IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2019 Vol.:15, Issue:4

Sublingual Fast Dissolving Niosomal Films: A Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

JULIE E JAMES[1]*, SHAIJU S DHARAN[1], BINEESHA K B[1], JICKY T PANICKER[1], SOJAN ABRAHAM JOSHUA[1]

[1]Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara-695124, Thiruvananthapuram, Kerala,

Submission: 24 June 2019
Accepted: 30 June 2019
Published: 30 July 2019

Keywords: Niosome, Superdisintegrants, Sublingual film.

ABSTRACT

Sublingual drug delivery refers to a mode of drug delivery by which the drug substances are placed under the tongue and are directly absorbed via the blood vessels under the tongue. Niosomes are promising drug carriers having a bilayer structure formulated using nonionic surfactant and cholesterol. The prepared niosomes are incorporated into the film-forming polymers containing super disintegrating agents to obtain sublingual liposomal films. These films consist of oral strips formulated using hydrophilic polymers that rapidly disintegrate and dissolve when placed in the oral cavity to release the medication, which becomes available for oromucosal absorption, without chewing and intake of water. Hence, it offers a convenient way for patients who cannot be dosed orally especially pediatric and geriatric patients and also for patients who are unable to swallow a large quantity of water, such as those suffering from dysphagia, repeated emesis, motion sickness, and mental disorders.

INTRODUCTION

The Fast Dissolving Drug Delivery Systems was a headway that started to be in the early 1970s and combats over the utilization of the tablets, syrups, capsules which are the other oral drug delivery system. Fast Dissolving Drug Delivery Systems serves as a real benefit over the conventional dosage forms since the drugs get quickly disintegrated & dissolves in the salivation without the utilization of water[1].

The orally fast-dissolving film is a new drug delivery system for the oral delivery of the drugs. It was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of $500 million in 2007 and could reach $2 billion in2012[2]. Based on upward global growth trends of the past decade, the fast-dissolving dosage market could produce revenues of $13 billion by 2015.

This fast-dissolving drug delivery system (FDDS) is fitted for the drugs which undergo high first-pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and aswell accomplish it cost-effective.

Drug delivery systems using colloidal particulate carriers have significant advantages over conventional dosage forms as the particles can act as a reservoir for the loaded drug. Niosomes are closed bilayer vesicles formed by self-assembly of nonionic surfactants in aqueous media. These structures are analogous to liposomes but can increase the stability of their entrapped drugs. Due to the flexibility of their structural characteristics (composition, fluidity, and size) and ease of storage and handling, these lipid vesicles can be tailored for delivery of a wide variety of drugs for drug targeting, controlled release, and permeation enhancement. Drug delivery by per-oral administering appear some problems such as hepatic first-pass metabolism and enzymatic degradation within the GI tract. For certain class of drugs, these problems can be overcome by their administration through sublingual mucosa[3].

ADVANTAGES OF FAST DISSOLVING SUBLINGUAL DRUG DELIVERY

- Provides better patient compliance
- Taste masking of the drug
- Improved stability
- No need for water
- Rapid onset of action
- Improve bioavailability
- Accurate dosing

DISADVANTAGES OF FAST DISSOLVING SUBLINGUAL DRUG DELIVERY

- Fast dissolving films are hygroscopic so kept in dry places.
- Special packaging should be required for product stability and safety[4].

METHODS

Formulation of drug-loaded niosomes:

Niosomes were prepared by the conventional thin-film hydration method using span 60 as a nonionic surfactant and cholesterol as an enhancer of liposomal membrane rigidity. The drug to surfactant ratios were 1:2 and the drug and cholesterol ratio was similar in all formulations. The drug, nonionic surfactant, and cholesterol were weighed and dissolved in chloroform in a round bottom flask. The solvent was evaporated at a temperature of 60°C under reduced pressure using a rotary evaporator to form a thin film on the flask wall. The resulting film was hydrated with ultrapure water (deionized water) for 30 minutes at room temperature with gentle shaking. This film was hydrated with 10 mL of deionized water at 60°C. The resulting liposomal suspension was mixed by vortex mixing for 10 minutes and sonicated for 20 minutes at 25°C. The niosomal suspension was left overnight at 4°C and stored at refrigerator temperature (4°C–8°C) for further studies.

