (B-SD) was prepared using Soluplus as a solubilizing agent through the solvent evaporation method. Buccal patches of B-SD (BU1–BU9) were formulated using the solvent casting technique. The patches were evaluated for drug content, weight variation, thickness, folding endurance, moisture content, mucoadhesive strength, swelling index, and *in vitro* drug release.

Results: The formulations exhibited statistically significant differences in physical properties ($p<0.05$). Formulation BU9, containing higher polymer concentrations, showed significantly greater swelling index, mucoadhesive strength, and sustained *in vitro* drug release (96.41±0.003%) compared to the pure drug patch (PDP) (40.13±0.015%, $p<0.0001$). Drug release followed a non-Fickian Super Case II transport mechanism. Ex vivo permeation studies of BU9 demonstrated a cumulative permeation of 4.26±0.042 mg/cm^2 with a flux of 0.133 mg/cm^2/h, both significantly higher than the PDP ($p<0.05$). The optimized BU9 patch was further characterized by FT-IR, differential scanning calorimetry, and X-ray diffraction, confirming the absence of drug-excipient interactions.

Conclusion: Buccal patches of BUD can be successfully formulated using XG in combination with HPMC E-15 to achieve sustained drug release with enhanced mucoadhesive and permeation properties.

Keywords: Budesonide, Xanthan gum, Solid dispersion, Mucoadhesive buccal patch, Nocturnal asthma

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INTRODUCTION

Asthma is a persistent respiratory disease that affects 1–18% of the population. Fluctuating symptoms, such as wheezing, shortness of breath, chest tightness, and/or coughing, may be experienced by people with asthma, often accompanied by varying limitations in exhaled airflow [1,2]. Nocturnal asthma is a phenomenon of airway inflammation which occurs due to low plasma cortisol concentrations that occur during the early hours of the day as part of circadian changes [3]. Nocturnal asthma exacerbation is a common and significant phenotype Clinical significance affects more than two-thirds of asthma patients affecting quality of life [4]. This condition is associated with poor asthma control, increased reliance on asthma medications, and a higher risk of asthma-related morbidity and mortality [5,6]. Remarkably, a greater proportion of asthma-related deaths occur during the night compared to the daytime [7]. Therefore, recognizing and addressing nocturnal asthma is vital, as it represents a serious and potentially life-threatening manifestation of the disease. Several factors have been implicated in its nighttime exacerbation, including physiological changes during sleep, circadian rhythm–regulated processes, nocturnal exposure to environmental triggers, and the presence of comorbid medical conditions. Collectively, these contribute to reduced expiratory flow rates and worsening of asthma symptoms at night [8,9]. Oral drug delivery remains the most widely utilized route for systemic administration of pharmaceutical products across various dosage forms [10]. However, its effectiveness is often limited by enzymatic degradation within the gastrointestinal tract and other factors such as first-pass metabolism [11]. In contrast, buccal drug delivery offers an attractive alternative to conventional systemic delivery methods, as the oral mucosa is relatively permeable, highly vascularized, and provides an excellent site for drug absorption [12,13].

Buccal drug delivery enables the direct transport of drug molecules into the systemic circulation, thereby avoids hepatic metabolism and minimizing degradation in the gastrointestinal environment, which are common limitations of oral administration [14,15]. Moreover, the oral cavity is easily accessible, making buccal delivery convenient for self-administration. This approach is considered safe and patient-friendly, as buccal patches can be applied with ease, removed from the site of application when necessary, and discontinued at any time [16].

A high-molecular-weight polymer, xanthan gum (XG), is an extracellular heteropolysaccharide produced by Gram-negative bacterium *Xanthomonas campestris*. It is widely used for modifying drug release properties due to its mucoadhesive nature. Structurally, XG consists of repeating pentasaccharide units and exhibits excellent bioadhesive strength. Due to these properties, it finds extensive applications in pharmaceutical formulations as a thickener, suspending and stabilizing agent, binder, and controlled-release mucoadhesive excipient for oral drug delivery. Furthermore, it is proved to be nontoxic and non-irritant at the recommended levels employed in pharmaceutical excipient [17-21].

Budesonide (BUD) is a well-established corticosteroid used in the treatment of several chronic inflammatory diseases such as obstructive pulmonary disease, Crohn's disease, and asthma. Decades ago, clinical evidences have proved that BUD has the ability to reduce nocturnal symptoms [22]. It belongs to bio-pharmaceutical classification (BCS) – II which has poor solubility but good permeability. Its biological half-life is 2–4 h and has a bioavailability of 9–21% which is poor due to extensive first-pass metabolism [23].

