

Formulation and Characterization of Sublingual Film of Dapagliflozin Propanediol Monohydrate

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ABSTRACT

The name of the study is to develop and characterize sublingual film of Dapagliflozin Propanediol Monohydrate using Different Excipients. Compared to pills and capsules, sublingual films are more advantageous since they usually dissolve a minute after being placed under the tongue. Dapagliflozin is a drug of choice used in treatment of diabetes and heart failure. Administering the drug by Sublingual route enhances bioavailability and sublingual films bypasses the metabolism of the first pass of drug. The drug content, disintegration time, dissolution, thickness, tensile strength, folding durability, and surface pH of the film will all be assessed.

KEY WORDS: Sublingual film, Dapagliflozin, Antidiabetic, Cardiovascular.

Saliva dilutes the medication, which is then absorbed throughout the mouth cavity.

Sublingual Formulations

A. Bioadhesive Sublingual Tablet

The novel sublingual tablet idea that is being introduced is predicated on interaction mixes that comprise a bioadhesive component and a water-soluble carrier that is coated with tiny medication particles. This method allows the medication to dissolve quickly while maintaining its bioadhesive retention in the oral cavity.

B. Fast Disintegrating Sublingual tablet

The elderly, young patients, and those who have trouble swallowing can all benefit from the fast-dissolving tablets, which can come in handy when drinking water isn't an option. Usually, only a tiny amount of saliva is needed to get a pill to dissolve in the oral cavity. Drugs can then be absorbed by sublingual mucosal blood vessels, either fully or partly, into the systemic circulation.

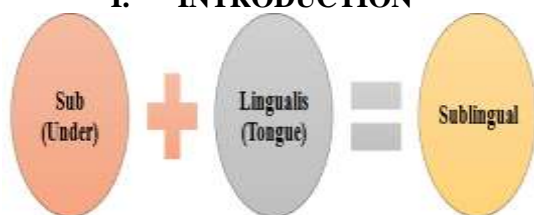
C. Thin film Drug Delivery

Delivering drugs to the systemic circulation via a thin film that dissolves when in contact with liquid referred to as a dissolving film or strip. Thin film is made using different grade of biopolymers. The advantage of this type of formulation is it has potential to improve the onset of action in lower dose.

D. Lipid Matrix Sublingual Tablet

Lipid Matrix Sublingual Tablet formulation creates a dosage form that provides a quicker and more thorough absorption than conventional oral modes of administration. For many specialised nutraceuticals that are frequently used orally, the Lipid Matrix Sublingual Tablet offers a bioavailable, rapid, convenient, and consistent dose form. Examples include methylcobalamin, or glutathione MB12.

I. INTRODUCTION



Salivary glands which are present in the mouth's floor under beneath the tongue. Another name for them is sublingual glands.

The term "sublingual" refers to the pharmacological method of delivery in which medications permeate the tissues behind the mouth and enter the bloodstream and improve the dose form bioavailability.

The absorption of the drug following this way Sublingual > Buccal > Gingival > Palatal. The sublingual route can cause a quick beginning of effect due to its high permeability and robust blood supply, allowing for frequent dosing of drugs with short delivery periods.

E. Sublingual Immunotherapy

SLIT is a type of immunotherapy in which allergen extract drops are placed beneath the tongue. SLIT is often administered in one of two ways: the patient swallows or spits out allergen extract drops (or tablets) under the tongue. It appears that swallowing the extract works better. Oral immunotherapy, which is taken by mouth and is not retained under the tongue for any length of time, is not utilised because it has too many gastrointestinal adverse effects, such as nausea, vomiting, and diarrhoea. It is mostly recommended for Paediatric patients with allergic rhinitis and/or asthma due to grass pollen.

F. Sublingual Vitamin Tablet

Vitamin B12 (Cyanocobalamin) is the only vitamin which can be taken sublingually. Recommended dose to be taken is once a day.

Ideal Characteristics of Drug to be selected

- The drug should have pleasant taste.
- The drug to be incorporated should have a low dose up to 40mg.
- It is better to use drugs with lower and intermediate molecular weights.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionised at the pH of oral cavity.
- It should have the ability to permeate the oral mucosal tissue.