CHARACTERIZATION OF PREPARED NIOSOMES

Determination of entrapment efficiency:

Niosomes containing drug were separated from the free drug by cooling centrifugation at 15,000 rpm for 60 minutes at 4°C. The niosomal pellets were suspended in methanol and centrifuged again. The integrity of vesicles was not affected by centrifugation as reported in the literature. The washing procedure was repeated two times as reported previously. The supernatant was separated each time and assayed spectrophotometrically. The amount of entrapped drug was obtained by subtracting the amount of free drug from the total drug. The percent of entrapment efficiency (EE%)was then calculated according to the Equation (each result is the mean of three separate experiments):

$$EE\% = \frac{\text{Amount of entrapped drug}}{\text{Total drug amount}} \times 100$$

Particle size and zeta potential:

The mean particle size (nm) and polydispersity index of the prepared niosomes in both niosomal dispersion and niosomal film were measured by dynamic light scattering laser using a Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK) equipped with a 4 mW helium/neon laser (λ=633 nm) and thermoelectric temperature controller. The corresponding zeta potentials (mV) were determined by photon correlation spectroscopy using the same Zetasizer Nano instrument[2].

METHODS FOR THE DEVELOPMENT OF FAST DISSOLVING SUBLINGUAL FILMS

Rolling method:

Solution or suspension of the drug is prepared with film-forming polymers and this is subjected to the roller. The rheological properties for solution or suspension of the drug should be considered before processing them. The solvent which is mainly used is water or a mixture of water with alcohol. The film which is placed on the roller is dried and then after drying film is cut into specific pieces of desired shapes and sizes.

Hot-melt extrusion:

In this method, heating is used to convert the polymeric solution into a film. In this method API and other ingredients are mixed in a dry state and then subjected to the heating process. The mixture is then extruded out in the molten state without using any solvent [Figure no 1]. The molten mass is thus used to cast the film and then film is cut into the desired size and shape. This process is not suitable for thermolabile ingredients. Optimization of the speed of casting and drying time is important from the commercial-scale output.

The drug is mixed with carriers in solid form.

⇩

The extruder having heaters melts the mixture

⇩

Finally, the melt is shaped in films by the dies

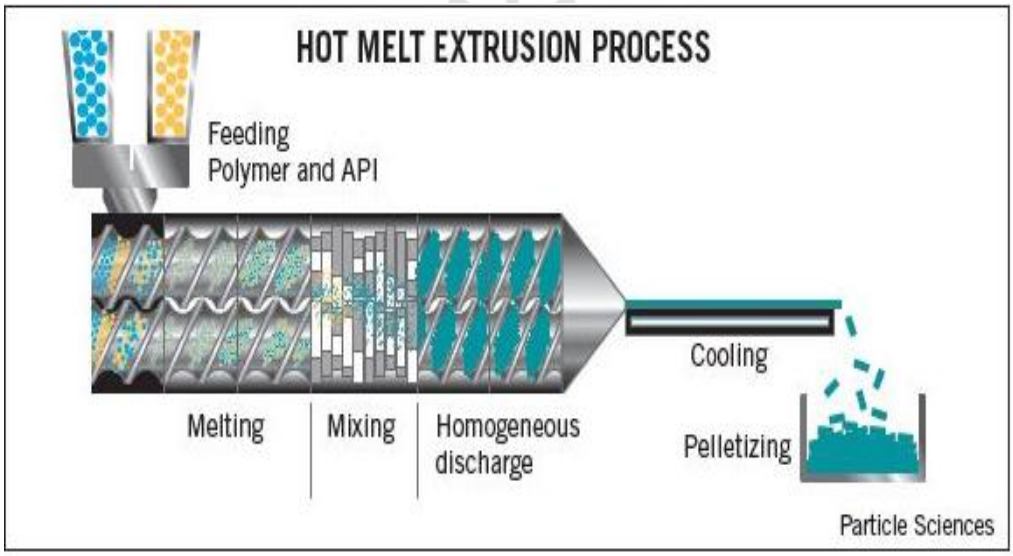


Figure no 1: Hot melt extrusion process

Solid dispersion extrusion:

In this technique, immiscible components are extruded with drug and then solid dispersion is prepared. Finally, solid dispersion is shaped into the films.

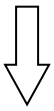
Spray drying:

A solvent system containing film former and other excipients are sprayed or coated on suitable carrier material, dried and peeled off to get the film. The carrier materials used for the film are glass, nonsiliconized kraft paper or polyethylene film, etc.