Among the various approaches of enhancing solubility and bioavailability, solid dispersion (SD) is one of the simplest methods

to enhance solubility of BCS class II drugs using different surfactants such as Soluplus and Kolliphor RH40 [24]. For example, the SD of carbamazepine and tolbutamide enhanced the solubility by reducing the particle size [25].

Understanding the importance of the natural polymer xanthan gum (XG) for its excellent mucoadhesive properties in buccal drug delivery systems, the present study employed a fixed and optimized concentration of XG based on prior evaluations. A systematic investigation was subsequently carried out by varying the levels of hydroxypropyl methylcellulose (HPMC) E-15 and polyvinyl alcohol (PVA) to assess their influence on the patch's physical characteristics, drug content, *in vitro* drug release, and *ex vivo* permeation profiles.

METHODS

BUD gift sample was provided by Strides Pharma (Bengaluru, India). Soluplus was obtained by BASF (Mumbai, India). Dialysis Membrane-50 and Xanthan Gum are purchased from HiMedia Lab Pvt. Limited (Mumbai, India). HPMC E15, PVA, propylene glycol (PG), and all other chemicals were procured from SDfine-Chem Ltd (Mumbai, India).

Phase solubility studies

Various concentrations of carriers 0.1%, 0.2%, 0.3%, 0.4%, and 0.5% were prepared, namely, Gelucire44/14, Kolliphor RH40, PEG-6000, and Soluplus using 6.8 pH phosphate buffer solutions. The drug was added to the solution at a constant amount and subjected to agitation on vortex shaker for 20 min at 100 rpm and kept for overnight. Later, the supernatant solution was separated by centrifuging the mixture for 10 min at 10000 rpm. The supernatant solution was then diluted as required and analyzed for the drug content by ultraviolet (UV) spectrophotometer at a wavelength of 246 nm. The phase solubility graph was plotted by BUD solubility on the Y-axis versus carrier concentration on the X-axis [26].

Preparation of solid dispersion of BUD (B-SD)

SD of drug and carrier ratio (1:1) was prepared by solvent evaporation technique. Required quantity of drug and carrier mixed and dissolved in the methanol of known volume. The obtained SD was finally grounded into powder and stored for subjected use [25].

Preparation of buccal patch of BUD

The mucoadhesive buccal patches (MBP) BUD were prepared using the solvent casting method [13,14]. Initially, XG and PVA are mixed and dissolved in hot water. The mixture was then cooled to room temperature and HPMC E-15 and PG were added and dissolved. Separately, the (B-SD) was dissolved in 5 mL of methanol before mixing with the polymer solution. The solution was sonicated to remove air bubbles, poured onto a glass Petri dish, and dried in a hot air oven at 50°C for 5 h. A total of nine formulations from BU1 to BU9 (Table 1) were prepared and the dried patches were stored at room temperature in a desiccator for future experiments.

Evaluation parameters for buccal patch

Thickness and weight of patches

The buccal patches were cut into sections of 2×2 cm^2 and weighed accurately using a digital balance. Their thickness was measured at three different points with the aid of a Vernier caliper. The same procedure was carried out for all nine formulations of the prepared BUD MBP [27].

Drug content uniformity

UV spectroscopic analysis was employed to determine the uniformity of drug content in the patches. From each patch, three different sites were selected, and sections of 1 cm^2 were cut. Each section was dissolved in 100 mL of pH 6.8 phosphate buffer, followed by filtration. The absorbance of the resulting solution was measured at 246 nm using a UV spectrophotometer. The procedure was repeated for three patches from each formulation, and the drug content was subsequently calculated [28].

Folding endurance

Buccal patches containing B-SD were manually measured for their folding strength by repeatedly folding them in the same position until the patch breaks [29].

Measurement of moisture content

Each buccal patch was initially weighed and placed in a desiccator containing anhydrous calcium chloride for storage. After a period of 3 days, the patches were removed and reweighed. The percentage of moisture loss, representing the moisture content, was calculated using Equation (1) [30].

$$Moisture\ content\ \% = \frac{Intial\ wt - Final\ wt}{Intial\ wt} * 100 \quad \text{Eq (1)}$$

Surface pH measurement

To determine the surface pH, three randomly selected buccal patches were placed in a Petri dish containing 5 mL of distilled water and allowed to swell for 1 h. The surface pH of each hydrated patch was measured using a digital pH meter by gently placing the electrode in contact with the surface of the patch. The procedure was performed in triplicate, and the average surface pH was recorded [31].

