Mucoadhesive Film Forming Spray for Buccal Drug Delivery: A Review

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Abstract:

Film-forming sprays provide a number of advantages over conventional topical treatments, including equal medication distribution and dosing, increased bioavailability (increase local drug concentration), and less irritability (Dosing frequency). Polymers and excipients that improve the characteristics of preparations and increase the stability of active substances are the building blocks of mucoadhesive film-forming sprays. Films made from diverse combinations of polymer and excipient exhibited a wide range of characteristics. This reveiw examines the many types of polymers and excipients, the different types of sprayers, the different evaluations, as well as the essential criteria that are involved in defining the sprayability and film properties. This comes to the conclusion that natural and synthetic polymers with viscoelastic properties can both be employed to optimize the administration of buccal drugs.

Key words: Film-Forming spray, Polymer, Buccal Drug Delivery System

رذاذ تشكيل غشاء مخاطي لتوصيل الأدوية الشدقية: مراجعة

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الخلاصة:

عند مقارنة البخاخات المكونة للغشاء بالعلاجات الموضعية التقليدية، فإن البخاخات المكونة للغشاء لها العديد من الفوائد لأنها يمكن أن توفر توزيعًا موحدًا للأدوية والجرعات، وتوافرًا حيويًا أكبر، ونسبة أقل من التهيج. تتكون البخاخات اللاصقة المخاطية المكونة للغشاء من بوليمرات وسواغات تعمل على تحسين خصائص المستحضرات وتزيد من ثبات المكونات النشطة، وسوف ينتج كل بوليمر وسواغ أغشية ذات خصائص مميزة .
يفحص هذا الاستعراض أنواعًا عديدة من البوليمرات والسواغات ، وأنواع مختلفة من المرشات ، والتقييمات المختلفة ، فضلاً عن المعايير الأساسية التي يتم تضمينها في تحديد قابلية الرش وخصائص الفيلم. يأتي هذا إلى استنتاج مفاده أنه يمكن استخدام البوليمرات الطبيعية والاصطناعية ذات الخصائص اللزجة المرنة لتحسين إدارة الأدوية الشدقية.
الكلمات المفتاحية: البخاخات المكونة للغشاء، بوليمر، نظام توصيل الأدوية الشدقية.

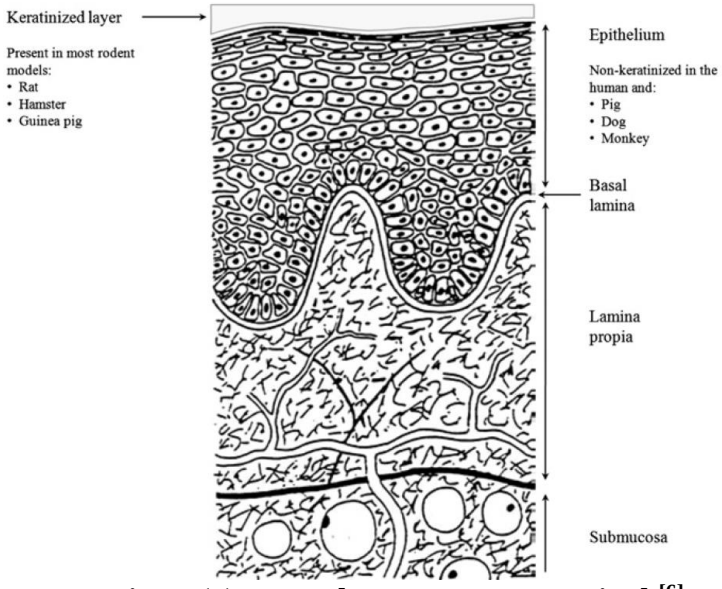
Introduction

Film dosage forms have acquired popularity in the pharmaceutical industry, patient-friendly, and convenient products. Orally dissolving films have just recently been brought to attention due to the higher mechanical properties that they possess [1]. When compared to pills, mucoadhesive buccal films have a higher patient compliance because of their more manageable size and thickness [2]. There are different mucoadhesive buccal films that have been developed to administer medications locally in the mouth cavity in

order to treat fungal diseases such oral candidiasis [3].

