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**RESEARCH ARTICLE**

# Preparation and *In vitro, Ex vivo* Evaluation of Benzidamine Hydrochloride Loaded Fast Dissolving Oral Strip Formulations: Treatment of Oral Mucositis Due to Side Effects of Chemotherapy and Radiotherapy

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**Abstract:** ***Background*:** Rapidly dissolving oral strips have many advantages, especially in pediatric and geriatric use. Benzydamine hydrochloride is an active substance with local analgesic, anesthetic, antimicrobial and non-steroidal anti-inflammatory properties.

***Objective*:** The aim of the study was to formulate and characterize orally dispersible benzydamine hydrochloride-loaded fast dissolving oral strips for the sufficient treatment of oral mucositis with high loading capacity as well as high patient compliance considering ease of use.

***Methods*:** Oral strips were prepared by solvent casting method with many different polymer combinations and evaluated for different characteristics. *In vitro and ex vivo* characterizations were performed.

***Results*:** In appearance oral strips were smooth and they were also uniform in thickness and weight. The release rates of the active agent from oral strips reached 100% within 25 minutes. The disintegration time was within the range of 15.5 ± 1.2 seconds. Due to *ex vivo* permeation studies steady-state flux of benzydamine hydrochloride in simulated saliva and pH 6.8 were found to be 27.1 μg $cm^{-2}$ $h^{-1}$ ± 1.4 and 26.2 μg $cm^{-2}$ $h^{-1}$ ± 1.7, respectively. No significant difference ($p$>0.05) in permeability studies was observed using pH 6.8 phosphate buffer compared to simulated saliva.

***Conclusion*:** Active agent was successfully loaded into the strips and the targeted system was successfully performed. Benzydamine hydrochloride as oral strips can be a better solution for the efficient treatment of oral mucositis for cancer patients during chemotherapy and radiotherapy stages.

**Keywords:** Benzydamine hydrochloride, oral strip, hydroxypropyl methylcellulose, wound healing, cancer treatment, HPLC.

## 1. INTRODUCTION

Chemotherapy and radiotherapy are frequently used methods for the inhibition of the proliferation of cancer cells for the treatment of various types of cancer [1, 2]. However, both chemotherapy and radiotherapy have severe side effects on epithelial cells of the oral mucosa [3]. Since epithelial cells of oral mucosal have the ability to divide more rapidly than other cells, chemotherapeutic agents suppress the growth and maturation of oral mucosal cells and disrupt the primary mucosal barrier in the mouth and throat to a great extent [4]. Moreover, oral mucositis develops during the therapy resulting in disruption of the mucosal barrier, weakening of epithelial cells, erythema, edema, bleeding, frequent ulcerations, hoarseness, even difficulty in speaking, chewing and swallowing [5]. The use of opioid analgesics increases due to pain of the mucositis and the transition to total parenteral nutrition might be needed due to the mucositis-related oral nutritional problems [6]. In addition, oral mucositis enhances the incidence of opportunistic infections which result in extended hospitalization with increased treatment costs as well as increased mortality rates due to enhanced incidence of sepsis [7]. In addition, for severe cases alteration of the treatment might be needed with reduced doses for enhanced patient compliance which will affect the whole treatment strategy [8].

Considering the ease of application, versatility, applicability of different dosage forms (such as powders, tablets, capsules, elixirs, syrups, emulsions *etc*.) oral route remained one of the most preferred routes for the treatment of such severe conditions [9]. The biggest disadvantage of this route is the difficulty in swallowing or chewing solid dosage forms, especially for pediatric and geriatric patients [10, 11]. Many cases of choking have been reported due to fear of swallowing, therefore sometimes alternative routes are required [12]. To overcome the associated difficulties , oral application of drug delivery systems has led to the development of several rapidly dissolving drug delivery systems [9]. Without the need for water or chewing to aid swallowing, these fast-dissolving drug delivery systems can

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dissolve or disintegrate in a patient's mouth within seconds or minutes [9].

The physical and mechanical properties of the oral strips mostly depend on the characteristics of film-forming polymer. The selection of polymer, therefore, is one of the most important and critical parameters for the development of fast-dissolving oral strips [10]. A variety of polymers are available for the preparation of oral fast-dissolving strips. The polymers can be used alone or in combination to obtain the desired strip properties [9-11]. HPMC has been used extensively in different formulation studies due to its good film forming properties properties [9, 13].

