FULL LENGTH	Iranian Biomedical Journal 29 (4): 236-246 July 2025

Designing Oral Films Based on Beeswax: Comparative Assessment of 3D Printing and Solvent Casting

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OPEN ACCESS

Article type: Research Article
Received: February 3, 2025
Revised: May 3, 2025
Accepted: May 21, 2025
Published online: May 22, 2025

How to cite:
Torabi P, Bohlooli S, Shahsavari S, Rezaei Shirmard L. Designing Oral Films Based on Beeswax: Comparative Assessment of 3D Printing and Solvent Casting. *Iran. Biomed. J.* 2025; 29(4): 236-246.

ABSTRACT

Background: From the perspective of DDSs, OFs have received increased attention, mainly for pediatric and geriatric applications. Beeswax, a naturally derived and FDA-approved material, is often mixed with other polymers to enhance its mechanical properties. This study presented the first use of precisely controlled, solvent-free pressure-assisted micro-syringe printing to produce OFs.

Methods: Solvent casting and pressure-assisted micro-syringe printing were employed to produce hybrid film structures composed of beeswax, PVA, borax, and hydroxypropyl methylcellulose, loaded with betamethasone as a model drug. The films were characterized by SEM for their physical appearance, mechanical properties, surface structure, and ultrastructural morphology, as well as their drug content and in vitro drug release.

Results: Films without the drug showed greater irregularities and roughness compared to the drug-loaded films. The physical properties of the formulations improved through 3D printing.

Conclusion: By using 3D printing methods in pharmaceuticals, the treatment procedure would be highly acceptable to patients, increasing their treatment adherence. It is also useful for personal drug delivery.

DOI: 10.61882/ibj.5098

Keywords: Flagellin, Urinary tract infections, Uropathogenic *Escherichia coli*, Vaccines

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INTRODUCTION

Chronic oral ulcerative lesions are typically characterized by discomfort and pain, which can lead to significant nutritional deficiencies[1]. These lesions can occur in various diseases, including immunobullous disorders[2].

Currently, common therapies for oral ulcers involve mouthwashes, creams, or ointments. However, these methods often show limited effectiveness due to insufficient contact time with the lesion. Moreover, existing buccal DDSs do not allow for simultaneous food and drink consumption, and in somsee cases, they can interfere with speech, causing additional discomfort for patients[3].

The oral mucosa is considered a crucial route for drug delivery due to its high permeability, accessibility, and rich blood supply, facilitating systemic absorption of medications[4]. Furthermore, minimal exposure of the drug to the gastrointestinal environment helps the drug to directly enter the systemic circulation via rapid absorption[5]. In recent years, there has been significant focus on developing new drug delivery systems. Mucoadhesive multiparticulate systems have attracted interest due to their strong therapeutic potential and low risk of dosage clearance[6].

List of Abbreviations:
3D: three-dimensional; **DDS:** drug delivery system; **FDA:** US Food and Drug Administration; **HPLC:** high-performance liquid chromatography; **HPMC:** hydroxypropyl methylcellulose; **OF:** oral film; **PVA:** polyvinyl alcohol; **PVP:** polyvinylpyrrolidone; **SEM:** scanning electron microscopy; **SSE:** semi-solid extrusion; **SSF:** simulated saliva fluid; **USP:** United States Pharmacopeia

[DOI: 10.61882/ibj.5098]

Buccal delivery is a kind of oral delivery of drugs that refers to the administration of drugs via the buccal mucosa and drug localization in the affected region. Also, local drug delivery via buccal films is an appropriate choice for shielding wound surfaces, reducing pain, and improving the treatment efficiency. In addition, the buccal region is considered an actual route of use for systemic drug delivery since it can be a good alternative option for many advantages[7].

Development of novel therapeutic agents is often a time-consuming process; hence, the need to develop existing pharmaceuticals via innovative delivery systems is crucial[8]. A considerable number of studies have explored the use of 3D printing in drug delivery. The 3D printers have been employed in the pharmaceutical industry for manufacturing a variety of products, including controlled-release tablets, polypills, orodispersible films, gastro-floating tablets, self-emulsifying DDSs, microneedles, and transdermal films[9]. Additive manufacturing allows for personalized medicine, such as the production of drug-eluting patches that match the patient's anatomical features, including OFs proportional to lesion size[10]. The SSE approach contains a subset of optimal ratios of polymers and appropriate solvent(s) using sequential deposition to prepare gel layers with unique sizes and structures. SSE 3D printing operates at low printing temperatures, making it suitable for biomedical applications. In other words, the progression of SSE 3D printing provides benefits for pharmaceutical use, mainly by employing low printing temperatures, which makes it a better option for drug delivery[11].