Measurement of swelling index

Each patch was cut into sections of 2×2 cm^2, and their initial weight (W1) was recorded. The patches were then immersed in pH 6.8 phosphate buffer solution, and at predetermined time intervals of 10 min up to 1 h, they were removed, gently blotted to remove excess surface moisture, and reweighed (W2). The percent swelling index was calculated using Equation (2) [31,32].

$$\%SI = \frac{w2 - w1}{W1} \times 100 \quad \text{Eq (2)}$$

Fourier transform infra-red (FT-IR) spectroscopy

The BUD, excipients, B-SD, and selected buccal patch are subjected to FT-IR analysis using Jasco 460 Plus, Japan. A small amount of sample mixed with equal quantity of KBr is triturated and loaded to the sample cell and scanned in the range of 400–4000 cm^{-1} and functional groups are identified in the infrared spectra [32].

Table 1: Composition of BUD buccal patches

Ingredients	BU1	BU2	BU3	BU4	BU5	BU6	BU7	BU8	BU9
BUD (mg)	15	15	15	15	15	15	15	15	15
Soluplus (mg)	15	15	15	15	15	15	15	15	15
XG (mg)	30	30	30	30	30	30	30	30	30
HPMC E-15 (mg)	100	150	200	100	150	200	100	150	200
PVA (mg)	20	30	40	20	30	40	20	30	40
PG (mL)	1	1	1	1	1	1	1	1	1
Methanol (mL)	5	5	5	5	5	5	5	5	5
Water (mL)	5	5	5	5	5	5	5	5	5

BUD: Budesonide, XG: Xanthan gum, HPMC: Hydroxypropyl methylcellulose, PVA: Polyvinyl alcohol, PG: Propylene glycol, BU1 to BU9:Formulation code

Differential scanning colorimetry (DSC)

DCS analysis of BUD, excipients, B-SD, and selected buccal patch were analyzed by DSC 60-Shimadzu. Samples weighing between 2 and 10 mg into aluminum pans, which were then sealed underwent heating within a temperature range of 25–300°C at a rate of 4°C/min, all while maintaining a nitrogen atmosphere [33].

Powder X-ray diffraction (XRD)

XRD analyses of BUD, excipients, B-SD, and selected buccal patch were analyzed using the Rigaku Miniflex 600 (5th gen). The samples were examined utilizing Ni-filtered Cu ka radiation at 40 kV/15 mA, covering a 2θ range of (5–80)°C [34].

Ex vivo mucoadhesive strength

The modified two-arm balance technique was adopted to determine adhesive strength [27]. The buccal mucosa of a goat was obtained from a nearby slaughterhouse. A 2 mm thick mucous membrane was prepared after removing fat and loose tissue. After rinsing with distilled water and a pH 6.8 phosphate buffer at 37°C, piece of buccal mucosa using cyanoacrylate glue was attached to the bottom of a smaller glass beaker. A buccal patch was attached to the balance's left-hand side pan brought into touch with the mucosa and covered with adhesive tape. After holding the balance in place for 5 min, the right side pan's weight was steadily added until the patch came away from the mucosal surface. Mucoadhesive strength, reported in grams, represents the weight required to separate the mucosa from the patch. Three duplicates of each experiment were run, and average results were reported.

In vitro drug release studies

In vitro release was carried out by Franz diffusion cell. The receiving chamber was filled with Phosphate buffer solution with a pH of 6.8 and it was heated to 37±0.5°C with a water jacket and stirred with a magnetic stirrer with 50 rpm to ensure the sink conditions [36]. The dialysis membrane, rinsed with phosphate buffer solution with pH 6.8, was placed between the donor and receptor compartments. The patch was cut 2*2 cm^2 and placed on the dialysis membrane which was rinsed with phosphate buffer and at regular intervals, 5 mL sample was pipette out and replaced by fresh volume of phosphate buffer solution with a pH of 6.8 till 8 h. The drug concentration in the sample was analyzed by spectroscopy at 246 nm.

Kinetics of drug release

Dissolution data of selected formulation BUD9 were fitted into first-order, zero-order, Higuchi model, Korsmeyer-Peppas model, and Hixson Crowell model to determine the mechanism of drug release. The model which gives the highest values of correlation coefficient suggests the release mechanism. The best-fitting model is the model with the highest correlation coefficient [37,38].

Ex vivo permeation study

The *ex vivo* permeability study of the BUD9 buccal patch formulation and buccal patch with pure drug was performed using the Franz diffusion cell method [27,35]. Each patch was cut into 2*2 cm^2 and a diffusion area of 0.75 cm^2 and a pH 6.8 phosphate buffer solution was used to fill the receptor chamber, which was then heated to 37±0.5°C using a water jacket and then stirred with a magnetic stirrer. Fix freshly excised goat buccal mucosa between the donor and receptor chambers the patch was placed. During the experiment, at regular intervals, 5 mL of sample was taken and replaced with fresh new volumes of 6.8 pH of phosphate buffer solution. Drug concentrations in the samples were analyzed by Shimadzu UV spectrophotometry against the blank at the 246 nm.