Benzydamine hydrochloride; 3-(1-benzylindazol-3-yl)oxy-N,N-dimethylpropan-1-amine;hydrochloride (BNZ) is an indazole analogue and a member of non-steroidal anti-inflammatory drugs (NSAID). BNZ has analgesic, antipyretic, and anti-edema properties besides its anti-inflammatory effects. BNZ does not inhibit cyclooxygenases (COX); however, it stabilizes membranes which reveal a local anesthetic effect. BNZ also inhibits the production of pro-inflammatory cytokines. Inhibition of the generation of reactive oxygen species results in the inhibition of leukocyte aggregation and adhesion; which reveals the antimicrobial properties [13-15]. Although many studies were carried out over the years for the prevention and treatment of oral mucositis, no accepted standard treatment is present yet [16]. BNZ is prescribed as a mouthwash as a standard application. It can be used both for the prevention and treatment of mucositis. Therefore, the aim of the study was to formulate and characterize orally dispersible BNZ-loaded oral strips (OS) for the sufficient treatment of oral mucositis with high loading capacity as well as high patient compliance considering ease of use.

## 2. MATERIALS AND METHODS

Benzydamine hydrochloride (BNZ) was donated by Deva İlaç (Istanbul / Turkey).

Hydroxypropyl methylcellulose (HPMC; mA:10000, mA:90000, mA:120000), Kollicoat IR (BASF Pharma), Xanthan gum, Methanol, Monobasic potassium phosphate, Polyethylene glycol-400 (PEG-400), phosphate buffer tablets (pH 6.4, pH 6.8, pH 7.4), Polyvinyl alcohol (PVA), Pullulan, Polypropylene glycol, Polyvinylpyrrolidone (PVP), Citric acid, Sodium alginate instacoat, Sodium phosphate dibasic, Sodium hydroxide, Sorbitol, Ethanol and Glycerol 85% purchased from Sigma-Aldrich (St Louis, MO, USA). Deionized water was used in all experiments (Milli-Q Academic, Millipore, Molsheim, France). All other chemicals were of analytical grade.

### 2.1. Experimental

#### *2.1.1. Preparation of Benzydamine Hydrochloride Oral Strip*

OS formulation containing BNZ was prepared by solvent casting method with different polymers and film-forming agents which were shown in Table **1** [17, 18].

Briefly, an aqueous solution was prepared by dissolving film-forming polymer and plasticizer in a specific proportion in distilled water maintained at 70°C and was stirred (250 rpm) for 2 h with a magnetic stirrer. The obtained dispersion was then cooled down to 30°C. BNZ, sweetening agent, saliva stimulating agent and plasticizers were then added in the required quantity as given in Table **1**. The dispersion was stirred for 1 h and cooled down to room temperature. The dispersion was used after at least 12 h of rest to remove all the air bubbles entrapped. The resulting mixture was poured into multi-compartment and single-compartment petri dishes and allowed to dry in a hot air oven at 50°C ± 1°C for 12 h, the dried batch was carefully removed and cut into strips. Each strip has a surface area approximately of 4 $cm^2$ (2 cm×2 cm) and loaded with 2 mg of BNZ and preserved in well closed containers until being analyzed [19-21].

### 2.2. Evaluation of Oral Strips

#### *2.2.1. Thickness*

The thickness of the strips was measured with a micrometer screw gauge (China Factory, Guangzhou, China). Each strip was measured from different locations (centre and four corners) and the average thickness of 6 measurements was calculated [22].

#### *2.2.2. Folding Endurance*

Folding strength in strips was determined by folding the strip (4 × 4 cm) at the same location repeatedly until the strip breaks into two. The number of folding times without breaking was calculated and evaluated with the folding strength/endurance value [20, 23].

#### *2.2.3. Surface pH*

The surface pH of BNZ oral strips was measured by using a combined pH electrode. The strip was slightly wetted with 2 drops of water and pH was measured by contacting the surface of the strip. The experiments were performed three times.

#### *2.2.4. Elongation Percentage*

The elongation percentage was determined by noting the length before rupture, according to the formula given at Eq. (1).

$$\text{Elongation percentage} = [(L1-L2)/L2] \times 100 \quad (1)$$

Where, L1 is the final length of each strip and L2 is the initial length of each strip [24].

#### *2.2.5. Disintegration Time*

Disintegration time was measured in an artificial saliva medium at room temperature (25°C ± 2°C) by placing six strips (2 cm × 2 cm) in United State Pharmacopoeia (USP) disintegrating test apparatus (DIST 3 Pharma Test, Germany) [10, 25].