Given the limited data on treating oral mucosal lesions with betamethasone and the lack of efficient methods for oral ulcer treatment, herein, we propose a heated inductive-enabled syringe pump extrusion 3D printing to protect oral mucosal lesions by creating OFs of varying sizes, utilizing cost-effective raw materials such as beeswax. Beeswax has been widely employed in pharmaceutical formulations, including nanoparticles for controlled drug delivery[11]. The solvent-free printing method eliminates the need for rigorous solvent selection. Previously, 3D printing of OFs has been conducted through various approaches, such as hot-melt extrusion and the fused deposition modeling method[12,13]. Our study introduces a novel strategy for dosage form manufacturing employing 3D printing.

MATERIALS AND METHODS

Ink preparation and printing process

The heated inductively enabled syringe pump extrusion multifunction module was designed to replace the extrusion system of a mechanical-assisted microsyringe 3D printer. This innovation allows pump-assisted microsyringe 3D printers to work with a variety of 3D printing materials (e.g., oily substances, hydrogels, material blends, or waxy-based formulations) in different forms (e.g., hydrogels, paste, emulsion, or oil/water mixes). The module was designed to be simple, easy to replicate, and cost-effective. One of the main advantages of the heated inductive-enabled syringe pump technique, compared to fused deposition modeling and SSE, is that the process does not require high temperatures or organic solvents. For printing pharmaceutical products using a semisolid extrusion-based 3D printing technique, the selected polymers included beeswax, paraffin, HPMC, and PVA. In addition to these polymers, binders, surfactants, and plasticizers were incorporated into the material to improve the physicochemical characteristics of the paste. PVA and HPMC were mixed with glycerol, serving as a plasticizer, and distilled water to create polymer solutions. The preparation process began by adding beeswax and paraffin to a beaker and mixing them at 70 °C using a hot water bath. Once the oily mixture was ready, it was transferred to a separate beaker, where measured borax and glycerol were added and mixed with a spatula. The final step involved the addition of the aqueous mixture in 3–5 tranches, mixing with a spatula after each tranche. Preliminary formulations were evaluated (data not shown) until an extrudable product was achieved, ensuring that it did not spread and clog. The drug-loaded formulation was constantly agitated at 40 °C for 3 h before printing.

Film fabrication

Solvent casting was used to prepare betamethasone polymeric films. In beaker No. 1, a 20% w/v solution of beeswax was prepared. Meanwhile, an aqueous polymeric solution was prepared by dispersing solid HPMC and PVA in 80 °C water while continuously stirring at 600 rpm for 1 h. In beaker No. 2, glycerol was added as a plasticizer at a concentration of 0.5% w/v and also borax as a surfactant at 4% w/w based on the weight of the polymer, and this mixture was stirred for another 1 hour at 700 rpm. In the next step, the organic beeswax solution was slowly added to the aqueous solution, and the mixture was stirred at room temperature for at least 12 h to obtain a suitable emulsion. The prepared emulsion was then poured onto non-adherent polytetrafluoroethylene plates. The cast films were dried under a vertical laminar airflow chamber at room temperature for 24 h and stored at room conditions (Fig. 1).

[DOI: 10.61882/ibj.5098]