II. FORMULATION OF MOUTH DISSOLVING FILM

A mouth dissolving film is a thin layer that has an active component and is 5 to 20 cm². The rapid disintegration in either saliva or water is accomplished by use of a unique matrix composed of water-soluble polymers. Typically, a composition has the following elements:

Composition of Fast Dissolving Oral films

Sr. No	Composition of strip	Quantity
1	Active pharmaceutical agent	1-25%
2	Film forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%

5	Sweetening agent	3-6%
6	Flavoring agent	10%
7	Coloring agent	1%

➤ **Active Pharmaceutical Agent**

The medications chosen for oral films should be low dosage medications with good stability in water and saliva. One to two thirds of the film should include the medication. The most suitable candidates for incorporation into an oral fast-dissolving film are small dosage compounds. Micronized API is usually helpful as it enhances the texture of the film and promotes improved dissolution and homogeneity in oral fast-dissolving films. For the drug that is water soluble there is no issue of uniformity of distribution. But in water insoluble, the uniformity may variate, thus to overcome it and for homogeneous distribution for better drug content uniformity the water insoluble drug is added in milled, micronized form or nanocrystals or microcapsules to get smooth texture of film.

➤ **Film Forming Polymer**

To achieve the required strip qualities, the polymers can be utilised singly or in combination. Oral films can be produced using both synthetic and natural polymers. Excipients or polymers with a low molecular weight and good film-forming ability must be water soluble in order to create a water-soluble film formulation. The polymer that is used needs to be non-irritating, non-toxic, and free of contaminants that can be leached. It should possess good spreading and wetting properties. There should be enough peel, shear, and tensile strengths in the polymer. At least 45% w/w of polymer should generally be present based on the total weight of dry film. The various natural as well as synthetic polymers to make fast dissolving films

➤ **Plasticizers**

Plasticizers should be used to improve the flexibility as well as the mechanical properties of the film like tensile strength and elongation and reduced a breakability of the film. A plasticizer selected should be compatible with API as well as with other ingredients. For improving the strip property of plasticizer the glass transition temperature of polymer for non aqueous solvent system reduced in range of 40-60 and for aqueous system the glass transition temperature of the polymer is reduced below 75. Examples of some

plasticizers are castor oil, polyethylene glycol, Citrate derivatives etc. Various examples of API along with plasticizer used is described in below table:

Examples of API with Plasticizer used

API	Name of Plasticizer
Triclosan	PEG
Montelukast Sodium	Glycerine
Sertraline	PEG
Loperamide	PEG
Famotidine	PEG
Ropinirole HCl	PEG
Cetirizine	PEG
Telmisartan	PEG

➤ **Saliva Stimulating Agent**

In order to facilitate the faster disintegration of the rapid dissolving strip formulations, saliva stimulating chemicals are used to boost the rate of saliva production. These agents can be employed in combinations or alone, making up 2-6% w/w of the strip. Salivary stimulants include, among others, tartaric acid, ascorbic acid, lactic acid, malic acid, and citric acid.¹¹

➤ **Sweetening Agents**

Sweetening agents should be used for masking the bitter taste of APIs approximately 3 to 6% w/w concentration of sweeteners should be used in preparation, either alone or in combination. In the formulation both natural and artificial sweeteners may be used. Natural sweeteners like sorbitol, Mannitol and isomalt and artificial sweeteners include neotame, Sucrose, Aspartame, Cyclamate may be incorporated in the films. However, artificial Sweeteners are mostly preferable, because natural sugars are restricted for diabetic patient as well as in people who are on diet.