Statistical analysis

As per the study requirements, the experimental data were analyzed using Student's t-test or analysis of variance (ANOVA), followed by appropriate *post hoc* tests, employing GraphPad Prism version 10.6.1. The statistical significance of differences among the formulations was determined at $p<0.05$.

RESULTS AND DISCUSSION

Phase solubility study

Since budesonide (BUD) belongs to BCS Class II, a solid dispersion technique was adopted as one of the approaches to enhance its solubility [33]. From the literature search, various carriers were selected such as PEG-6000, Kolliphor RH40, Gelucire 44/14, and Soluplus and BUD phase solubility was conducted. The results are depicted in Fig. 1. As the carrier amount increases, the solubility of the drug also increases. At the highest concentration of carrier (5%w/v), Soluplus exhibited the highest solubilizing (0.782±0.001), followed by the Kolliphor RH40 (0.467±0.006), Gelucire 44/14 (0.294±0.001), and PEG-6000 (0.107±0.004). Based on this phase solubility, Soluplus was selected for the preparation of SD (1:1).

Formulation of buccal patch

During the preliminary formulation of transdermal patches aimed at increasing the proportion of natural polymers, XG was incorporated at concentrations ranging from 10 mg to 50 mg, by keeping the polymer quantities of HPMC E-15 and PVA constant. It was observed that patches containing more than 30 mg of XG exhibited excessive stickiness, which caused handling difficulties and rendered them unsuitable for practical application. Therefore, 30 mg of XG was selected as the optimal concentration, as it offered an appropriate level of adhesiveness while preserving the physical integrity of the patches. With this concentration fixed, subsequent formulations were developed by varying the ratios of HPMC E-15 and PVA (Table 1) to improve mechanical strength, enhance flexibility, and optimize drug release characteristics, ultimately leading to a more efficient and manageable transdermal delivery system.

Characterization of buccal patch

All the formulated buccal patches were evaluated for folding endurance, average weight, thickness, drug content, surface pH, moisture content, swelling index, and mucoadhesive strength. The results are presented in Table 3 and Figs. 2 and 3. The average weight of BUD buccal patches ranged from 86.19±0.95 to 96.32±1.22 mg, while the thickness varied between 0.66±0.02 and 0.80±0.05 mm. An increase in thickness was observed with higher concentrations of XG and HPMC E-15, which may be attributed to the greater viscosity of XG. The denser gel formed during casting likely resulted in thicker patches [20].

The drug content in each 1 cm^2 patch ranged from 85.23±0.006% to 98.65±0.021%, indicating uniform drug distribution throughout the polymeric matrix. Folding endurance values were between 285 and 359, with higher concentrations of HPMC E-15 and XG leading to improved flexibility. This suggests that the patches were not brittle, as HPMC E-15 functioned as a film-forming agent, while PG acted as a plasticizer [39]. The surface pH values of the patches were

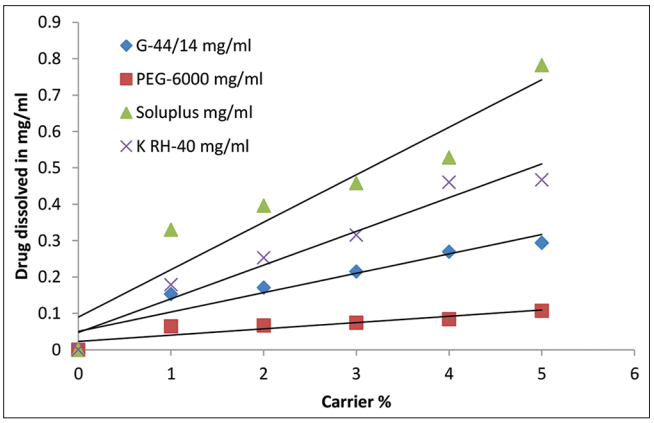

Fig.1: Phase solubility study using different carriers

Table 2: Physiochemical properties of BUD buccal patches

Parameters	BU1	BU2	BU3	BU4	BU5	BU6	BU7	BU8	BU9	Analysis of variance	
										F-value	p-value
Thickness (mm)	0.67±0.02	0.66±0.02	0.66±0.01	0.75±0.01	0.77±0.02	0.80±0.02	0.80±0.03	0.80±0.03	0.80±0.02	43.61	<0.0001
Weight Variation (mg)	86.19±0.95	91.05±1.50	91.17±1.19	91.20±1.57	91.54±0.79	92.34±0.82	94.42±0.61	95.08±1.00	96.32±1.22	21.16	<0.0001
Folding endurance	285	310	320	330	338	315	345	350	359	--	--
Drug content (%)	85.23±0.01	94.12±0.06	95.18±0.02	96.32±0.01	93.12±0.03	96.08±0.01	97.02±0.06	98.02±0.03	98.65±0.02	15.86	<0.0001
Moisture content (%)	1.11±0.05	1.29±0.03	1.18±0.09	1.29±0.03	1.14±0.06	1.29±0.02	1.44±0.07	1.59±0.02	1.62±0.03	34.74	<0.0001
Surface pH	6.7±0.04	6.7±0.11	6.8±0.09	6.8±0.11	6.9±0.05	6.8±0.14	6.9±0.08	6.8±0.09	6.9±0.12	1.826	0.1375