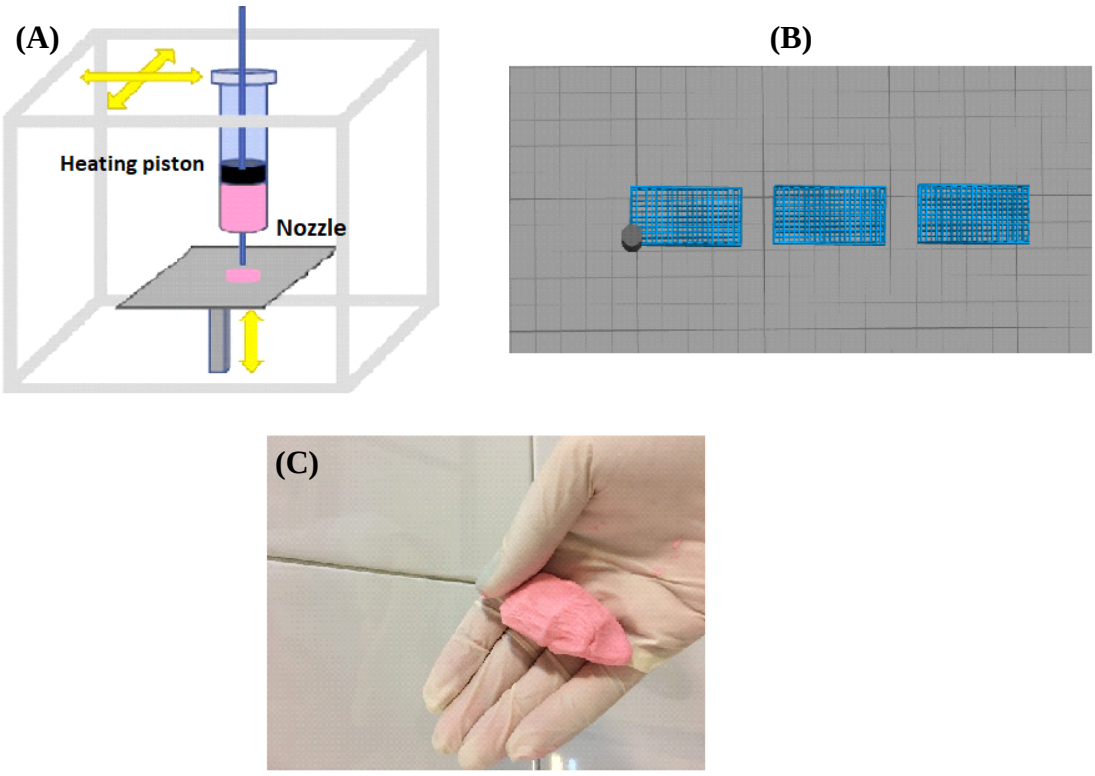

Fig. 1. (A) Film preparation, (B) obtained films, and (C) the prepared ink.

Characterization of the dosage forms

Physical appearance

The appearance of the prepared films was evaluated through visual observation[14]. Five films were weighed immediately after printing, and the mean weight and standard deviations were calculated. To evaluate the weight of the films, five films with a smooth surface and uniformity of both formulations (with and without the betamethasone drug) were selected and weighed using a digital scale. The average weight of these five films was then reported. For measuring thickness, a caliper device was used. A total of five films from both groups were selected, and the thickness of each film was measured at a minimum of five points: one at the center and two on each side. The average thickness of these films was finally reported.

Surface pH test

The pH of the surface of the films was measured at room temperature by adding 1 mL of deionized water to the top of both the unloaded and drug-loaded films, allowing it to remain for 30 s. The pH was then measured by bringing the electrode of the pH meter into contact with the solution on the patch surface. The average pH value was calculated (n = 3)[15]. To determine the surface pH of the films, they were first kept in distilled water for 15 min to allow sufficient swelling. Afterward, the films were removed from the water, and pH meter paper was placed on the swollen surface of each film to measure its surface pH.

Drug content

The drug content of the films was determined by immersing them in a 50 mL beaker containing 20 mL of SSF, which consists of 0.8% sodium chloride, 0.019% monobasic potassium phosphate, and 0.238% dibasic sodium phosphate (w/v), at pH 6.8. The solution in the beaker was stirred at 100 rpm for 240 min at an adjusted temperature of 37 °C. After 240 min, the drug content was measured by HPLC according to the USP-adjusted method. First, the films were cut into five pieces, each measuring 20 × 15 mm², and placed in a Petri dish containing 20 mL of artificial saliva at 37 °C. The beakers were then placed in a water bath and stirred at a speed of 100 rpm for 420 min until the films were completely disintegrated. One mL of each sample was filtered twice, following the USP methods, before being injected into the HPLC system. The drug content of each film was determined using a standard calibration graph and a regression equation for calibration. The HPLC method was established based on the USP guidelines for betamethasone determination. The mobile phase was

[DOI: 10.61882/ibj.5098]

prepared using a mixture of acetonitrile and deionized water at a ratio of 2:3, which was then filtered through a filtration system. A C18 column was used, with a flow rate of 1 mL/min and a UV detector set to a wavelength of 254 nm[16].

In vitro dissolution

In vitro drug release studies were performed on films to determine their drug release profiles. The films were weighed and placed in a 50 mL beaker containing 20 mL of SSF, which consisted of 0.8% sodium chloride, 0.019% monobasic potassium phosphate, and 0.238% monobasic sodium phosphate (w/v) at pH 6.8. The solution in the beaker was stirred at 100 rpm for 240 min while maintaining a temperature of 37 °C. Samples were taken at specific intervals: 0.5, 1, 2, 3, 5,10, 15, 30, 45, 60, 120, 180, and 240 min. At each time interval, 2 mL of the release medium was withdrawn, and the beaker was immediately replaced with the same amount of fresh SSF, also maintained at 37 °C. The samples were then analyzed utilizing HPLC according to the USP-adjusted method[17]. Additionally, to assess the in vitro drug release pattern of the films, a medium containing 20 mL of artificial saliva (temperature: 45 °C and pH: 6.8) was used. Given that the solubility of betamethasone (as sodium phosphate) in saliva is 1.52 mg/mL, the sink condition was established based on the amount of drug present in each film (4 mg). At time intervals of 30, 60, 90, 120, 150, 240, 300, and 360 min, 1 mL of the medium was removed, and it was replaced with 1 mL of artificial saliva to maintain the sink condition. The amount of betamethasone was then determined at different times according to the HPLC protocol specified in the USP, and the corresponding data were documented in a chart created using Excel.