➤ **Flavouring Agents**

Flavours are added to the Fast dissolving film formulations, preferably up to 10%w/w. The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from the synthetic

flavor oils, oleo resins, extracts derived from various parts of plants like leaves, fruits and flowers. Any flavour can be added, including acidic fruit flavours like lemon, orange, or clove, strong mints like peppermint, sweetmint, spearmint, wintergreen, cinnamon, and clove, and water-soluble menthol extracts or essential oils. Flavours like chocolate, vanilla, raspberry, cherry, or pineapple essence, or flavours like vanillin. Flavoring agents used for masking different taste is described below in table;

Flavoring agents used for masking of different taste is described as under

Taste	Flavouring agents used
Bitter	Mint, walnut, chocolate, wild cherry, anise
Salty	Peach, butterscotch, vanilla, Apricot, maple, winter green
Sweet	Vanilla, fruit berry
Sour	Raspberry, citrus, liquorice root

➤ **Coloring Agents**

A full range of colors is available including FD&C colors, EU colors, natural coloring agents and natural juice concentrates, pigments such as titanium dioxide, silicon dioxide and zinc oxide and custom pantonematched colors.

III. MANUFACTURING METHODS

Following processes can be used to manufacture fastdissolving films:

- Solvent casting
- Semi solid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method

• **Solvent Casting Method**

This method is most commonly used for manufacturing of fast dissolving oral film. In solvent casting method, the water soluble polymers are mixed in water to form homogeneous solution. Then, the API and remaining excipients are dissolved in smaller amount of other suitable solvent. Both the solutions are combined by constant stirring and mixing, the air entrapped is removed by sonification. Finally solution is poured in petridish and then dried at room temperature or in the oven.

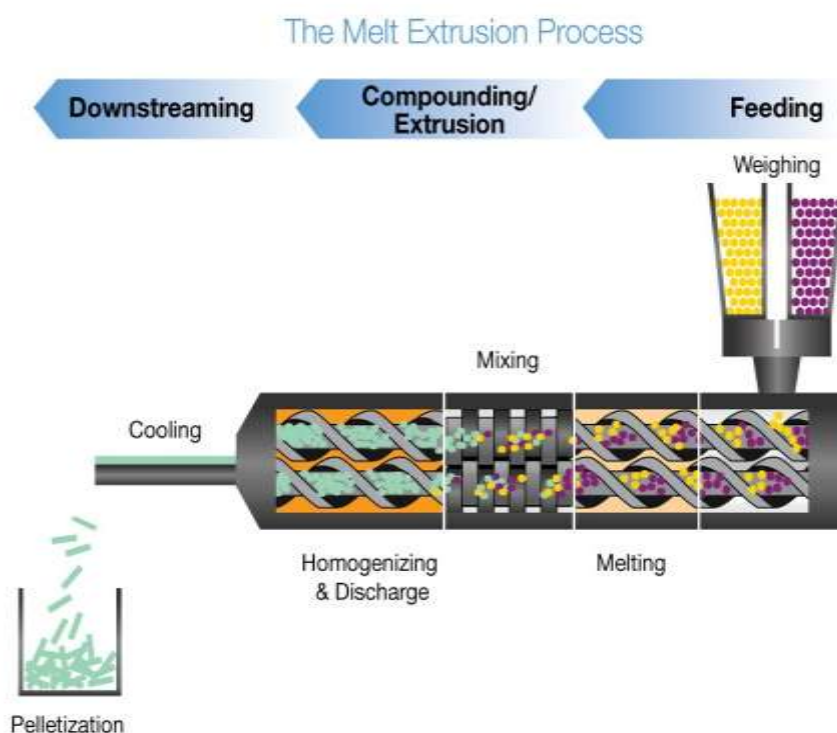
• **Semi Solid Casting Method**

When film is being prepared using acid-insoluble polymers, this approach is recommended.

The water soluble film-forming polymer solution is first made using this procedure. After that, the produced solution is added to an acid-insoluble polymer solution. Then plasticizer is added in appropriate amount to obtain gel mass. Ultimately, using heat-controlled drums, the resultant gel mass is cast in the films or ribbons. It is recommended to utilise a 1:4 ratio of acid-insoluble polymer to film-forming polymer.