#### *2.2.6. Moisture Loss*

The strips were accurately cut and weighed to determine the percent moisture loss in the 4 $cm^2$ surface area. Strips were accurately weighted and stored in a boiled anhydrous calcium chloride desiccator for 72 hours [22]. At the end of

**Table 1. Formulations of BNZ-loaded OS.**

| Polymers | Polymer (% w/w) | BNZ (% w/w) | Sorbitol (% w/w) | Glycerol (% w/w) | Citric Acid (% w/w) | Tween 80 (% a/a) | Alcohol (% w/w) | Water (% w/w) |
|---|---|---|---|---|---|---|---|---|
| **HPMC-1** | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | 40 | 40 |
| HPMC-9 | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | 40 | 40 |
| HPMC-12 | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | 40 | 40 |
| Pollunan | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | 40 | 40 |
| Collicoat-IR | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| Eudragit S-100 | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| Eudragit RS-100 | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| Xanthan Gum | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| Carragen | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| PVP | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| HPMC-1+ PEG 400 | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| HPMC-9+ PEG 400 | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| HPMC-12+ PEG 400 | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| PVA + PVP | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| MCC | 10 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| Pollulan + PVA | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| HPMC-1 + Pollulan | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| HPMC-9 + Pollulan | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| HPMC-12 + Pollulan | 5+5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |
| Pollulan + Xanthan Gum + Carragen+ PEG 400 | 2.5+2.5+2.5+2.5 | 1.5 | 2.5 | 5 | 0.5 | 0.5 | - | 80 |

the period, the strips were removed and weighed again, and the percentage of moisture loss of the strips was calculated using Eq. (2).

Percent moisture loss = (Initial weight - Final weight) / Initial weight × 100 (2)

### *2.2.7. Drug Content and Content Uniformity*

Each strip (2 cm × 2 cm) was taken into a 100 mL volumetric flask containing phosphate buffer pH 6.8 and shaken continuously for 20 minutes. The solution was filtered through a 0.22 µm filter and absorbance was measured at 306 nm for the determination of the BNZ amount [10].

### *2.2.8. In vitro Drug Release Test*

The strips were placed in the containers of the dissolution apparatus (PT-DT 70 Pharmatest, Germany). The test medium was 900 mL of phosphate buffer (pH 6.8) at 37°C ± 1°C, speed set at 100 rpm. At the predetermined time intervals, samples were withdrawn, filtered through a 0.45 µm membrane filter and assayed at 306 nm using a Shimadzu UV Vis-160A (Shimadzu, Kyoto, Japan). Then, cumulative drug release percent was calculated [26].

### *2.2.9. Evaluation of Release Kinetics*

Data obtained in the *in vitro* release studies was further investigated for release kinetics using the DDSolver software program. DDSolver computer program was used to shorten the calculation time, eliminate calculation errors and determine the correct release profile [27, 28]. After obtaining the release profiles, data were transferred to the DDSolver program to determine the four most important and popular criteria: coefficient of determination ($R_{sqr}$, $R^2$, or COD), adjusted coefficient of determination ($R_{sqr_adj}$ or $R^2_{adjusted}$), Akaike Information Criterion (AIC), Model Selection Criterion (MSC). The highest $R^2$, $R^2_{adjusted}$ and MSC values and the lowest AIC values were used for evaluating kinetic models [29].

### *2.2.10. Ex vivo Permeation Studies*

Permeation studies were carried out with Franz diffusion cells [30]. Oral mucous membranes of the sheep were used as membrane in Franz diffusion cell analyses. Oral mucous

membranes were collected from the local slaughterhouse in Eskisehir just after sacrification. The mucosa was separated from the fat and muscle tissues and washed with 0.9% NaCl solution was stored in the formaldehyde solution in the freezer. Analyses were performed in pH 6.8 buffer and simulated saliva fluid (SSF). The procedure followed is the same for pH 6.8 buffer and SSF (2.38 g $Na_2HPO_4$, 0.19 g $KH_2PO_4$, and 8.00 g NaCl per liter of distilled water adjusted with $H_3PO_4$ to pH 6.8, with stirring for 24 h and filtered using 0.45 µm membrane filter [18]). The mucosa was soaked with receptor compartment SSF/pH 6.8 buffer) 24 h before the experiment. Experimental work was started by placing the oral mucosa into the Franz diffusion cells (Hanson vertical diffusion cells part #58-001-455). pH 6.8 (≈ 3.5 mL)/SSF was placed in the receptor compartment. Prepared strips (4 $cm^2$) were placed in the donor compartment and a 100 µL receptor compartment was added to the strips. The volume of (3.5 mL) was used as the receptor phase in order to examine the penetration of the active substance from the prepared formulation through the oral mucosa of the sheep. Analysis results were evaluated according to Eq. (3).

$$J_{ss} = \Delta Q_t / \Delta t \text{ x } S \quad (3)$$

Steady state flux ($J_{ss}$, µg $cm^{-2}$ $h^{-1}$) was calculated as the amount of BNZ passing through 1 $cm^2$ of the permeation membrane per unit time [31].