In vitro disintegration

Disintegration was determined for drug-loaded films. A single patch was placed in simulated salivary fluid at 37 °C and stirred at 100 rpm. The time required for the patch to disintegrate was recorded. The disintegration time was further assessed using a special device containing artificial saliva, maintained at 37 °C. According to the last study[18], the device included a clip to hold the film and applied a 3 g weight to exert pressure on the film. The weight was selected based on the available evidence indicating that 0.03 newtons is the minimum force exerted by the tongue on OFs. The sample moved vertically within the container, immersed in artificial saliva with a pH of 6.8—matching the pH of the oral cavity. The artificial saliva was prepared in the laboratory and consisted of 12 mM of potassium dihydrogen phosphate (KH_2PO_4), 40 mM of sodium chloride (NaCl), sodium hydroxide to adjust pH, and distilled water to reach a volume of one liter. The endpoint was defined as the moment when the clip is connected to the weight and touches the bottom of the container, indicating complete film disintegration. Each film was tested in triplicate, and results were reported as mean ± standard deviation.

Swelling index

Films were initially weighed and placed in 5 mL of deionized water. At specified time intervals, the films were removed from deionized water, and excess moisture was absorbed using tissue paper before reweighing them. The increase in weight was recorded at each time interval until a constant weight was observed[17]. After dividing the films into equal pieces of 20 × 15 mm², the initial weight of each film (W_1) was accurately determined. The pieces were then placed in a steel sieve, which was immersed in a container containing artificial saliva. At intervals of 5, 10, 20, 40, 60, 90, and 120 min, the films were removed from the sieve. Excess water was removed with a paper towel, and the films were weighed again until an increase in weight was confirmed. This weight (W_2) was recorded as the secondary weight, and the percentage of swelling was then determined[19]. The swelling index (SI) was calculated using the formula:

$$\frac{(W_t - W_0)}{W_0} \times 100$$

The degree of swelling was measured using the weights recorded at times t (W_t) and zero (W_0).

Scanning electron microscopy

In the first stage, bulk samples were prepared using conductive aluminum adhesive tape, while powder samples were mounted using Agar standard double-sided adhesive. Surface conductivity of the samples was enhanced using the physical vapor deposition method with a COXEM device. The prepared samples were examined using a scanning electron microscope. Depending on the specific test, imaging of the samples was performed using backscattered electron and secondary electron detectors at different magnifications with a FEI ESEM QUANTA US-made microscope. Elemental analysis of the observed phases was conducted using an EDAX EDS Silicon Drift Detector (USA). To evaluate the shape and surface morphology of the films, a scanning electron microscope was used. The samples were observed at different magnifications at a voltage of 25 kV.

[DOI: 10.61882/ibj.5098]

Table 1. Physical properties of the films

Physical properties	Red film (drug-loaded)	White film (without drug)
Thickness (µm)	208.6 ± 12.3	203.3 ± 11.5
Weight (mg)	0.338 ± 0.03	0.33 ± 0.03
Surface pH	6.66 ± 0.40	6.75 ± 0.25

RESULTS

Physical appearance

The prepared films were homogeneous and flexible, with a smooth and checkered surface. The uniform weight of the films indicated a consistent distribution of the drug content (Table 1). Additionally, the film demonstrated acceptable weight linearity (R^2 = 0.95). Their dimensions closely matched the intended design specifications. Ideal buccal films typically exhibited a thickness ranging from 50 to 1000 µm. The thickness of the printed films was between 900 and 1000 µm, which was within the recommended range for OFs[15,20].

Surface pH test

Surface pH is measured to assess potential side effects in vivo. If the films are acidic or alkaline, they may cause irritation or allergic reactions upon administration, leading to patient discomfort. Both the unloaded and the drug-loaded films exhibited a neutral surface pH, suggesting they will not produce sensations or irritation in the oral mucosa[15]. The average surface pH of the drug-loaded films was slightly lower, at 6.95, compared to the unloaded films, which had an average surface pH of 7.07. An examination of the physical and appearance characteristics of the films indicated a uniform and smooth surface, free from wrinkles or bubbles. The uniformity and weight of the films were consistent, showing no significant differences. In the final analysis, the films were considered uniform, and the measured thickness variations were less than 5%. The physical properties of both types of the prepared films (drug-loaded and drug-unloaded) are presented in Table 1. The physiological pH of saliva often ranges between 5.8 and 7.4. If the pH of OFs was not within this range, it could cause local irritation of the oral mucosa. A reduction in saliva pH below 5.5 is harmful to the soft and hard tissues in the mouth, especially to tooth enamel and dentin. Therefore, the final films should have a neutral pH to prevent irritation and sensitivity in the oral cavity and mucous membrane. The surface pH of the films was monitored to assess potential side effects, and both the acidity and alkalinity of the films were also evaluated. The results, presented in Table 1, indicates that the surface pH of the films is ideal for maintaining a neutral environment similar to that of saliva.