Oral Mucosa Physicochemical Properties:

About 25% of the oral cavity is made up of keratinized gingival and hard palate and about 60% is covered by not keratinized mucosa lining the inside of the cheeks, the floor of the mouth and the tongue [4][5]. Figure 1. Showed that the epithelium is connected to a lamina propria, separated by a basal lamina



Figure(1): Buccal mucosa cross-sectionb[6]

The lamina propria and lining mucosa regions mainly serve as mechanical supports but do not pose a significant obstruction to the entry of active substances [7]. The blood vessels that empty into the internal jugular vein, as well as the lingual, facial, and retromandibular veins, are located in the connective tissue [8]. The main advantage of buccal delivery over oral administration is that the drug is absorbed directly into the portal vein, skipping the stomach and its related conditions (such as enzyme concentrations, first pass effect, and the gastric pH). As a result of the ease with which a given drug molecule can be transported after it enters connective tissue, the stratified epithelium's entire thickness serves as the penetration barrier [9].

Mucoadhesion and mechanical properties of buccal mucosa

Mucoadhesion is the interaction between the buccal mucosa, (which is a biological membrane that lines the buccal cavity) and polymers of the buccal drug delivery system (BDDS). In general, the adherence between a biological and synthetic surface is referred to as bioadhesion. A mucosal membrane's specific interaction with a synthetic surface is known as mucoadhesion [10]. Various theories explained this observation like wetting, electronic, adsorption, diffusion, mechanical, and fracture. All these hypotheses describe the influencers on mucoadhesion for example the bonds that hold mucoadhesive polymers and mucins together [11].

Film-Forming Spray Mechanism

A film forming spray (FFS) is a medication delivery system that sprays a solution or suspension onto a target treating site, where it contacts the site and uses the polymer as matrices to build a film [12]. Following the formation of the film, the drug will be released gradually similarly to a patch [13]. Naturally, this makes it much easier for drugs to reach their target tissues (long contact time with the buccal tissue).

Drug doses in a film-forming spray may be adjusted for systemic or local effects by changing the amount of solution per each spray. Additionally, an FFS offers a good spread and an even distribution of medications. The simplicity of the treatment can also help in increasing patient compliance [14,15]. It is simple to clean the thin film with water in contrast to gels, ointment, and other similar substances (that have viscous consistency when used), the film has a smooth, elastic consistency, boosts patient comfort during activities [16][17]. Marketed oral spray examples are shown in Table 1.

Table (1): Marketed oral sprays[18]

Product	Content	Commercial name	Special technology or properties
Buccal Mist	Mouth spray of Insulin	Oral-lyn™ spray	RapidMist™ spray dose Technology
Sublingual Spray solution	Sublingual spray of Glyceryl trinitrate	Glytrin Spray®	Metered-dose spray
Throat spray	Throat spray of Flurbiprofen	Benactiv®	Metered-dose spray
Sublingual	Isosorbide dinitrate	Isocard spray	Metered-dose aerosol.

Parts of Film-Forming Sprays and Types

Nozzle design, aperture size, spray pressure, and liquid type all have substantial impacts on FFS sprayability [19,20]. A regular spray pump in a can or bottle is the most convenient and efficient method of dispensing the product. A preferred valve actuator is a mechanical breakup actuator [21] (Figure 2).

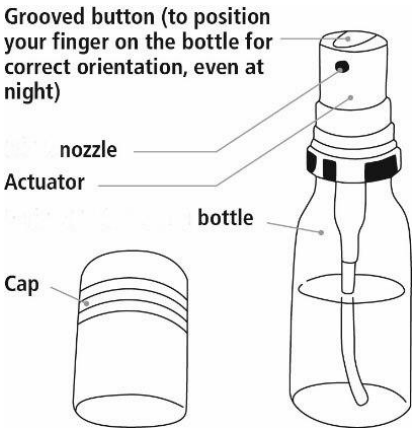


Figure (2): Parts of buccal spray [22]

The spray pressure, liquid characteristics, and nozzle type also have a role in determining the size of the resulting droplets. However, a single nozzle is capable of producing droplets of varying sizes, which is not always necessarily uniform, as shown in Figure 3. The volume sprayed per area, the uniformity of application, the coverage, and the possible danger of drift are all affected by the spray nozzles that are used [23].