Solvent casting technique:

Fast dissolving films are ideally formulated using the solvent casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution and the drug along with different excipients are dissolved in a suitable solvent then both the solutions are mixed and stirred and lastly cast into the Petri plate and dried[Figure no 2].

Water soluble ingredients are dissolved in water



API and other agents are dissolved in a suitable solvent to form a clear viscous solution

Both the solutions are mixed

Degassed under vacuum

The resulting solution is cast as a film

The film is dried in a drying oven and collected [2,3]

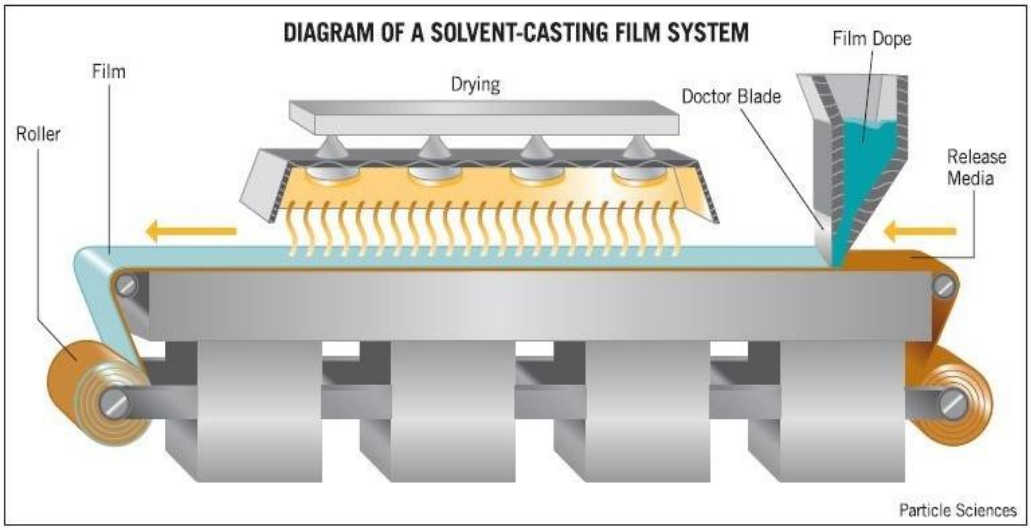


Figure no 2: Solvent casting method

INGREDIENTS USED IN THE FAST DISSOLVING FILMS

Film-forming polymers:

These are the agents which are used as film formers. It is used as the base of the FDF's. It helps in the rapid disintegration and provides mechanical properties to the FDF's. It provides good mouthfeel also. The disintegration rate of the polymer is decreased by increasing the molecular weight of the polymer film base. Polymers which are mainly used in the FDF's are HPMC (Hydroxyl Propyl Methyl Cellulose), PVA (Polyvinyl Alcohol), pullulan, eudragit, sodium alginate, gelatin, Pectin, etc.

Plasticizer:

These plasticizers are important for providing the mechanical properties to the FDF's. Mechanical properties which are mainly improved by using these plasticizers are percentage elongation and tensile strength. Optimized amount of plasticizers are used to get a better FDF's. The commonly used plasticizers are Polyethylene Glycol (PEG 400, 4000, etc.), and glycerols.

Flavors:

Flavors are added to provide taste to the film. There are various flavors which are added to the film formation. Any flavor can be added i.e. intense mint, sour fruits flavor, or other sweet confectionery flavors are also added to the fast-dissolving film formulation. Optimized

amount of flavor was added to the FDF's. These flavoring agents should be compatible with the drug and other ingredients. The choice of flavors changes with the conditions like age i.e. geriatric patients like mint or orange flavor, while youngsters like fruit flavors.

Coloring agents:

The coloring agents are added to the film formation to impart color to the FDF's. Coloring agents should be compatible with the drug and other ingredients.

Sweetening agents:

It is the most important part of the oral pharmaceutical product. Sweetening agents help in the taste masking of the bitter drugs. There are varieties of sweetening agents which are used in the formulation of FDF's i.e. sucrose, dextrose, fructose, glucose, etc. There are also polyhydric alcohols such as sorbitol, mannitol, and isomalt. These are preferably used in the combination for having less carcinogenic activity and also used as cooling agents [4].

CHARACTERIZATION OF DRUG

Physical appearance test:

Observe the color, odor and physical state.

Melting point:

The melting point of the drug was determined using the capillary method. Drug was filled into the capillary tube sealed at one end up to the height of 3 mm from the sealed end. Capillary was introduced into the digital melting point apparatus. The melting point was noted from the temperature at which drug starts melting to the temperature at which the entire sample melts.