Drug content

To measure the drug content in the films using a simulated medium (artificial saliva), we employed the calibration curve generated from the HPLC method. By applying the equation derived from this curve to the sub-curve obtained from the drug content analysis, we found that the drug values in the printed films were approximately 3.2 mg (Table 2). To identify and determine the amount of betamethasone in the films, we utilized the HPLC method, and the results are shown in Figure 2. The mobile phase comprised two components: phase A (acetonitrile) and phase B (deionized water), at a ratio of 65% A to 35% B. A C18 column was employed with a flow rate of 1 mL/min, and the UV detector was set to 254 nm. To determine the calibration equation, we prepared five standard concentrations of betamethasone. After injecting these samples into the HPLC and performing the relevant calculations, we obtained the calibration equation with an R^2 value of 0.9983 (Fig. 2)[21]. To measure the amount of drug in the artificial saliva, we utilized the calibration curve from the HPLC method. Using the obtained equation, we calculated the drug content in the films. According to the USP Pharmacopeia (http://www.usp.org/), an average drug content in the films was within the range of 85-115%, which was considered acceptable. The results indicated that the drug content in all films ranged from 94% to 98%. This consistency shows the uniform distribution of the drug throughout the polymeric film **(Fig. S1)**[21].

Table 2. Drug concentration released from the films in artificial saliva over time

Time (min)	Area (cm^2)	Concentrate
180	225.429	0.111
240	324.725	0.1593
270	284.462	0.147

Results showed that the drug content in the printed films was approximately 3.2 mg.

[DOI: 10.61882/ibj.5098]

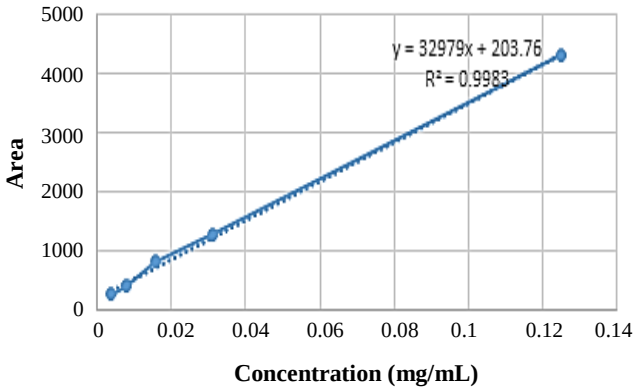

Fig. 2. Calibration curve of betamethasone.

In vitro dissolution

The in vitro drug release studies showed that drug release begins approximately one min after placing the patch in the environment. This release continues for up to 240 min. All films released 60% of the drug within 180 min and about 91% within 240 min. The amount of drug release primarily depends on the amount of water-soluble polymer in the formulation. The reduction in the rate of drug release observed from 30 to 60 min is likely due to the gelation of HPMC upon contact with water. The gel formation traps the drug, preventing its release. After gel erosion, the drug is released slowly (Table 3)[22]. The evaluation of the drug release profile for the films is shown in Figure 3 and indicates that about 25-30% of the drug is released within the first 20 min in an in vitro environment. This initial release is probably attributed to the surface of the film. Gradually, the swelling rate of hydrophilic polymers such as HPMC increases, resulting in a gradual enhancement in drug release. After a time period of six hours, more than 90% of the drug was released. Research on the release characteristics of these polymers indicates that the solubility of the polymer in water is a key factor influencing drug release. Due to the uniformity of the samples and consistent measurement methods and test conditions, the release amounts are almost the same.

Table 3. Drug release pattern in films

Time (min)	Area (cm^2)	Concentrate (mg/mL)	Release (%)
1	44.28	0.0029	1.8
2	66.738	0.0147	9.1
3	81.484	0.025	15.6
5	86.432	0.028	17.5
10	104.123	0.039	24.3
15	119.751	0.0485	30
30	97.591	0.035	22
45	106.632	0.040	25
60	114.395	0.045	28
120	148.979	0.066	31.2
180	194.132	0.093	58
240	280.317	0.145	91

All films released 60% of the drug within 180 min and about 91% of the drug during 240 min.

In vitro disintegration

The disintegration time of the films was determined, though no standard test currently exists for assessing the parameter. The two factors, including the environment and its temperature, as well as the presence or absence of motion in the test settings, had a great impact on the test results. In this study, the time for complete disintegration of the films was about four hours[23]. It is important to note that the disintegration time of the films is affected by the swelling abilities of the film. The films were swollen in contact with water due to the hydrophilic properties of polymers such as HPMC, and finally, they were completely disintegrated. Films containing a drug with A high swelling percentage were disintegrated more rapidly than those without a drug. Specifically, the disintegration time for films that did not contain a drug was 400 min, whereas those containing a drug had a disintegration time of 370 min. The swelling behavior was tested on three films loaded with betamethasone and three films without any drug content. The results showed that the swelling index was higher in the drug-loaded films.