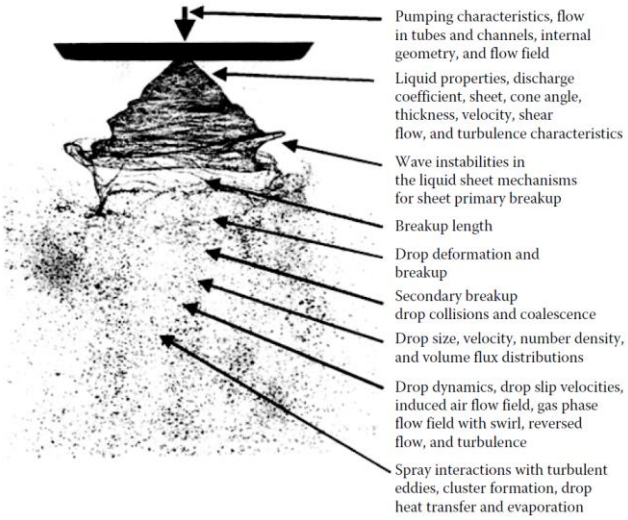


Figure (3):Shape and characteristics of the spray [24]

Aerosol systems which use the pressure of compressed or liquefied gas to force the contents of the container. Metered dose sprays, which do not use propellants rely on solvents and polymers to deliver a controlled quantity of medicine per each actuation, have recently replaced the propellant based sprays [25].

The propellant provides the force to expel the product from the container in the desirable form (spray, semisolid, foamy form). The propellant can be as a liquefied gas or mixing of liquefied gases, moreover, it can be used as the product concentrate's solvent. An example of propellant used in an oral formulation is Chlorofluorocarbon (CFC) [26].

Metered dose spray was invented by a Victorian College of Pharmacy (Australia) and commercialized by Acrux Limited [27]. It is a spray apparatus that can calibrate the amount of spray as shown in Figure 4. This device is often used for transdermal or transmucosal administration of preparations destined for the systemic compartment. In assessing a film forming spray, volume of spray is crucial to drug dose [28].

Figure (4): Metered dose spray [28]

The characteristics of the spray film, such as its viscoelasticity, in situ gelation, pH sensitivity, and temperature sensitivity, are essential to determining what considerations should be made when selecting polymeric materials, surfactants, and other optimized formulations. These characteristics are important because they help determine what factors should be taken into account [29]. Research on the components applied through buccal spray was included in the compiled literature as in the formation of Lidocaine Hydrochloride buccal spray where two different types of carbopol (934 and 940) were employed as film forming polymers and both types of carbopol and Lidocaine Hydrochloride precipitate when combined. Precipitate formation was avoided and preparation stability was increased by using additional polymer like xanthan gum, also they used propylparaben as a preservative [30].

Components of Film Forming Spray

Film Forming Spray Polymers

A summary of the many polymers that are put to use in the manufacture of buccal films in their various concentrations. There are natural polymers (such as hydroxypropyl methylcellulose HPMC), semi-synthetic polymers (such as ethyl cellulose), and synthetic polymers (such as polyvinyl pyrrolidone) [31]. Also, there are non-ionic polymers (such as hydroxyl ethyl cellulose HEC), anionic polymers (such as sodium carboxymethyl cellulose SCMC) as well as a cationic polymer (such as chitosan) [32,33].

Film-Forming Spray Excipients

To enhance the preparation's quality and therapeutic effectiveness, excipients other than polymers are also included such as the plasticizer which keeps the film elastic during film formation and stops it from cracking, increasing drug permeability while ensuring the stability of productivity [34], as shown in Table 2.

Table (2): List of excipients used for buccal film-forming spray

Class of excipient	Examples	Function
Surfactants	Sodium dodecyl sulfate [35] Sodium lauryl sulfate [36]	Permeation enhancer
	Polyethylene glycol 200 [37]	Plasticizer
	Polyethylene glycol 400 [28]	
Bile salts	Sodium glycocoholate [38,39] Sodium taurocholate, sodium glycol deoxycholate, and sodium tauro deoxycholate [38] Sodium deoxycholate [40]	Permeation enhancer
Fatty acids	Oleic acid [41–43] Eicosa pentaenoice acid [44] and or docosa hexaenoice acid [43]	Permeation enhancer
Fatty acid ester	Propylene glycol (PG) [45]	Plasticizer and permeation enhancer
Alcohol	Ethanol [46,47]	Permeation enhancer

Propylene glycol (PG) and polyethylene glycol (PEG) play a part in enhancing the penetration of antifungal medications. In addition to its function as a plasticizer, PG also serves as a solubilizer, which helps deliver medications [48]. The concentration of PG is important since it has a large impact on the film forming liquid's viscosity [49].