FTIR spectra analysis:

An FT-IR spectrum of the drug was recorded by Potassium bromide (KBr) palletization method. The drug was mixed with KBr and was compressed into a small thin disk, which was subsequently analyzed by FT-IR spectrophotometer. Obtained spectra were analyzed for characteristic peaks corresponding to specific functional groups present in the drug molecule. These peaks were considered as a reference for further drug-excipient compatibility studies.

PREPARATION OF FAST DISSOLVING NIOSOMAL FILMS

Fast dissolving films were prepared by solvent casting technique. HPMC and MC were used as film-forming polymers. Polyethylene Glycol 400 was used as a plasticizer, saccharine as a sweetener, and menthol as a flavoring agent and to give mouth refreshment feeling. Concentrations of plasticizer, sweetener, and flavoring agents were kept constant. Microcrystalline cellulose (Avicel), croscarmellose sodium, crospovidone, and sodium starch glycolate were used as super disintegrants. Specified weight of the film-forming polymer was first dissolved in 20 mL of the casting solvent (warm distilled water), and sweetener and flavoring agent were dissolved in the polymeric solution. The calculated amount of super disintegrant was incorporated into the polymeric solutions after levigation with the required volume of the plasticizer. For the preparation of medicated films (containing free drug), the required amount of drug was directly added and completely dissolved into the polymeric solution before the addition of super disintegrant. For the liposomal film, a specified volume of the selected niosomal dispersion (corresponding to the required drug dose) was incorporated and gently mixed with the selected polymeric solution. The final volume was adjusted to 25 ml with distilled water, and the beaker was covered with aluminum foil to prevent solvent evaporation. The casting solution was subjected to gentle stirring for 2 hours using magnetic stirrer.

The casting solution (25 mL) was transferred into a previously cleaned and dried Teflon-coated plate (area =28 cm2, every 4 cm2 containing a specified amount of drug). The solvent was allowed to evaporate for 72 hours, and the film was then removed from the Teflon plate and was allowed to dry in a desiccator at least 48 hours before evaluation. The patches were punched into 4 cm2 pieces containing the drug, then wrapped in an aluminum foil (to maintain the integrity and elasticity of the films) and were finally stored in a dry place at ambient room temperature. The films were subjected to evaluation within 1 week of their preparation[2].

EVALUATION OF SUBLINGUAL FILMS

Physical evaluation:

- **Film-forming capacity:**

Film formers can form desired films. It is categorized according to film-forming capacity such as very poor, poor, average, good, very good and excellent.

- **The appearance of films:**

  It is evaluated by visual observation such as transparent or opaque.

- **Weight variation:**

The film of dimension 2×2 cm^2 was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

- **Thickness:**

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different position of the film. The thickness was measured at five different positions of the film and the average was taken and the standard deviation was calculated.

Mechanical evaluation:

- **Folding endurance:**

To determine folding endurance, a film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

- **Tensile strength:**

The Tensile strength (psi) is the property of the film that requires a load to cause the load-deformation failure of a film. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke.

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-sectional area of the sample}}$$

- **Percent elongation:**

The percent elongation is measured when the film snaps as sufficient force applied to exceed the elastic limit. Percentage elongation was obtained by the following equation.

$$\% \text{ Elongation} = \frac{\text{Increase in length at breaking point (mm)}}{\text{original length (mm)}} \times 100$$

- **Surface pH:**

The surface pH of fast dissolving film was determined to investigate the possibility of any in vivo side effect. As an acidic or alkaline pH may irritate the mucosa, so the surface pH of the films was determined to check whether it's neutralizing or not. A pH electrode was used for this purpose. The film was allowed to swell in closed Petri dish for 30 min. The pH was measured by bringing the electrode in contact with the surface of the sublingual film. The procedure was performed in triplicate and average with standard deviation was reported.

- **In-vitro Disintegration:**

The disintegration time is the time when the film starts to break or disintegrates. In-*vitro* disintegration time was determined in a Petri dish containing 25ml of pH 6.8 phosphate buffer at 37±0.5^{0}C with swirling every 10 sec.

- **Drug Content:**

Drug content determination of the film was carried out by dissolving the film of 4 cm2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically. The determination was carried out in triplicate and average with standard deviation was recorded.