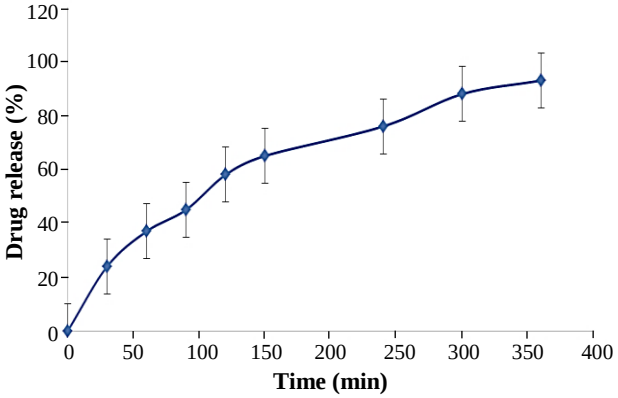

Fig. 3. Drug release pattern in films. Results indicate a 25-30% drug release during the first 20 min under in vitro conditions.

Swelling index

The swelling index for the films increased gradually, and approximately all films reached 98% of their original weight and their own weight within 60 min (Table 4). Additionally, the swelling indices for the drug-unloaded films were 59.52% for film 1, 58.43%

[DOI: 10.61882/ibj.5098]

Table 4. Weight of the films after 60 min of swelling

Film	Time (min)	0	1	5	10	15	20	35	50	60	70
1		145.6	181.7	202.9	218.9	239.2	245.4	252.2	274.2	286	238.6
2		139.3	167.7	219.6	222.4	235.6	236.1	248.6	258.7	279.3	272.6

for film 2, 56.24% for film 3. For drug-loaded films, it was 70.20%, 73.98%, and 78.07% for films 1, 2, and 3, respectively. Overall, the degree of swelling index for the films was slow.

Scanning electron microscopy

The SEM images showed a layer-by-layer printing well. Imaging was conducted on both drug-unloaded and -loaded films. In the image of the drug-loaded patch (Fig. 4A), darker areas indicate the presence of the drug, which is not seen in the sample without the drug. As shown in Fig.4B (Fig. 4B), pores are more visible in the patch using a high magnitude, demonstrating its ability to load the drug. SEM was used to investigate the distribution of the drug within the film. The microscopic imaging helps study drug distribution as well as drug recrystallization in the films. Images of the films (in the absence of betamethasone) by a scanning electron microscope showed a porous structure, which is associated with a high capacity for water absorption. As a result, the time needed for the film to disintegrate in the oral environment depends on the amount of saliva. A comparison of SEM images of the drug-loaded and -unloaded films with different magnifications is depicted in Figure 4. The Figure indicates that films without the drug had greater irregularity and roughness compared to those containing the drug.