Polyethylene glycol 400 can be used to increase the volume of a film-forming solution of each puff. With higher polyethylene glycol 400 concentrations, the amount of each spray rises. Increasing polyethylene glycol 400 levels also increase the covered spray area [50]. Because PEG is a nonvolatile solvent [51], so the vapor pressure decreases [52]. Permeation enhancers also involved in film forming spray (FFS) that enhanced the paracellular penetration of the drug through the mucosal membrane such as; sodium glycocholate, oleic acid, lauric acid, and propylene glycol [53].

Solvents

The FFS employs both volatile and not volatile solvents. To maintain a steady rate of drying for the film. Films which have fast drying time make difficulty for the drug to enter and release from the produced hard films. In most cases, the active substance is dissolved within the solvent until it comes close to being saturated, which speeds up the drying process of the film [54].

Evaluation of Film-Forming Sprays

pH

The pH value is evaluated and changed to maximize the active ingredient's stability or suitability for the application area. The content and volume of saliva has a pH range of 5.9 to 7.3 [55]. In order to avoid irritation and changes in the physiological state, the preparation's pH has been adjusted [56]. As shown in pH of Rizatriptan benzoate films was in the range of 6.54 to 6.98 for all formulations indicating that no irritation is expected [57]. Also in Tizanidine hydrochloride buccal formulations, pH results ranged from 5.7 to 6.8 [58].

Viscosity

The viscosity of the polymer will vary depending on its type and dosage. The film-forming solution's viscosity will influence its sprayability, making it a crucial factor, especially in MDS [59]. The spray's coverage can be adjusted by adjusting the concentration of the film-

forming solution [12]. Low viscosity leads to easy administration, that was observed in Clove oil buccal spray formulations, their viscosity range was from 11.44-65.83 cp [60]. Low viscosity also was found in Clotrimazole buccal spray formulations due to the weak inter/intramolecular interaction of fatty acids that used so the range of viscosity was 4.61-13.93 cp [61].

Water Washability

The wettability of the film is determined by first analyzing it in its dry state. The film is washed and ranked on a scale on a regular basis, with easily cleaned getting the greatest possible score and poorly cleaned getting the lowest possible score. In the event that the film-forming solutions come into contact with the delicate areas of the body, such as the eyes or the mouth, a simple spritzing with water will be of great help [62]. It could be shown that the water washability in Fluconazole and Clotrimazole film forming spray was helpful for choosing the optimal formula [63][64].

Film Formation/Drying and Evaporation Time

Once the solution is sprayed, the film's drying period will influence how quickly the film formed. In some cases, the glass' surface is sprayed with the solution, which is then allowed to dry [65]. An alternative method of absorption testing involves coating a glass plate with a combination of activated silica gel and dye [29]. In Oxybutynin metered dose spray, an evaporation time was measured by spraying the formulation on ethanol sensitive paper and noting down the drying time and the results were from 65-85 seconds, so it was helpful to select the optimal formula [66].

Spray Angle

The produced spray patterns can easily be seen when a sheet of paper has been wetted with indicator reagents. This depends on the kind of solvent used and the pH of the solution that was used to make this film, also increasing the solute concentration and the viscosity of dosage form could decrease the coverage area of spray as in Clotrimazole film forming buccal spray, the spray angles were exhibited from 41.93 degree to 53.56 degree which led to conclusion that high amount of fatty acid lowered the spray angle of formulation [61]. see Figure 5.

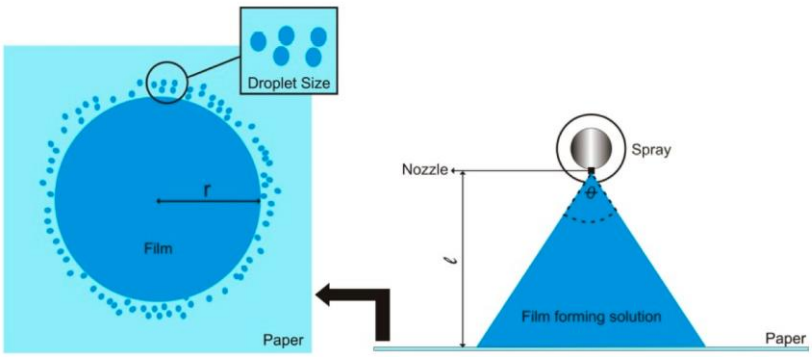


Figure (5): measurement of spray angle [28].