p<0.05 indicates significantly different from each other, all values are mean±standard deviation, n=3

Table 3: Kinetic release study of selected buccal patch BU9

Release model	R^2
First order	0.9582
Zero order	0.9084
Korsmeyer–Peppas	0.9775
Higuchi	0.7388
N	1.44

found to be within the range of 6.5–7.4, which closely matches the buccal environment, indicating that the formulations are unlikely to cause mucosal irritation [29]. The moisture content ranged from 1.11±0.005% to 1.62±0.035%. The relatively low moisture levels are advantageous, as they reduce the risk of microbial contamination and help maintain the stability of the patches by preventing them from becoming dry and brittle [40]. Statistical analysis using ANOVA confirms that the variations in thickness, weight, drug content, and moisture content of buccal patches BU1 to BU9 are significantly different from each other, as indicated by p<0.05. This demonstrates that polymer concentration significantly affects these critical parameters, justifying its impactful role in formulation quality and consistency. In contrast, p-value for surface pH is >0.05, indicating that polymer concentration does not have a significant effect on the surface pH of the patches. This suggests that while formulation variables strongly influence the physical and chemical properties of the patches, they do not alter the patch surface pH within the tested range, supporting the suitability of the patches for buccal administration.

Swelling index

The swelling behavior of mucoadhesive patches is crucial for both mucosal attachment and controlled drug release. At 37°C, the swelling ratio of BUD buccal patches after 1 h ranged from 205% to 273%, as shown in Fig. 2. It was observed that increasing concentrations of XG and HPMC E15 led to higher swelling indices. This effect is likely due to the hydrophilic and ionic characteristics of XG, which enhance water affinity and promote gel layer formation through hydrogen bonding with water molecules.

Statistical comparison using one-way ANOVA demonstrated a highly significant difference in swelling index among the nine formulations ($F[8,18]=322.4$, $p<0.0001$), with an R^2 value of 0.9931, indicating that nearly all the variance in swelling index can be explained by the formulation differences. These data confirm that compositional modifications particularly the proportions of XG and HPMC substantially influence the hydration properties and swelling capacity of the patches [41].

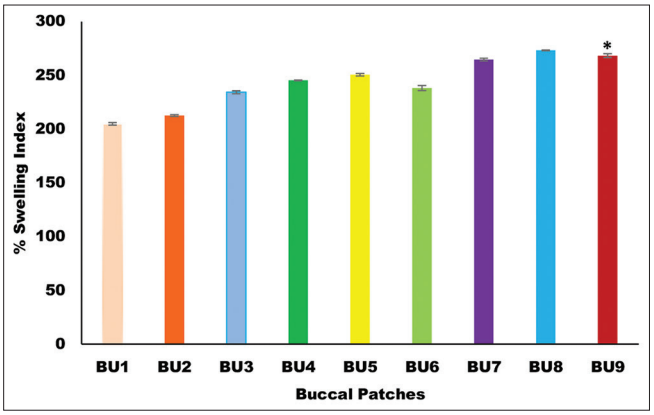

Fig. 2: Swelling index of budesonide buccal patches, n=3, all values are mean±standard deviation, *p<0.05

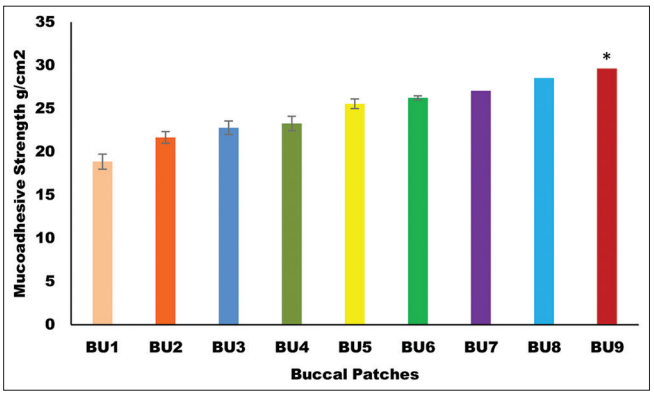

Fig. 3: Mucoadhesive strength (g/cm²) of budesonide bucal patches, n=3, all values are mean±standard deviation, *p<0.05

***Ex vivo* mucoadhesion strength**

The mucosal adhesion strength for buccal patch formulations BU1–BU9 ranged from 18.88±1.24 to 29.64±0.69 g/cm², as displayed in Fig. 3. Formulations BU8 and BU9 showed the highest adhesion strength values (28.55±0.59 and 29.64±0.5 g/cm²), which may be attributed to their greater swelling capacities (273% and 268%, respectively). Enhanced swelling increases the contact area and polymer hydration, leading to stronger mucosal adhesion at the application site.