With the jackets of the device, the temperature of the water bath was kept constant at 37°C ± 1°C. Samples were taken at certain time intervals 1, 5, 15, 30 min. and 1 h). Penetrated BNZ amounts were analyzed at a 306 nm UV spectrophotometer (Shimadzu UV VIS 160, Japan). Analyses were performed in triplicate [32, 33].

### 2.3. Drug-polymer İnteraction Studies

Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part in the formulation stage during the development of solid dosage form [10, 13]. Fourier Transformer Infra Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (X-RD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities because it shows changes in appearance, the shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction [9]. The DSC thermograms of pure drug, HPMC and physical mixture of active agent and polymer were recorded by Differential scanning calorimeter (DSC) on Shimadzu C60. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30°C to 300°C with 5 mg of amount against a blank DSC aluminum cell as a reference [25].

### 2.4. Stability Tests

Strips were stored in well-closed containers at 25°C ± 2°C / 65% ± 5% RH and at 40°C ± 2°C/75% RH ± 5% RH (accelerated condition) for 8 weeks. At the end of studies, samples were analyzed for physicochemical-characterization and drug content [34].

### 2.5. Statistical Analysis

Data were analyzed using SPSS software (Version 20, SPSS Inc., Chicago, IL). The data were expressed as mean ± standard error of the means. To compare the study groups, one-way analysis of variance (ANOVA) was used followed by Tukey's post hoc for pairwise comparison [35]. Statistical significance was evaluated at a 0.05 probability level.

## 3. RESULTS AND DISCUSSION

### 3.1. Preparation of Oral BNZ OS

The solvent casting method is the most widely used method for preparing OSs since it is simple, easy and does not require any special equipment [36, 37]. In this method, an aqueous or hydroalcoholic mixture of excipients and APIs was poured into a petri dish, dried and then cut into required sizes.

Mixtures of different polymers (HPMC-1, HPMC-9, HPMC-12, Carragen, xanthan gum, Eudragit S-100, Eudragit RS-100, Pollulan, Kollidon IR) were used to form the strips. Formulations prepared with HPMC (mW 10000 Da) showed higher transparency therefore strips prepared with HPMC were selected for further studies therefore only HPMC formulation compositions were presented in Table **2**.

The BNZ dose was kept constant at 15 mg [38, 39]. About 2 cm x 2 cm strips were used for a single dose. The drug required for each batch was calculated considering the surface area of the petri dish. Accordingly, the amount of active substance was recalculated for a 4 $cm^2$ strip for the analyses [40]. According to the literature reviews, OS was developed with different polymers with the plasticizer by solvent casting method, and low polymer and plasticizer concentration showed optimum performance [21, 23, 41]. The bitter taste of the active substance can be masked with auxiliary excipients. Dissolution is mostly accelerated with the saliva enhancers like sorbitol, menthol, *etc*. and better strip structures can be formed with the plasticizing agents like glycerol, and PEG 400 [10, 42, 43].

### 3.2. Characterization of BNZ Loaded OS

The results of thickness, folding endurance (FE), surface pH, percent elongation (PE) , *in vitro* disintegration time, moisture loss and uniformity of drug content were presented in Table **3** [43-45].

The thickness of the strip is directly related to the accuracy of the dose of the strip, which is important to determine the uniformity in the thickness of the strip [46]. The thickness was found in the range of 0.120 ± 0.9 mm to 0.110 ± 0.5 mm in accordance with former studies [18, 47]. Besides thickness, the ideal OS formulation should be elastic and flexible enough to withstand breaking [14]. There is a direct link between the mechanical strength and durability of the strips. Since the mechanical strength is governed by the plasticizer concentration, the plasticizer concentration is also thought to indirectly affect the folding strength value [48]. Results of folding endurance of E2 strips have exhibited good mechanical strength (>128), which was caused by its long chain polymer (HPMC) network [49]. This high folding

**Table 2. Composition of optimum formulation.**

| Code | BNZ (mg) | HPMC (mg) | PEG 400 (mg) | Glycerol (mg) | Citric Acid (mg) | Sorbitole (mg) | Tween 80 (%) | Water (%) |
|---|---|---|---|---|---|---|---|---|
| **E1** | 700 | 3000 | 450 | - | 10 | 50 | 0.07 | 45 |
| **E2** | 700 | 3000 | - | 450 | 10 | 50 | 0.07 | 45 |
| **D1** | 700 | 3000 | 675 | - | 10 | 50 | 0.07 | 45 |
| **D2** | 700 | 3000 | - | 675 | 10 | 50 | 0.07 | 45 |
| **Y1** | 700 | 3000 | 900 | - | 10 | 50 | 0.07 | 45 |
| **Y2** | 700 | 3000 | - | 900 | 10 | 50 | 0.07 | 45 |