The spray angle and coverage area are then computed based on the pattern's diameter[67]:

$$\textbf{Spray Angle } \theta = \tan^{-1}\left(\frac{l}{r}\right) \quad \text{Eq. 1}$$

Where r is the circle's radius and l are the distance measured from the surface of the paper to the nozzle. The film-forming solution is more difficult to disseminate when sprayed at greater spray angles [12].

Drug Content per each spray actuation

The volume or amount of solution upon each spray is measured to establish drug content, and the concentration of the film-forming solution is used to quantify the dose uniformity. It is also possible to collect the sprayed solution and use instruments to determine the concentration of the active ingredient [49].

In order to get an accurate reading of the volume of spray that is produced, it is necessary to measure the total amount of solution that is contained within the sprayer rather than the weight of the film-forming solution that is expelled through the nozzle. Due to the fact that the spray droplets are so small and are easily carried by the wind, it is highly unlikely that all of the spray will be collected in order to be weighed. For calculating spray volume, use the formula below[14]:

$$V = \frac{Wt - Wo}{D} \quad \text{Eq. 2}$$

Where V represents the volume of spray that is produced with each actuation,
Wt represents the weight of the spray solution after it has been sprayed,
Wo represents the weight of the spray solution before it has been sprayed,
and D represents the density of the solution [14].

When working with metered-dose sprays, this test is absolutely necessary.

In vitro Drug Release Study

Franz diffusion cells or USP dissolution apparatus type II (paddle Method), are typically employed in this test as compartment separators, along with cellulose membranes (pore size 0.44 μm), nylon membranes (particle size 0.21 mm), or silicone membranes [62]. A phosphate buffer with a pH of 6.8 is the medium [68]. After the system for the compartments has been established, the solution for making the film is poured into the donor compartment. At certain intervals of time, a quantity of the solution that is being measured is collected from the cells, and the equipment that is being used to measure it is then adjusted accordingly. After samples have been taken, they are followed by the replacement of the exact same volume of fluid [69]. After that, the drawn samples were examined with a UV visible spectrometer.

Conclusion

The buccal mucosa is a suitable route to deliver drugs that cannot be absorbed via the digestive system (due to acidic medium of stomach, intestinal enzymes, or a strong hepatic first pass effect). It can also be inhaled or injected instead of being administered topically, intravenously, or nasally. The buccal mucosa's physiology permits the penetration of active compounds, and because of its quick cellular cycle and regeneration, penetration enhancers can be used. The latest studies have also demonstrated that adding permeability enhancers to buccal films did not impede production or cause mucosal irritation or toxicity. The design of buccal films still has a lot of possibility, including their recent application as system for the administration of nanoparticles and macromolecules to produce patient-friendly and safe dosage forms