Statistical analysis using one-way ANOVA demonstrated a significant difference in mucosal adhesion strength among the nine formulations

(F[8,9]=32.93, p<0.0001). These results indicate that formulation composition has a substantial effect on bioadhesive properties, highlighting the superior performance of BU8 and BU9 over the others. The findings are consistent with the hypothesis that increased swelling index directly supports stronger mucosal adhesion [42].

In vitro release studies

The *in vitro* drug release from BUD buccal patches was evaluated using a Franz diffusion cell. Among the nine formulations (BU1–BU9), the percentage drug release ranged from 76.49% to 96.41% after 76.49% to 96.41%. add (Fig. 4). Notably, formulations BU1, BU2, and BU3 disintegrated within 7 h likely due to reduced patch thickness, whereas BU4 to BU9 remained intact for over 8 h, enabling longer sustained release. Statistical analysis using one-way ANOVA revealed a significant difference in drug release among the formulations ($F[6,14]=185.52$, $p=1.61\times10^{-12}$), confirming that formulations are significantly different from each other ($p<0.05$). *Post hoc* analysis further demonstrated that the drug release from BU9 (96.41%) was significantly higher than that from the other formulations and from the pure drug patch (PDP) (40.13%±0.015) with $p<0.001$.

Sustained release was evident in all patches, primarily attributed to the presence of hydrophilic polymers XG, HPMC E15, and PVA which swell on contact with the dissolution media, forming a viscous gel layer that modulates and prolongs drug diffusion from the matrix. This behavior is consistent with previous literature, where hydrophilic matrices facilitate controlled drug release through a combination of swelling, diffusion, and gradual erosion. Specifically, the polymers' water-absorbing properties enable the formation of hydrated gel layers, which act as diffusion barriers, effectively sustaining drug release over extended periods [11,15,17]. The superior performance of BU9 in terms of both release profile and solubility enhancement compared with the pure drug can be attributed to the incorporation of B-SD, which optimizes both matrix swelling and drug diffusion.

Ex vivo permeation study

Formulation BU9 which exhibited significantly greater ($p<0.05$) swelling index, mucoadhesive strength, and *in vitro* drug release in comparison with other formulations was subjected to further evaluations. *Ex vivo* drug permeation studies for the selected buccal patch formulation BU9 were performed using goat buccal mucosa mounted on a Franz diffusion cell over an 8-h period, directly comparing BU9 to a PDP. The cumulative amount of drug permeated per unit area and the steady-state flux are evaluated and presented in Fig. 5. The BU9 formulation achieved a cumulative drug permeation of 4.26±0.08 mg/cm^2 and a steady-state flux of 0.133 mg/cm^2/h, substantially higher than the PDP, values of 2.03±0.08 mg/cm^2 and 0.06 mg/cm^2/h, respectively. The difference between these patches was statistically analyzed using an unpaired t-test with $p<0.0001$. This result confirms the highly significant difference between the two formulations. These findings confirmed the crucial role of the Soluplus® carrier in improving drug solubility and permeation. Furthermore, a comparison of the *ex vivo* permeation results with *in vitro* diffusion studies revealed that drug diffusion through goat buccal mucosa (4.65 mg/cm^2) was lower than through a dialysis membrane (5.2 mg/cm^2), likely due to the epithelial barrier in the mucosal tissue impeding drug diffusion [43].

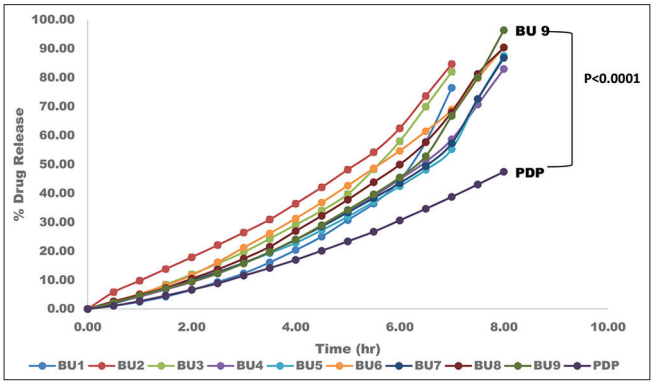

Fig. 4: *In vitro* drug release of budesonide patches using 6.8 phosphate buffer, n=3, all values are mean±standard deviation