**Table 3. Characterization results of the strips (Mean ± SD).**

| Code | Elongation (%) | Thickness (µm) | FE (sec.) | Surface pH | Drug content (%) | Disintegration Time (Sec.) | Moisture loss (%) |
|---|---|---|---|---|---|---|---|
| E1 | 10.45 ± 0.43 | 110.2 ± 0.5 | >122 | 6.67 ± 0.15 | 99.4 ± 1.2 | 15.3 ± 1.6 | 1.2 ± 0.9 |
| **E2** | 10.55 ± 0.35 | 110.3 ± 0.8 | >128 | 6.53 + 0.13 | 99.3 ± 1.4 | 15.5 ± 1.2 | 1.2 ± 0.4 |
| D1 | 10.68 ± 0.18 | 120.2 ± 0.1 | >100 | 6.65 0.11 | 99.2 ± 1.4 | 27.8 ± 1.3 | 1.6 ± 0.9 |
| D2 | 10.65 ± 0.45 | 120.8 ± 0.9 | >110 | 6.57 ± 0.14 | 89.6 ± 2.3 | 28.4 ± 2.7 | 1.3 ± 0.5 |
| Y1 | 10.68 ± 0.35 | 120.6 ± 0.5 | >115 | 6.43 + 0.12 | 89.8 ± 1.5 | 32.4 ± 1.5 | 1.3 ± 0.7 |
| Y2 | 10.65 ± 0.11 | 110.6 ± 0.7 | >113 | 6.35 + 0.14 | 99.1 ± 3.2 | 36.6 ± 1.1 | 1.5 ± 1.5 |

endurance of strips was due to the high mechanical strength and flexibility of HPMC (Fig. **1**) [50, 51].

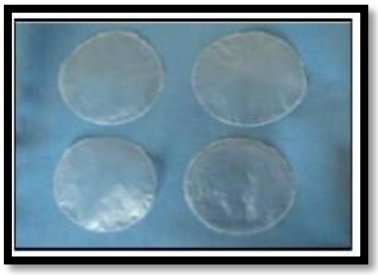


**Fig. (1).** Visual inspection of BNZ loaded OS. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Acidic or alkaline pH can irritate the oral mucosa and affect the degree of hydration of the polymer, which is why the surface pH of oral strips determines drug permeability [47]. In the formulation of oral strips, it is necessary to keep the pH of the strips as close as possible to the pH of saliva. The surface pH of all strips was found to be in the pH range of oral mucosa [52, 53]. Percent elongation is quantitatively related to the amount of plasticizer used in the strip formulation. In our study, percent elongation was found to be between 4-7% and revealed that the higher the percentage of polymer and plasticizer, the greater the percent elongation (Table **3**). The increased concentration of plasticizer in the strip usually causes the strip to stretch more [54]. The disintegration time of all formulations was found to be in the range of 15-36 seconds (Table **3**). It was clearly observed that the increase in polymer concentration affected the disintegration time [51, 55]. The disintegration time limit for the orally dispersible tablet is 30 seconds or less [56]. The accuracy of this guide can also be considered for oral strips. In many other studies, it has been proven that increasing the percentage of HPMC causes an increase in the disintegration time, and our results (<16 sec for E2 strip) are consistent with the literature (Table **3**) [50, 57]. Moisture uptake studies have shown an increase in moisture uptake with the increase in polymer concentration and ranged from 1.2% to 9.51.6% w/w [58]. Even though all the formulation drug content is within the specification range, 100.6% and 99.6% of BNZ in each formulation developed with HPMC (Table **3**). As a result of the characterization studies, it was stated that cellulose derivatives have good film-forming properties [12, 24].

Strips prepared with different polymers and different ratios had different mechanical strengths due to their compositions (Table **1**). Some of the strips were very thin, and brittle and can be broken easily, which will cause problems during the manufacturing, storage and transportation stages. Glycerol has been used as a plasticizer in prepared molecular strips due to its small molecular weight, which allows it to be more easily inserted between polymeric chains and consequently exerts a greater influence on mechanical properties than larger molecules [59]. Strips of the E2 formulation were

found to contain an almost uniform amount of drug, according to content homogeneity studies demonstrating the reproducibility of the production method. The drug content in the strips was evaluated and the values ranged from 89.6 ± 2.3% to 101.3 ± 1.3% for different formulations (Table **3**). In this study, the strip thickness was also analyzed. Due to the different densities of the polymers thickness and weight variations were revealed (Table **3**) [23]. E2 formulation showed minimal disintegration time compared to other formulations and is in accordance with the literature and it is preferred especially for the paediatric and elderly patient group due to rapid disintegration [21, 41]. The optimized oral fast-dissolving E2 formulation was chosen as the best formulation because of its excellent characterization results and *in vitro* release and stability studies were carried on with the E2 formulation [51, 60].