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References

1- Bogue MH. Orally dissolving film strips (ODFS): The final evolution of orally dissolving dosage forms. Drug Deliv Technol. 2009;9(2):24–9.
2- K K Peh 1 CFW. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. J Pharm Pharm Sci. 1999;2(2):53–61.
3- Singh S, Jain S, Muthu MS, Tiwari S, Tilak R. Preparation and Evaluation of Buccal Bioadhesive Films Containing Clotrimazole. AAPS PharmSciTech. 2008 Jun;9(2):660–7.
4- DAWES LMCC and C. The Surface Area of the Adult Human Mouth and Thickness of the Salivary Film Covering the Teeth and Oral Mucosa. Res, J Dent. 1987;66(8):1300–2.
5- Alopaeus JF, Hellfritzsch M, Gutowski T, Scherließ R, Almeida A, Sarmento B, et al. Mucoadhesive buccal films based on a graft co-polymer – A mucin-retentive hydrogel scaffold. Eur J Pharm Sci. 2020;142:105142.
6- Caon T, Jin L, Simões CMO, Norton RS, Nicolazzo JA. Enhancing the buccal mucosal delivery of peptide and protein therapeutics. Pharm Res. 2015;32(1):1–21.
7- Morales JO, Brayden DJ. Buccal delivery of small molecules and biologics: of mucoadhesive polymers, films, and nanoparticles. Curr Opin Pharmacol. 2017;36:22–8.
8- Bagan J, Paderni C, Termine N, Campisi G, Lo Russo L, Compilato D, et al. Mucoadhesive polymers for oral transmucosal drug delivery: a review. Curr Pharm Des. 2012 Oct;18(34):5497–514.
9- Chinna Reddy P, Chaitanya KSCC, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru. 2011;19(6):385–403.
10- Pelin IM, Suflet DM. Mucoadhesive buccal drug delivery systems containing polysaccharides. Cellul Chem Technol. 2020;54(9–10):889–902.
11- Płaczek M, Sznitowska M. [The mucoadhesion phenomena and importance in drug application]. Polim Med. 2009;39(2):49–64.
12- Zhong Y, Zhuang C, Gu W, Zhao Y. Effect of molecular weight on the properties of chitosan films prepared using electrostatic spraying technique. Carbohydr Polym. 2019 May;212(February):197–205.
13- Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. Asian J Pharm Sci. 2017;12(6):487–97.
14- Ranade S, Bajaj A, Londhe V, Babul N, Kao D. Fabrication of topical metered dose film forming sprays for pain management. Eur J Pharm Sci. 2017 Mar;100:132–41.
15- Geh KJ, Stelzl A, Gröne A, Wagner L, Förster B, Winter G. Development of a sprayable hydrogel formulation for the skin application of therapeutic antibodies. Eur J Pharm Biopharm. 2019 Sep;142:123–32.
16- Tan X, Feldman SR, Chang J, Balkrishnan R. Topical drug delivery systems in dermatology: a review of patient adherence issues. Expert Opin Drug Deliv. 2012 Oct;9(10):1263–71.
17- Mahmood A. Haiss, Nidhal K. Maraie. Preparation and evaluation of oral capsules containing apigenin nanocrystals prepared by ultrasonication. Al Mustansiriyah J Pharm Sci. 2022;21(3):16–24.
18- Ghosh TK, Pfister WR, editors. Drug Delivery to the Oral Cavity. CRC Press; 2005.
19- Baio FHR, Antuniassi UR, Castilho BR, Teodoro PE, Silva EE da. Correction: Factors affecting aerial spray drift in the Brazilian Cerrado. PLoS One. 2019 Jun;14 (6):e0217957.
20- Gaytan I, Nicolas B, Gouriou F, Leru JP, Mallarach J. Effect of working

pressure, fluid temperature, nozzle type and nozzle orifice size, on spray characteristics using viscous feed additiveDL-2-hydroxy-4-(methylthio) -butanoic-acid. Powder Technol. 2018 Aug;336(2017):383–92.
21- Amar Lulla C. and Malhotra M. TOPCAL SPRAY COMPOSITIONS. Long Island City, NY.USA. Novamber 2005. Vol. 8.
22- Joseph Sandor. VARIABLE SPRAY NOZZLE FOR PRODUCT SPRAYER. USA: United States Patent (19); 5,941,462, 1999. p. 8.
23- Nogueira Martins R, Moraes HMF e, Freitas MAM de, Lima A da C, Furtado Junior MR. Effect of nozzle type and pressure on spray droplet characteristics. Idesia (Arica). 2021;39(1):101–7.
24- Lefebvre AH, Mcdonell VG. Atomization and Sprays, Second Edition. 2nd ed. CRC Press, Taylor and Francis. 2017. 300 p.
25- Kumar R, Philip A. Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin. Trop J Pharm Res. 2007;6(1):633–44.
26- Thosar MM. Intra oral sprays -An overview. Int J Pharm Life Sci. 2011;2(11):1235–46.
27- Kovács G, Zelei T, Vokó Z. Comparison of efficacy and local tolerability of estradiol metered-dose transdermal spray to estradiol patch in a network meta-analysis. Climacteric. 2016 Oct;19(5):488–95.
28- Umar AK, Butarbutar M, Sriwidodo S, Wathoni N. Film-Forming Sprays for Topical Drug Delivery. Drug Des Devel Ther. 2020 Jul;14:2909–25.
29- Bajaj A, Malhotra G, Madan M, Amrutiya N, Bakshi A. A novel metered dose transdermal spray formulation for oxybutynin. Indian J Pharm Sci. 2008;70(6):733.
30- Sulaiman HT, Jabir SA, Kadhem Al-kinani K. Investigating the effect of different grades and concentrations of ph-sensitive polymer on preparation and characterization of lidocaine hydrochloride as in situ gel buccal spray. Asian J Pharm Clin Res. 2018;11(11):401–7.
31- Maraie NK, Almajidi YQ. Effect of different mucoadhesive polymers on release of ondansetron HCl from intranasal mucoadhesive in situ gel. Al Mustansiriyah J Pharm Sci. 2018;17(2):10.
32- Sharma M, Rathore A, Sharma S, Sadhu V, Reddy KR, Kulkarni R V. Recent progress in mucoadhesive polymers for buccal drug delivery applications. Nanomaterials in Diagnostic Tools and Devices. INC; 2020. 213–240 p.
33- Lu W, Luo H, Zhu Z, Wu Y, Luo J, Wang H. Preparation and the Biopharmaceutical Evaluation for the Metered Dose Transdermal Spray of Dexketoprofen. J Drug Deliv [Internet]. 2014 Feb 11;2014:1–12.
34- Grip J, Engstad RE, Skjæveland I, Škalko-Basnet N, Holsæter AM. Sprayable Carbopol hydrogel with soluble beta-1,3/1,6-glucan as an active ingredient for wound healing - Development and in-vivo evaluation. Eur J Pharm Sci. 2017 Sep;107:24–31.
35- Nicolazzo JA, Reed BL, Finnin BC. Assessment of the Effects of Sodium Dodecyl Sulfate on the Buccal Permeability of Caffeine and Estradiol. J Pharm Sci. 2004;93(2):431–40.
36- Borrás-Blasco J, López A, Morant MJ, Díez-Sales O, Herráez-Domínguez M. Influence of sodium lauryl sulphate on the in vitro percutaneous absorption of compounds with different lipophilicity. Eur J Pharm Sci. 1997;5(1):15–22.
37- Sukhbir K, Navneet K, Sharma AK, Kapil K. Development of modified transdermal spray formulation of psoralen extract. Der Pharm Lett.