FT-IR spectroscopy analysis

FT-IR of drug, polymers, SD, and BU9 formulation was performed to confirm the drug-polymer compatibility. The FT-IR spectra of pure drug (BUD) exhibited different peaks at 3498.24 due to Ar-CH, 3092.1 due to O-H and 1722.12 due to C=O. All these peaks of pure drug retained to their respective places in SD and in selected formulation BU9 which indicates that there is no drug-excipient interaction, as shown in the Fig. 6.

XRD

The XRD profile of pure BUD drug in Fig. 7 showed a strong and intense peak, at 2θ diffraction of 5.96°,12.1°,15.9°, and 22.76° in the range of 24°C, indicating its crystalline nature [44]. The diffraction images of the excipients Soluplus, PVA, HPMC E-15, and XG, as shown in Fig. 7, did not have sharp peaks but showed large and broad peaks, proving that the excipients have amorphous characteristics. The XRD pattern of the SD shows a sharp decrease in peaks intensity, indicating a change from crystalline to amorphous form, [25] which is responsible for the enhanced solubility of BUD in pH 6.8 phosphate buffer. The lack of a drug peak in the formulation in Fig. 7(g) indicates that BUD may be converted to completely amorphous.

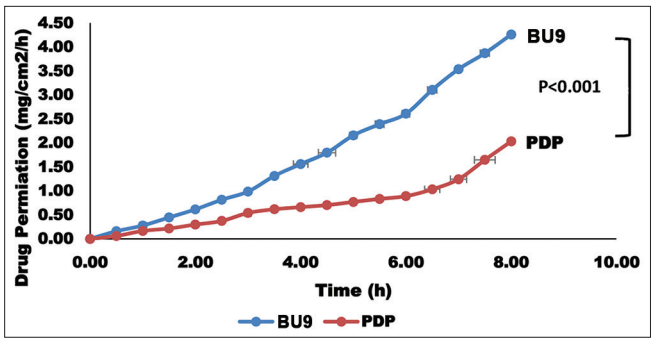

Fig. 5: *Ex vivo* permeation of selected BU9 and PDP for 8 h in 6.8 Phosphate Buffer, n=3, mean±standard deviation

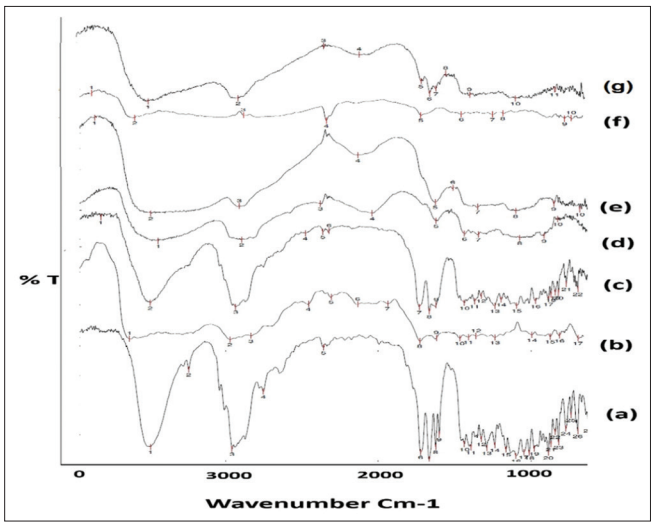

Fig. 6: Infrared spectra (a) Budesonide, (b) Soluplus, (c) solid dispersion of budesonide, (d) hydroxypropyl methylcellulose E 15, (e) xanthan gum, (f) polyvinyl alcohol, and (g) BU9

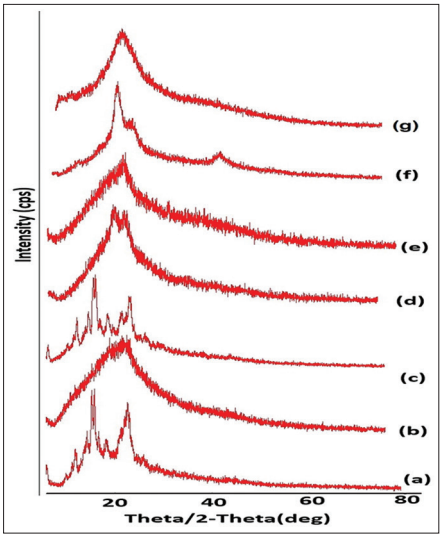

Fig. 7: X-ray diffraction spectra (a) Budesonide, (b) Soluplus, (c) solid dispersion of budesonide, (d) hydroxypropyl methylcellulose E 15, (e) xanthan gum, (f) polyvinyl alcohol, and (g) BU9