### 3.3. *In vitro* Drug Release Test and Release Kinetics

The BNZ *in vitro* release study was carried out with a selected E2 formulation. After the strips were cut to 2 cm x 2cm size, they were placed in USP Apparatus 1 basket. Six parallel experiments were performed for each formulation with 100 rpm in 900 mL pH 6.8 phosphate buffer at 37°C ± 1°C. Samples were taken at certain time intervals until 100% release occurred from the system operating at low speed (50 rpm). BNZ analyses of the samples were performed with a UV spectrophotometer at 306 nm. The cumulative released BNZ amounts were presented in Fig. (**2**).

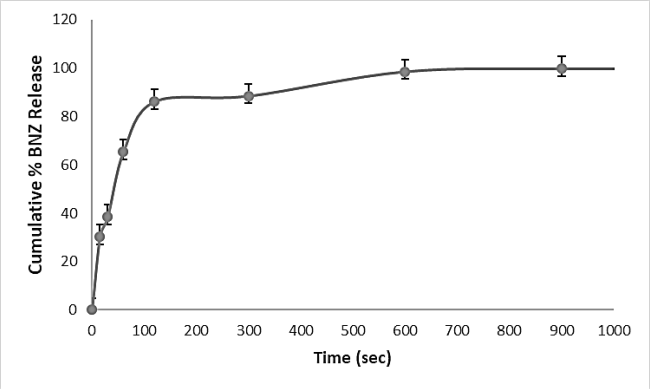



**Fig. (2).** *In vitro* dissolution profile for E2 formulation (Mean±SE, n=3).

Analytical method validation studies were performed for UV spectrophotometry [61]. For linearity studies, $r^2$ was found to be 0.9998 while the coefficient of variation of the analytical method developed in the precision studies carried out on 3 different days is below 2% and the precision of the method has been proven. Pure active substance and blank formulation for the selectivity study of the method were studied and no interference or peak formation was observed in the chromatograms. The accuracy of the analytical method developed in the accuracy and recoverability studies with 3 different concentrations has been proven. In the study, the active substance detection limit was calculated and the studies were carried out within these limits.

Among the variety of methods available for BNZ quantification, spectrophotometry remains very popular because of its simplicity, specificity, and low cost. The method, namely the UV spectrophotometric method, is a low-cost method as well as a less time-consuming method than the RP-HPLC method [62]. The results reveal that the proposed UV spectrophotometric method can be successfully applied for routine quality control analysis of BNZ, with fewer analysis costs and no complex instrumentation required compared to the other reported methods. A release rate was observed at approximately 30% in the first 15 seconds from E2 formulation and the release rate reached 100% within 25 minutes [16, 29, 63].

*In vitro* release rate analyses were evaluated for the determination of BNZ release models from the strips by DDsolver program and the $R^2$ and $R^2a_{djusted}$ values for the Zero-order, First-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Hopfenberg, Baker-Lonsdale and Peppas-Sahlin are smaller than Weibull model for E2 formulation, the drug release does not comply with these models. Depending on the $R^2$ (0.990), $R^2_{adjusted}$ (0.988) MSC (3.532) and AIC (70.228) values obtained, the Weibull model was found to be more suitable than the other release kinetics. The value of the exponent 'β' is a parameter of the mechanism of transport of a drug through the polymeric matrix. The estimated values of $\beta \leq 0.75$ indicate Fickian diffusion, while 'β' values in the range of 0.75-1 specify a combined mechanism of Fickian diffusion and swelling-controlled release [28]. The 'β' value of the strip prepared in this study was found to be 0.603 showing that the active substance from strips was released according to fickian diffusion [28].

### 3.4. *Ex vivo* Permeation Studies

In the *ex vivo* permeation studies, the permeability coefficient is calculated from the graph of the amount of active substance penetrating the tissue (µg/cm2) plotted against time. While the slope of the linear part of the graph gives the uniform flux value (Jss) at equilibrium, the permeability coefficient (P) is found by dividing this value by the active substance concentration in the donor phase [64]. E2 formulation was selected among the prepared formulations considering characterization studies, and permeation of this formulation from the oral mucosa was performed as described in the methods section. The profile of the permeation test was presented in Fig. (**3**).

When the experiments performed in simulated saliva and pH 6.8 buffer were examined and 89.9% and 99.1% diffusion occurred at the end of the 1st hour, respectively for E2 strip. Since the system was designed to act locally, this rate was found to be compatible with the resources and in line with the target [65]. Steady-state flux of BNZ in simulated saliva and pH 6.8 were found to be 27.1 µg $cm^{-2}$ $h^{-1}$ ± 1.4 and 26.2 µg $cm^{-2}$ $h^{-1}$ ± 1.7, respectively. No significant ($p$>0.05) difference in permeability studies was observed using pH 6.8 phosphate buffer compared to simulated saliva [33]. To be successfully delivered through the buccal route, drugs should have adequate permeability. Linear regression analysis of pseudo steady-state diffusion data allowed calculation of the steady-state flux ($J_{ss}$) [31, 32].