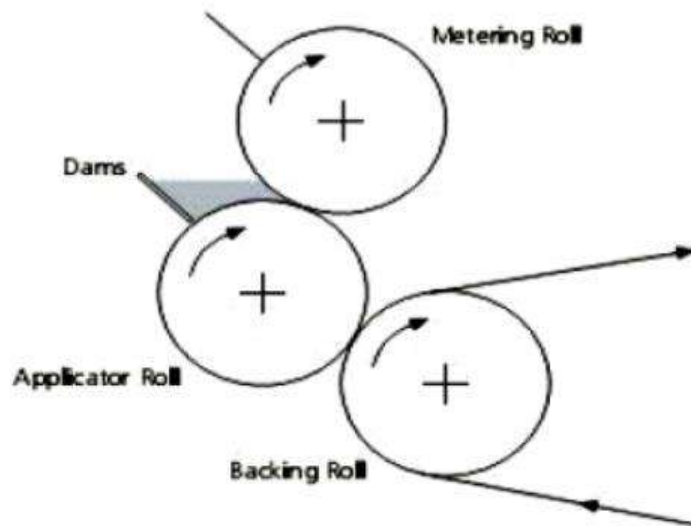
This method is mostly used for preparation of granules, transdermal drug delivery system, transmucosal drug delivery system and sustained release tablets. This method includes shaping of polymers through heating. In this method, the drug along with other excipients are combined in dry state, without use of any solvent and then subjected to extruder. Then the extruders having heaters that melt the mixture. The molten mass obtained is shaped in to the films.

- **Hot Melt Extrusion method**



- **Solid Dispersion Extrusion²⁰**
Solid dispersion method is dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Using suitable liquid solvent, the drug is dissolved. Incorporate solution into the melt of polyethylene glycol, below 70°C. At last the solid dispersions are shaped into the films by means of dies.

- **Rolling Method**
In this method, the solvent mainly used are water and mixture of water and alcohol. In small portion of aqueous solvent, the active agent and other ingredients are dissolved by means of high shear processor. Then to prepare homogeneous viscous solution water soluble hydrocolloids is dissolved in water. The solution containing drug is then rolled on a carrier. The films are dried on roller and cutted in desired shape and sizes.



IV. METHOD OF PREPARATION

Dapagliflozin propanediol monohydrate films are prepared by solvent casting method using hydrophilic polymer (HPMC), plasticizer, and saliva simulating agent in each formulation.

Firstly the required amount of drug is dissolved in water and then film forming polymer of required quantity is dissolved in water.

With constant stirring, mix both the solutions until clear solution is obtained, then add required quantity of plasticizer in this solution.

Remaining excipients were then dissolved in the solution step by step until clear solution is obtained.

Then pour the solution in petri dish, and allow the air bubbles to be removed, keep it in even level to avoid the difference in thickness of film

The film should be dried at room temperature upto 24 hours.

Care fully takeout the dried film from petridish and cut them into 2*2 cm size. The film were then packed in airtight plastic zipbags until further use.

V. EVALUATION PARAMETERS

1.1.1 Weight Variation

4 cm² films was cut at five different places in the cast film. The weight of each film strip was taken and the average weight was calculated.

1.1.2 Thickness of Film

The thickness of the patch was measured using digital Vernier Calipers with a least count of 0.01mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken.

1.1.3 Surface pH²²

To look into potential adverse effects in in vivo investigations, the pH of the film's surface was measured. It was made sure to maintain the surface pH as near to pH 6.8 (oral cavity pH) as possible since an acidic or alkaline pH may irritate the oral mucosa. Typically, a pH metre was used to measure the pH of an oral film by placing the film in a test tube, making a film solution with distilled water, and then recording the pH.

1.1.4 Tensile Strength²²

A 202 centimetre strip was cut from the film. Tensile test was performed according to ASTM International Test Method for Thin Plastic Sheeting. Each test strip was placed in a tensile grip on the texture analyzer. The test was considered concluded when the film breaks. Tensile strength, was computed with the help of load require to break the film and cross sectional area to evaluate tensile properties of the films.