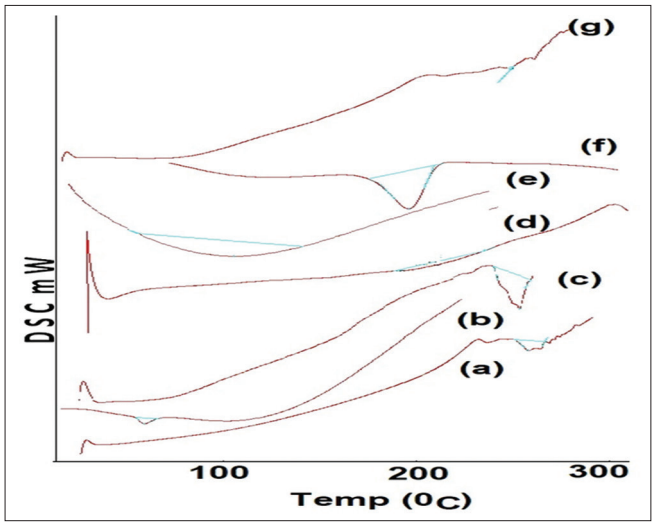

Fig. 8: DSC spectra (a) Budesonide (BUD), (b) Soluplus, (c) solid dispersion of budesonide, (d) hydroxypropyl methylcellulose E 15, (e) xanthan gum, (f) polyvinyl alcohol, and (g) BU9

DSC

DSC thermographs of BUD, B-SD, excipients (HPMC E-15, XG, Soluplus, and PVA), and formulation BU9 are represented in Fig. 8. The thermogram of BU showed an endothermic melting peak at 258°C, in good agreement with previous research, as shown in Fig. 8, which confirms the crystallinity and melting point of pure drug [35].

The decrease in peak intensity of drug in SD can be attributed to miscibility of drug and carrier and reduced crystalline properties of the drug. Similarly, in DSC of the formulation BU9, it was observed that the drug peak has been broadened and which may be due to the presence of other excipients and also may be due to conversion of drug from crystalline form to amorphous form [25,33].

Drug release kinetics studies

The selected BU9 patch is subjected to kinetic models including – Korsmeyer–Peppas, Higuchi, first order, and zero order. The best fit model was found to be Korsmeyer–Peppas (Fig. 9) with R^2 value of 0.9862 and "n" value from Peppas model was found to be 1.44. The

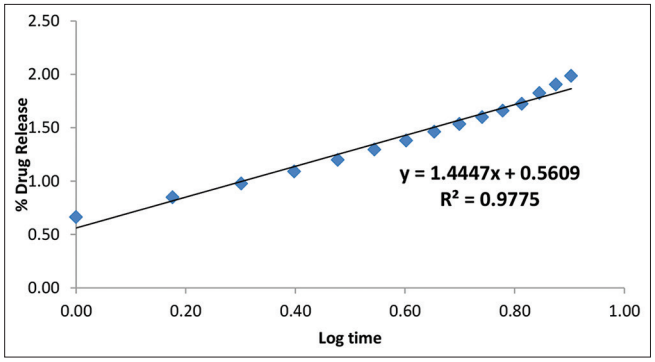

Fig. 9: Kinetic release of selected buccal patch BU9 (Korsmeyer–Peppas model)

R^2 value and "n" value (Table 3) confirmed that drug release follows complex release kinetics with non-Fickian Super Case II transport mechanism, where drug release is governed largely by polymer matrix relaxation and swelling rather than simple diffusion over a period of 8 h for buccal patch BU9 [38,45,46].

CONCLUSION

Prolong drug release BUD MBP was successfully prepared using XG as the mucoadhesive polymer and HPMC E-15 as the film-forming agent. To enhance BUD solubility, a B-SD with Soluplus was prepared by solvent evaporation method. MBPs of B-SD (formulations BU1-BU9) were created using solvent casting and evaluated for thickness, folding endurance, weight variation, drug content, moisture content, mucoadhesive strength, swelling index, *in vitro* drug release, release kinetics, and *ex vivo* permeation.

Among all the formulation BU9 exhibited superior patch properties and sustained *in vitro* drug release of 96.41±0.003% as compared to PDP 40.13±0.015% following zero-order release kinetics of non-Fickian transport.

AUTHORS' CONTRIBUTIONS

Preethi G. B.: Conceptualization, experimental planning, and manuscript editing. Subham Roy: Experimental execution and manuscript writing.

CONFLICTS OF INTEREST

Nil.

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