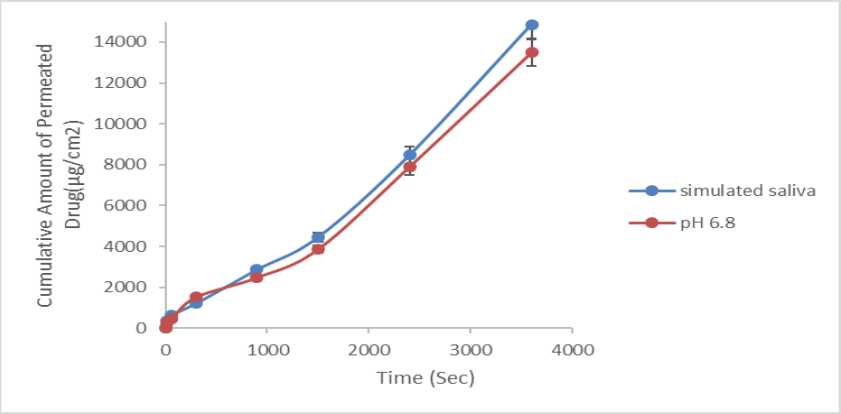



**Fig. (3).** *Ex vivo* permeation analyses results (Mean ± SD, n = 6). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

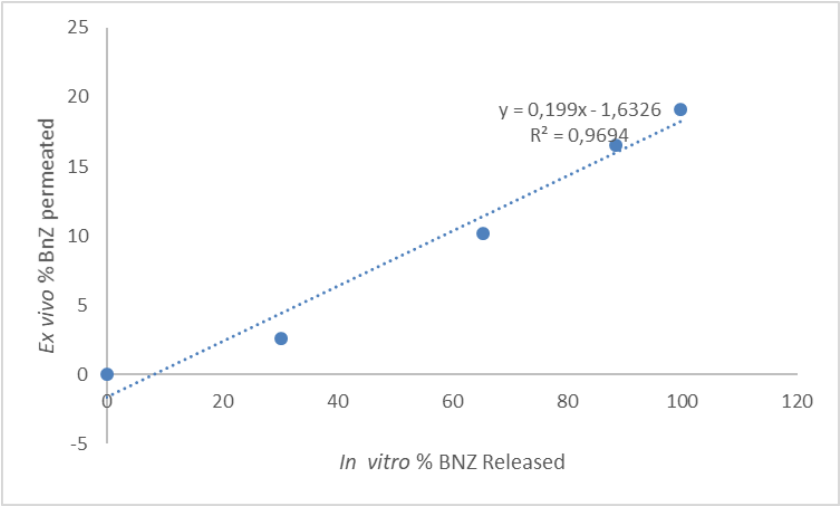



**Fig. (4).** Correlation between cumulative percentage BNZ released *in vitro* and percentage BNZ permeated *ex vivo* for E2 formulation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Both *in vitro* drug release and *ex vivo* permeation studies can be used as reliable assessment tools to screen the permeation of newly developed and established dosage forms [66]. The correlation between *in vitro* drug release and *ex vivo* permeation studies through excised biological tissue can be demonstrated from different aspects. Although biological tissues form a more complex barrier to drug permeability than the dialysis membrane, the role of other excipients in the proposed formulation in facilitating drug transfer can be understood here. Therefore, the permeability of drug molecules depends not only on the physicochemical properties of the drug substance but also on the formulation additives as well as the properties of the tissue on the site of permeation occurs [33].

Plotting the cumulative percentage of BNZ permeated through from sheep buccal mucosa *versus in vitro* release study for formulation E2 in Fig. (**4**), a linear correlation with a high R2 correlation coefficient of 0.96 was obtained proving a good correlation between *ex vivo* BNZ permeation and *in vitro* BNZ release from sheep buccal mucosa (Fig. **4**) [67, 68].

### 3.5. Drug-polymer İnteraction Studies

Fig. (**5a**) shows endotherm of pure benzydamine HCl was found to be 161.29°C. This represented the melting point for the active agent. Fig. (**5b**) shows the DSC graph of pure polymer (HPMC). Fig. (**5c**) shows the DSC graph of the physical mixture of the drug and the polymer. There was no change in the endotherm drug. The melting point of the drug was 161.08°C. The graph showed the compatibility of the drug and polymer. Fig. (**5d**) shows the DSC graph of a strip. It did not show the drug peak. This meant drug might have got changed into another form like amorphous.