Tensile Strength = Force at break (N) / Cross sectional area (mm²)

1.1.5 Folding Endurance

Folding endurance to determine mechanical properties of film and was measured by repeatedly folding of the film at the same place to the extent where film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value. This parameter was checked simply by visual inspection of films.

1.1.6 Disintegration time

Disintegration test was performed according to specification of oral dispersible tablet reported in European Pharmacopeia by USP disintegration apparatus on samples of area 2 cm × 2 cm. The disintegration time is the length of time it takes for a film to shatter or dissolve entirely;

with oral films, this usually happens in two minutes.

1.1.7 Diffusion Study²³

In-vitro diffusion study of prepared Sublingual film by Franz diffusion Cell method. Franz diffusion cell was employed for the in vitro characterization of oral soluble film formulations. The receptor compartment of the diffusion cell was filled with 30.0 ml of phosphate buffered saline (pH 6.8), and in vitro drug release studies were carried out using Chicken skin. The prepared formulations were placed on to the membrane in the donor compartment and were uniformly spread onto Chicken skin membrane. The assembly was constantly maintained at 37.0 ± 5.0 °C. Samples (1.0 ml aliquots) were then withdrawn at suitable time intervals (0, 5, 10, 15, 20, 30 Min) and replenished with an amount of medium to maintain the receptor phase volume to 30 ml. The samples were analysed spectrophotometrically at 225nm.

1.1.8 % Elongation

When the stress is applied to the sample of film strip it stretches that is referred as strain. Increase in concentration of plasticizer causes increase in elongation of strip. Percentage elongation of the film is calculated by following equation:

% Elongation = Increase in length X 100/ Original length

1.1.9 Drug Content

A film of size 2cm × 2cm was cut and kept in 10 ml of volumetric flask containing distilled water as solvent. Then the volume was made up to the 10ml with distilled water to acquire a concentration of 1000 µg/mL. The working standard solution of 10 µg/mL was prepared by appropriate dilution of the stock solution with distilled water. The drug content was determined spectroscopically after appropriate dilution and measured at 225 nm.

1.1.10 Stability Study

The optimized batch was subjected for stability study. All the films were suitably packed in aluminum foil. The films to be stored at 40°C/75% RH condition. At the end of 1 month, the sealed films were opened and evaluated for different parameters like, Appearance, drug content, disintegration time and dissolution study.

VI. CONCLUSION

Fast Dissolving Sublingual Film are the Novel approach in Oral Drug Delivery System. Fast Dissolving Sublingual film have emerged as revolutionary trend and extensive research activities involving various categories of drug are going on in this field. This formulation overcome problem which other solid formulation are facing. Patient compliance for this formulation more in geriatric and pediatrics. In most of severe case it can use because just keep into the mouth within few minute it will disintegrate and reach into blood circulation. So it can be concluded that the oral film with so many advantage and high patient compliance have flowing futuristic opportunities.