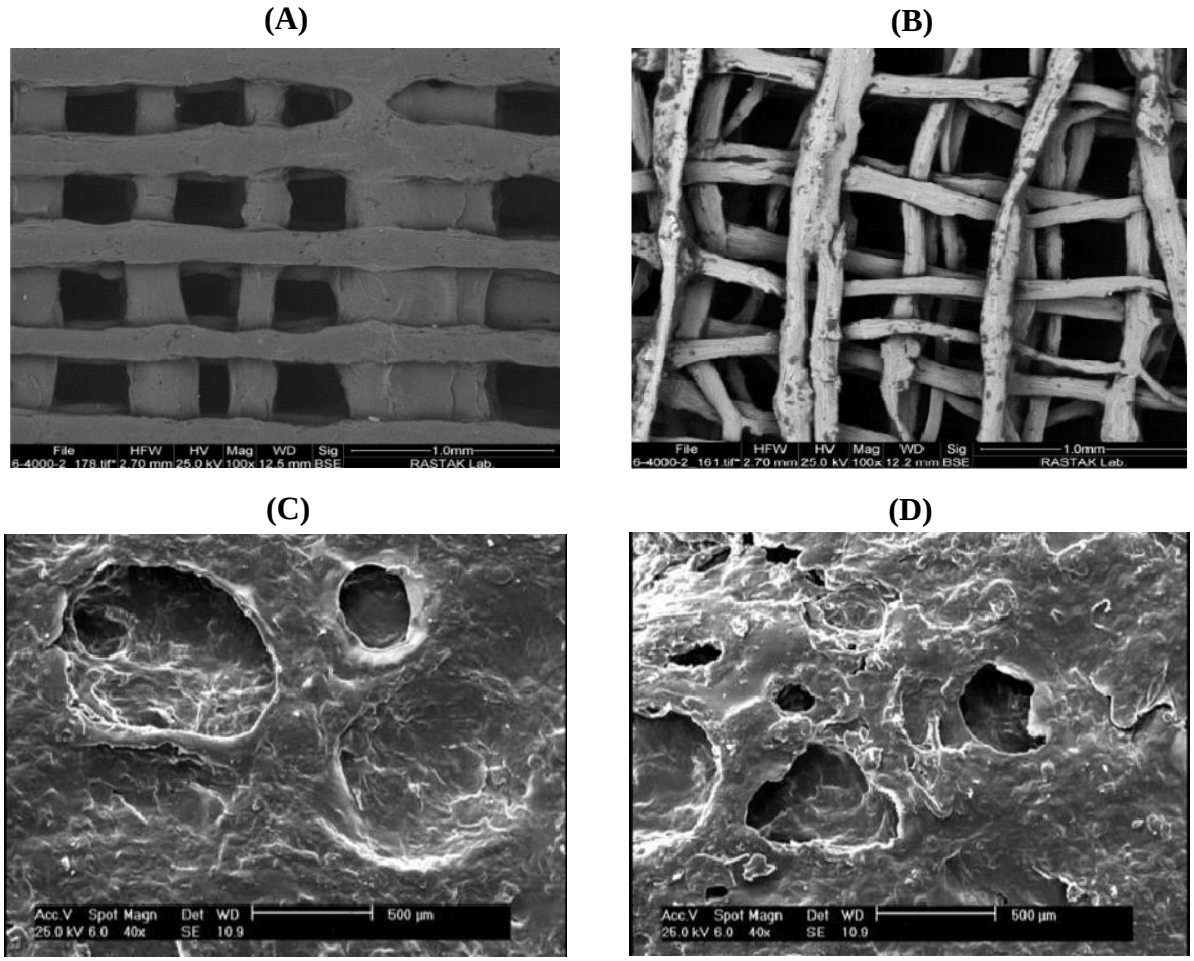

Fig. 4. Electron microscopy images of the prepared films. SEM image for (A) drug-loaded films (magnification of 1.00 mm); (B) drug-unloaded films (magnification of 1.00 mm); (C) drug-loaded films (magnification of 500 µm); (D) films without drug (magnification of 500 µm).

[DOI: 10.61882/ibj.5098]

DISCUSSION

The current study evaluated OFs made from beeswax, comparing a 3D printing method in which a heated inductive-enabled syringe pump extrusion is used with the conventional solvent casting. The key findings of this study include (a) greater irregularities and roughness in the drug-free films compared to drug-loaded films, (b) insights into the physical properties of formulations developed through 3D printing, and (c) enhanced personal drug delivery through the production of OFs utilizing a 3D printer.

One of the main goals of new DDSs is to create drug forms that minimize side effects while maximizing therapeutic effects. This feature allows patients to be treated more quickly with smaller doses of the drug[24]. Over the last decade, the use of 3D printing technology has significantly increased, not only in the pharmaceutical industry but also across other industries. Indeed, 3D printers represent a significant advancement in the realization of individualized therapies. Likewise, 3D printing enables the formulation of complex structures and dosing more rapidly compared to the traditional methods[13].

In the pharmaceutical sector, 3D printing is a hybrid technology that combines design, pharmacology, and materials engineering, allowing these fields to collaborate effectively in producing and developing the final product. Our study provides evidence for the successful production of OFs using 3D printers, making them suitable for clinical applications. The films produced are appropriate for drug delivery, considering the size and type of oral ulcers, along with anatomical and physiological differences, as well as patient drug allergies. For these films, we employed biodegradable polymers and materials that do not cause side effects in patients.

In 2004, a group of scientists in Italy researched the preparation of buccal ibuprofen mucoadhesive films. Their results showed that this buccal patch, made with polyvinylpyrrolidone and carboxymethylcellulose, was well-tolerated and comfortable. It was also non-irritating, flexible, and effective for wound protection and oral inflammation, making it preferable to mucoadhesive tablets. However, one limitation of these films was the low efficacy of ibuprofen for treating oral ulcers and inflammation[25]. In our study, we selected betamethasone, a corticosteroid known to be effective in healing oral inflammation. In 2010, another group of scientists in India formulated levofloxacin dental films for treating periodontitis. These films included polymers such as polyvinylpyrrolidone, lodranite, HPMC, and hydroxypropyl cellulose. Their findings revealed that these films could release 99.74% of the drug by the 10th day, suggesting that they can be used as a slow-release device for the treatment of periodontitis. In contrast, the films produced in our study were suitable for short-term use, particularly in treating oral ulcers such as aphthous ulcers, as their drug release occurs within approximately four hours[26]. A study by Zhang et al. concluded that the swelling of mucoadhesive films was directly related to their adhesive properties on the mucosa. When the patch closely contacts the oral mucosa, physicochemical interactions enhance adhesion. The mucoadhesive properties develop as dry or semi-dry films in contact with oral mucus, causing slight moistening and swelling, which forms a sticky layer on the surface. They also utilized polymers such as HPMC, hydroxyethyl cellulose, polyvinyl alcohol, polyethylene glycol, and chitosan[27]. While hydration increases mucoadhesive properties, excessive hydration can lead to the formation of a slippery mucilage layer on its surface that reduces mucoadhesion[28]. Thus, the speed and degree of swelling due to hydration significantly influence the mucoadhesion and release profiles of these films. In our study, the swelling observed was due to the presence of HPMC in the patch formulation, which absorbs water[29]. OFs can affect the oral mucosa without the need for water consumption, chewing, or swallowing. They also improve drug bioavailability by inhibiting the first-pass effect, which increases patient acceptance and compliance, especially in children and the elderly[30].