2013;5(2):85–94.
38- Hoogstraate AJ, Senel S, Cullander C, Verhoef J, Junginger HE, Boddé HE. Effects of bile salts on transport rates and routes of FITC-labelled compounds across porcine buccal epithelium in vitro. J Control Release. 1996;40(3):211–21.
39- Deneer VHM, Drese GB, Roemelé PEH, Verhoef JC, Lie-A-Huen L, Kingma JH, et al. Buccal transport of flecainide and sotalol: Effect of a bile salt and ionization state. Int J Pharm. 2002;241(1):127–34.
40- Sahni J, Raj S, Ahmad FJ, Khar RK. Design and in vitro characterization of buccoadhesive drug delivery system of insulin. Indian J Pharm Sci. 2008 Jan;70(1):61–5.
41- Taylor P, Abu-huwaij R. Potential Mucoadhesive Dosage Form of Lidocaine Hydrochloride : II . In Vitro and In Vivo Evaluation. (August 2015).
42- Manganaro AM, Wertz PW. The effects of permeabilizers on the in vitro penetration of propranolol through porcine buccal epithelium. Mil Med. 1996;161(11):669–72.
43- Morishita M, Barichello JM, Takayama K, Chiba Y, Tokiwa S, Nagai T. Pluronic F-127 gels incorporating highly purified unsaturated fatty acids for buccal delivery of insulin. Int J Pharm. 2001 Jan;212(2):289–93.
44- Abdullah Q. Khudhur, Nidhal K. Maraie, Ayad M.R. Raauf. Highlight on lipids and its use for covalent and non-covalent conjugations. Al Mustansiriyah J Pharm Sci. 2020;20(3):1–13.
45- Meng R, Yin D, Drapaca CS. A variable order fractional constitutive model of the viscoelastic behavior of polymers. Int J Non Linear Mech. 2019 Jul;113:171–7.
46- Nicolazzo JA, Reed BL, Finnin BC. Modification of buccal drug delivery following pretreatment with skin penetration enhancers. J Pharm Sci. 2004;93(8):2054–63.
47- Howie NM, Trigkas TK, Cruchley AT, Wertz PW, Squier CA, Williams DM. Short-term exposure to alcohol increases the permeability of human oral mucosa. Oral Dis. 2001;7(6):349–54.
48- Trottet L, Merly C, Mirza M, Hadgraft J, Davis A. Effect of finite doses of propylene glycol on enhancement of in vitro percutaneous permeation of loperamide hydrochloride. Int J Pharm. 2004 Apr;274(1–2):213–9.
49- Leichtnam ML, Rolland H, Wüthrich P, Guy RH. Formulation and evaluation of a testosterone transdermal spray. J Pharm Sci. 2006 Aug;95(8):1693–702.
50- Reid ML, Benaouda F, Khengar R, Jones SA, Brown MB. Topical corticosteroid delivery into human skin using hydrofluoroalkane metered dose aerosol sprays. Int J Pharm. 2013 Aug;452(1–2):157–65.
51- Mahdi ZH, Maraie NK, Al-Juboori ZA. Application of liquisolid technology to enhance the dissolution of cefixime from its oral capsules. Int J Appl Pharm. 2018;10(5):214–9.
52- Vervaet C, Byron PR. Drug–surfactant–propellant interactions in HFA-formulations. Int J Pharm. 1999 Sep;186(1):13–30.
53- Puratchikody A, Prasanth V V., Mathew ST, Kumar AB. Buccal drug delivery: Past, present and future - A review. Int J Drug Deliv. 2011;1(2):171–84.
54- Gohel MC, Nagori SA. Fabrication of Modified Transport Fluconazole Transdermal Spray Containing Ethyl Cellulose and Eudragit® RS100 as Film Formers. AAPS PharmSciTech. 2009 Jun;10 (2):684–91.
55- Ghareeb MM, Mohammad HA. Study the effects of secondary polymers on the properties of buccoadhesive polyvinyl alcohol patches of 5-