### 3.6. Stability Tests

When the values were examined after the stability tests in two different conditions for 8 weeks, it was seen that the ambient temperature at 25°C ± 2°C / 60% ± 5% RH was much better than 40°C ± 2°C / 75% RH ± 5% [24, 32, 69]. While a decrease was observed in the amount of active substance in the samples stored at 40°C ± 2°C / 75% RH ± 5%, an increase was observed in all other characterization values

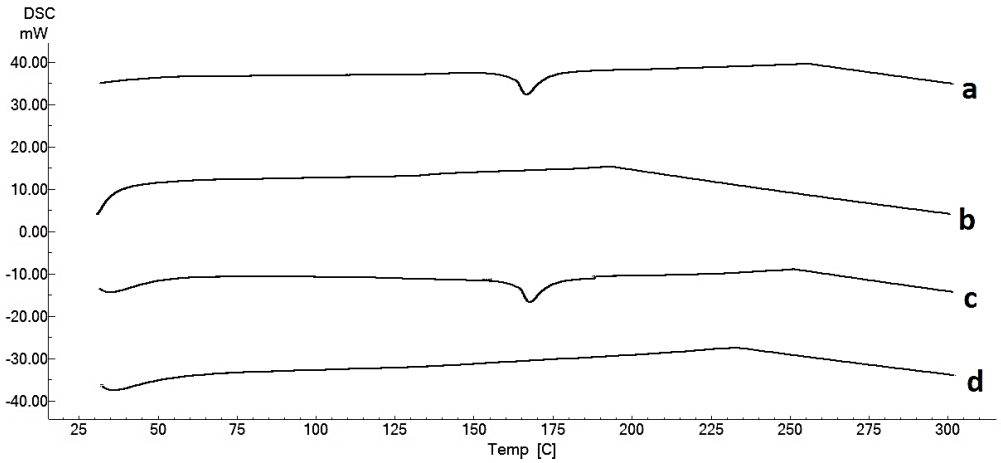



**Fig. (5).** DSC patterns of (**a**) Benzydamine HCl, (**b**) HPMC, (**c**) Physical mixture of benzydamine HCl and HPMC, and (**d**) Strip (E2).

**Table 4. Stability results of E2 formulation (Mean±SE, n=3).**

| Condition | Percent Elongation (%) | Thickness (µm) | Folding Endurance (Sec) | Surface pH | Drug Content (%) | Disintegration Time (Sec.) | Moisture Loss (%) |
|---|---|---|---|---|---|---|---|
| **25°C ± 2°C / 60% ± 5% RH** | 10.4 ± 0.5 | 109.3 ± 0.4 | >120 | 6.5 + 0.1 | 99.2 ± 1.2 | 14.4 ± 0.2 | 1.2 ± 0.4 |
| **40°C ± 2°C / 75% RH ± 5%** | 11.5 ± 0.8 | 120.3 ± 0.8 | >100 | 7.53 + 0.1 | 96.1 ± 0.3 | 19.5 ± 1.4 | 3.2 ± 0.7 |

as seen in Table **4**. It has been observed that the appropriate storage temperature for the strip is 25°C ± 2°C / 60% ± 5% RH.

## CONCLUSION

Fast dissolving oral strips of BNZ were prepared using different polymers like HPMC, Pollulan, Xanthan Gum, Eudragit, Carragen and PEG 400 by solvent casting method. From the present investigation, it was concluded that the amounts of polymers, plasticizers and surfactants have a significant effect on the prepared oral strips. Prepared strips were subjected to various evaluation parameters such as surface pH, the thickness of strip, % moisture absorption, drug content, *in vitro* disintegration time, *in vitro* drug release, stability studies and mechanical properties like folding endurance and tensile strength. By considering parameters (percent elongation, thickness (µm), folding endurance, surface ph, drug content, disintegration time and moisture loss), E2 strips were found to be stable during the storage period. The development of novel drug delivery systems of BNZ as oral strips can be a better solution for efficient treatment of oral mucositis for cancer patients during chemotherapy and radiotherapy stages with high patient compliance considering ease of use.

## LIST OF ABBREVIATIONS

AIC = Akaike Information Criterion

BNZ = Benzydamine Hydrochloride

COD = Coefficient of Determination

COX = Cyclooxygenases

FE = Folding Endurance

HPMC = Hydroxypropyl Methylcellulose

MSC = Model Selection Criterion

NSAID = Non-Steroidal Anti-Inflammatory Drugs

OS = Oral Strips

PE = Percent Elongation

PEG-400 = Polyethylene Glycol-400

PVA = Polyvinyl Alcohol

PVP = Polyvinylpyrrolidone

RH = Relative Humidity

SSF = Simulated Saliva Fluid

UV = Ultra Violet

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## FUNDING

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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