- **Dissolution test:**

I*n vitro* dissolution test was carried out according to the USP type II dissolution apparatus. 900ml of pH 6.8 phosphate buffer was taken as dissolution media, the temperature was maintained at 37±0.5°C with a rotation speed of 50rpm. Five ml of sample was taken at

regular intervals which were replaced with the same volume of fresh pH 6.8 phosphate buffer and take the absorbance with the help of double beam UV-Visible spectrophotometer.

- **Scanning electron microscopy (SEM):**

The morphological characteristics of the Sublingual films were studied by scanning electron microscopy (JEOL, JSM-6510 LV SEM). The film sample was placed in the sample holder and the SEM micrographs were taken at 10,000x and 3000 magnification using tungsten filament as an electron source. Films were fixed onto a metallic stub with double-sided conductive tape (diameter 12 mm) [4].

CONCLUSION

Sublingual absorption is more efficient since the percent of drug absorbed by this route is generally higher than that achieved by the oral route. The sublingual niosomal film must have potential as an efficient delivery system to enhance the bioavailability and prolonged the therapeutic effects of the drugs thereby improving the patient compliance by eliminating the frequent dosing of drugs. Films have several advantages over the conventional dosage forms. So, they are of great importance during the emergency condition like allergy, short term spasm and asthma a whenever immediate onset of action is desired. Therefore oral thin films are an accepted technology for systemic delivery of API's.

REFERENCES

1. Ayat A, Gihan F. Sublingual fast-dissolving niosomal films for enhanced bioavailability and prolonged effect of metoprolol tartrate. Drug Des DevTherapy. 2016;10(1):2421-2433.
2. Auda SH, Fathalla D, Fetih G, El-Badry M, Shakeel F. Niosomes as transdermal drug delivery system for celecoxib: in vitro and in vivo studies. *Polym Bull*. 2016;73(2):1229–1245.
3. El-Badry M, Fetih G, Fathalla D, Shakeel F. Transdermal delivery of meloxicam using niosomal hydrogels: in vitro and pharmacodynamic evaluation. *Pharm Dev Technol*. 2015;20(7):820–826.
4. Khan R, Irchhaiya R. Niosomes: a potential tool for novel drug delivery. *J Pharm Investig*. 2016;46(3):195–204.
5. Narayana PR, Kumar MS, Reddy M. Formulation and evaluation of fast dissolving films of loratadine by solvent casting method. Pharm Innova J. 2013;2(2):31-35.
6. Kamboj S, Saini V, Bala S. Formulation and characterization of drug-loaded niosomal gel for anti-inflammatory activity. Int J Med Health Pharm Biomed Eng. 2013;7(12):541-545.
7. Sidramappa BS, Gara RK, Ganesh GK. Formulation and evaluation of clotrimazole niosomal gel for topical application. J Pharm Sci. 2015;5(1):32-38.
8. Auda SH, Mahrous GM, El-Badry M, Fathalla D. Development, preparation and evaluation of oral dissolving films containing metoclopramide. *Lat Am J Pharm*. 2014;33(6):1027–1033.
9. Upendra CG, Pooja PP, Pravin DC. Optimization and Characterization of fast dissolving sublingual wafers by using film former. Journal of Chemical and Pharmaceutical Research. 2017;9(4):82-91.

10. Pravin KS, Pankaj KS, Gajanan ND, Birendra S. Development and evaluation of fast dissolving oral film of poorly water-soluble drug felodipine. Asian journal of pharmaceutics.2018;12(1):56-67.
11. Prabhakara P, Akhilesh D, Karthik K. Formulation and evaluation of fast dissolving films of lisinopril. Egyptian Pharmaceutical Journal. 2015;14:56-64.
12. Deepak S, Daljit K, Shivani V. Fast dissolving oral films technology-A recent trend for an innovative oral drug delivery system. Intl J Drug Del. 2015;7:60–75.
13. Prakruti MA, Gangurde AB. Oral film technology-Challenges and future scope for the pharmaceutical industry. Intl J Pharm Pharma Res. 2015;3(3):183-203.
14. Soorya KP, Gowtham M. A comparative study on different polymers for the preparation of fast dissolving oral films of loperamide hydrochloride. World J Pharma Res. 2018;7(10):911-931.
15. Kadam VS, Bharkad VB, Shete GA. Formulation and evaluation of fast dissolving oral film of metoclopramide hydrochloride. World J Pharm Pharma Sci. 2017;6(8):2052-2066.