REFERENCES

- [1]. Shruti C, Sarvesh D, Amitha S, Samuel S, Mohd A and Shabaraya A, "A Review on Fast Dissolving Sublingual Films for Systemic Drug Delivery", International Journal of Pharmaceutical and Chemical Sciences, **2014**, 3 (2), 501-512.
- [2]. Saini P, Kumar A and Sharma P and Visht S, "Fast disintegrating oral films: A recent trend of drug delivery". Int J Drug Dev & Res. **2012**, 4(4), 80-94.
- [3]. Pandya K, Patel KR, Patel MR and Patel NM, "Fast dissolving films: A novel approach to oral drug delivery". Int J Pharm Teaching & Practices., **2013**, 4(2), 655-651.
- [4]. Prajapati V, Bansal M and Sharma PK, "Mucoadhesive buccal patches and use of natural polymer in its preparation- A review". Int J PharmTechRes, **2012**, 4(2), 582-589.
- [5]. Ghodake, P.P., Karande, K.M., Osmani, R.A. Bhosale, "Mouth Dissolving films: Innovative Vehicle for Oral Drug Delivery Mouth Dissolving Films." Innovative Vehicle for Oral Drug Delivery, September., **2013**.
- [6]. Vishwakarma, D.K., & Banerjeer, "Acta Biomedica Scientia Mouth dissolving film: an approach to novel drug delivery system-a review", **2018**, 5(1), 29-36.
- [7]. Rajeev G., An Advanced Oral Solid Dosage Form: Oral Dissolving Film, **2019**, 9, 731-742.
- [8]. Tiwari, R.R., Umashankar, M.S., & Damodharan N, "Recent update on oral films: A bench to market potential", International Journal of Applied Pharmaceutics, **2018**, 10(6), 27-33.
- [9]. Gupta M, Gupta R., Khunteta A., & Swarnakar S., "An Overview of mouth dissolving films: Formulation Aspects", International Journal of Pharmaceutical and Biological Science Archive, **2017**, 5(5), 01-18.
- [10]. Sharma D., Kaur D., Verma S., Singh M., & Singh G., "Fast Dissolving Oral Film technology: A recent trend for an innovative oral drug delivery system.", International Journal of Drug Delivery, **2015**, 7(2), 60-75.
- [11]. Alagusundaram M., Development and Evaluation of novel-trans-buccoadhesive films of Famotidine, **2011**, 2(1), 17-23.
- [12]. Sandeep I.A., Bhavana N., Sankeerth P.T., Nandhini P., & Nandendla R.R., "Formulation and Evaluation of Loperamide Oral Films", **2017**, 8(10), 370-379.
- [13]. Thakur N., Bansal M., Sharma N., Yadav G., & Khare P., Overview "A Novel Approach of Fast Dissolving Films and Their Patents.", Advances in Biological Research, **2013**, 7(2), 50-58.
- [14]. Bhyan B., Jangra S., Kaur M., & Singh H., "Review Article Orally Fast Dissolving films": Innovations in formulation and technology, **2015**, 9(2), 50-57.
- [15]. Reddy M.R., "An Introduction to Fast Dissolving Oral thin Film Drug Delivery Systems: A Review", **2020**, 12(7), 925-940.
- [16]. Arya, A., Chandra, A., Sharma, V., & Pathak, K., "Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form", **2010**, 2(1), 576-583.
- [17]. R., Kumar, S. N., Kumar, K. R., Sundaram, S. R., Sudharsan, S., & Nadu, T., "An dissolving films.", **2021** 10(2), 656-673.
- [18]. Panda, B., "Fast Dissolving Film as an Effective Orally Disintegrating Drug Delivery System Development of Innovative Orally Fast Disintegrating Film Dosage Forms: A Review", July **2016**.
- [19]. Reza, K. H., & Chakraborty, P., "Recent industrial development in Oral Thin Film Technology: An Overview", **2016**, 4(8), 17-22.
- [20]. Kaur P, Kumar V. "Formulation development and evaluation of fast

- dissolving bioadhesive sublingual film of sumatriptan.”, **2017**;6(14):385-410.
- [21]. Aher SS, Sangale VD, Saudagr RB, “Formulation and evaluation of sublingual film of Hydralazine Hydrochloride”., Research Journal of Pharmacy and Technology. **2016**;9(10):1681- 90
- [22]. Sahoo S, Malviya K, Makwana A, Mohapatra Pk, Sahu A. “Formulation, Optimization and evaluation Of Sublingual Film OfEnalaprilmaleate Using 3² Full Factorial Design”. International Journal of Applied Pharmaceutics. **2021** Jan 7:178-86.
- [23]. Sarita rana et.al ‘Formulation and evaluation of Domperidone fast dissolving film by using different polymers’ Int Jr Ph Res &Health Sci, **2014**, 2(5) :374-378.
- [24]. Mante GV, Hemke AT, Umekar MJ. RP-HPLC Method for Estimation of Dapagliflozin from its Tablet. International Journal of ChemTech Research. **2018**;11(01):242-8.
- [25]. Dr D. Nagendrakumar et.al “Formulation and evaluation of fast dissolvingoral film of metoprolol succinate”, Int Jr En& App Sci, **2015**, vol 6 (4) :28-36.