Flourouracil. Int J Pharm Pharm Sci. 2013;5 (SUPPL.4):484–8.
56- Vávrová K, Lorencová K, Klimentová J, Novotný J, Holý A, Hrabálek A. Transdermal and dermal delivery of adefovir: Effects of pH and permeation enhancers. Eur J Pharm Biopharm. 2008 Jun;69(2):597–604.
57- Salehi S, Boddohi S. New formulation and approach for mucoadhesive buccal film of rizatriptan benzoate. Prog Biomater. 2017;6(4):175–87.
58- Patil BSST, Kulkarni U, Hariprasanna RC, Wadageri GV. Development and in-vitro evaluation of mucoadhesive buccal tablets of Tizanidine hydrochloride using natural polymer xanthan gum. Int J Pharm Sci Rev Res [Internet]. 2011;8(2):140–6.
59- Liu X, Doub WH, Guo C. Assessment of the influence factors on nasal spray droplet velocity using phase-Doppler anemometry (PDA). AAPS PharmSciTech. 2011 Mar;12(1):337–43.
60- Monton C, Settharaksa S, Suksaeree J, Chusut T. The preparation, characterization, and stability evaluation of a microemulsion-based oral spray containing clove oil for the treatment of oral candidiasis. J Drug Deliv Sci Technol. 2020;57:1–7.
61- Mahadlek J, Myo Thurein S, Thammasut W, Phaechamud T. Clotrimazole-loaded fatty acid-based in situ forming film oral spray. Mater Today Proc [Internet]. 2022 Jan 1 [cited 2022 Jul 20];52(xxxx):2479–84.
62- Paradkar M, Thakkar V, Soni T, Gandhi T, Gohel M. Formulation and evaluation of clotrimazole transdermal spray. Drug Dev Ind Pharm. 2015 Oct;41(10):1718–25.
63- Gohel MC, Nagori SA. Fabrication of Modified Transport Fluconazole Transdermal Spray Containing Ethyl Cellulose and Eudragit® RS100 as Film Formers. AAPS PharmSciTech. 2009;10(2):684–91.
64- Paradkar M, Thakkar V, Soni T, Gandhi T, Gohel M. Formulation and evaluation of clotrimazole transdermal spray. Drug Dev Ind Pharm [Internet]. 2015 Oct 3;41(10):1718–25.
65- Lu W, Luo H, Wu Y, Zhu Z, Wang H. Preparation and characterization of a metered dose transdermal spray for testosterone. Acta Pharm Sin B. 2013 Dec;3(6):392–9.
66- Bajaj A, Malhotra G, Madan M, Amrutiya N, Bakshi A. A novel metered dose transdermal spray formulation for oxybutynin. Indian J Pharm Sci [Internet]. 2008; 70(6):733.
67- Radhakrishnan A, Kuppusamy G, Karri VVSR. Spray bandage strategy in topical drug delivery. J Drug Deliv Sci Technol. 2018 Feb;43:113–21.
68- Edwards A, Qi S, Liu F, Brown MB, McAuley WJ. Rationalising polymer selection for supersaturated film forming systems produced by an aerosol spray for the transdermal delivery of methylphenidate. Eur J Pharm Biopharm. 2017 May; 114:164–74.
69- Sabri LA, Sulayman HT, Ameen DW. Formulation of Tinidazole as an Oral Suspension Dosage Form. Al Mustansiriyah J Pharm Sci. 2013;13(1):82–93.