Oral thin films serve as complex polymer networks that enable controlled drug release, with hydrophilic polymers playing an important role. These polymers are essential components of pharmaceutical and biomedical formulations and have particular importance in the design and construction of complex DDSs and devices[31].

In the preparation of OFs containing betamethasone, the solvent evaporation method was used alongside applying the addition of components such as HPMC, PVA, beeswax, borax, and glycerol. The resulting films exhibited properties, including uniform drug distribution, neutral surface pH, suitable swelling index, and desirable mechanical characteristics. PVA, a water-soluble polymer obtained from the hydrolysis of polyvinyl acetate, is commonly used as a film-forming agent. Betamethasone films provide a rapid onset of action due to a portion of the drug being loaded onto the surface of the film, while the remainder is released slowly over six hours. The rate of drug release can be adjusted by varying the proportions of hydrophilic and hydrophobic polymers[32]. Several studies have evaluated OFs loaded with various drugs, including diphenhydramine and ibuprofen, as well as corticosteroids such as triamcinolone acetonide,

[DOI: 10.61882/ibj.5098]

employing the solvent-casting method to address oral conditions such as recurrent aphthous ulcers and oral lichen planus. Research conducted in 2018 demonstrated the use of a combination of HPMC and PVA as film-forming polymers, with glycerol as a plasticizer, to produce dexamethasone OFs[33].

A recent study by Lim et al.[34] examined thin OFs containing chlorhexidine (main excipient), along with other drugs such as betamethasone, lidocaine, or diclofenac, all prepared via the solvent casting method. This research revealed a relatively low release rate of chlorhexidine in all films; however, the drug compounds in these films (lidocaine or betamethasone) exhibited a higher release rate. The antibacterial properties of these films were assessed on gum tissue isolated from pigs, indicating a high effectiveness and significant therapeutic effects against bacterial biofilms in oral and gum tissues. Another study found that beeswax in combination with oleic acid enhanced the plasticizing properties of the films, increasing their elasticity and stretch[35].

Films made from this biodegradable polymer exhibited acceptable adhesion when applied between the gum and the upper lip. They do not interfere with the patient's daily activities, eating, or drinking. Furthermore, these films can be removed quickly from the person's mouth without causing tissue damage when separating. In this study, the pH of the films was found to be within the optimal range for the oral cavity, ensuring they do not irritate the mucosa. Additionally, a higher swelling index of the polymers in the film is correlated with a faster drug release rate[36].

SEM images revealed that drug-free films exhibited greater irregularities and roughness compared to those loaded with drugs. This drug loading filled the empty spaces of the film surface, reducing its roughness. Evaluations showed uniform and excellent drug dispersion across all study films. The polymers used in the production of the films included beeswax, PVA, PVP, and HPMC, contributing both to the adhesive properties of the films and the slow release of the drug from the film. In addition, the results from swelling tests indicated that swelling and water absorption were higher in the drug-loaded films. Since hydrophilic polymers absorb water, this leads to a stronger bond between water and the hydroxyl groups of the polymer, justifying the greater swelling observed. According to previous studies on the effects of plasticizers in the production of OFs, glycerol was identified as the most effective plasticizer without altering the disintegration time of the film[37].

CONCLUSION

Our findings indicate that using PVA, HPMC, PVP polymers, and beeswax, in combination with the drug betamethasone, can be a practical option for the development of oral DDSs for lichen planus or oral ulcers. In this study, different excipients were tested at different percentages to select the components of the final formulation. Further research will help improve the formulation by determining the optimal composition for each component.

DECLARATIONS

Acknowledgments

The authors would like to acknowledge the staff at the School of Pharmacy of Ardabil University of Medical Sciences for their support. The authors declare that they did not use artificial intelligence in the preparation of this study.

Ethical approval

Not Applicable.

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

PT: Writing–original draft, methodology, investigation, data curation, and conceptualization; SHB: Software, methodology, data curation, investigation, review and editing; SHSH: Investigation, conceptualization, data curation, review and editing; LRSH: Review and editing, project administration, methodology, investigation, resources, validation, and conceptualization.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Ardabil University of Medical Sciences.

[DOI: 10.61882/ibj.5098]

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[DOI: 10.61882/ibj.5098]