Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2019; 9(1); 15-20
doi: 10.25258/ijddt.9.1.3

ISSN: 0975 4415

Research Article

Technological Advancements in Oral Films

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Received: 7th Dec, 18; Revised: 9th Feb, 19, Accepted: 12th Feb, 19; Available Online: 25th Mar, 2019

ABSTRACT

The aim of the review was to explore the necessity, advantages and different techniques of oral films for enhancing solubility of poorly soluble drugs with an emphasis on the newer, state-of the art technologies, such as 3D printing and hot-melt extrusion (HME). The historical background of oral films is presented along with the regularly used techniques. The modern approach of quality-by-design (QbD) is unravelled, identifying appropriate critical process parameters (CPP) and applied to oral films. A section is devoted modern technologies such as 3D printing and HME of oral films. Oral films are innovative formulations by which poorly soluble drugs have been founds to give positive results in enhancing their solubility and dissolution characteristics. With modern sophisticated techniques, precise mass production of oral films has been given a thrust. Oral films have better patient compliance, improved biopharmaceutical properties, improved efficacy, and better safety. By applying QbD and implementation of modern technologies the newer generation of oral films are yielding promising results.

Keywords: 3D printing, film formers, oral films, quality by design , hot melt extrusion.

INTRODUCTION

Non-invasive, pain-free or painless treatment is becoming a key formulation design, innovation and marketing strategy, as it is more patient-friendly and compliant. This would mean recurring sales and an improved portfolio of innovative products in the repertoire of a pharmaceutical industry. Oral administration of drug is one of the most favoured means for delivery of active pharmaceutical ingredients (APIs), since it has low expenditure and superior patient compliance[1]. In order to provide optimum therapeutic concentration, the drug should have good solubility and permeability. Various approaches such as salt formation, size reduction, use of lipids vehicles, cosolvency, complexation, and use of prodrugs, surfactant and more are used for enhancing solubility of poorly soluble drugs[2].

Oral fast dissolving film is a novel dosage form in which thin film is prepared using hydrophilic polymer which rapidly dissolves on tongue or buccal cavity[3]. It rapidly disintegrates in few seconds and dissolves to release medication for oral mucosal absorption or for ingestion. Due to high blood flow and permeability of oral mucosa it has quick absorption and improved bioavailability when compared to absorption through enteric mucosa[4].

It is used in pediatric, geriatric, emetic patient, and patients suffering from diarrhoea. It can be used locally such as for local anaesthetics for toothache, oral ulcer, cold sores or teething. Oral films incorporate various ingredients in its formulation *viz.*, polymers, plasticizers, sweeteners, flavours, colours, saliva stimulating agent and preservatives[3].

Different versions of oral films have been investigated, some of which became commercially viable[5]. (Refer table 1)

Advantages of oral films

Dosing flexibility: The dosage can be varied according to the size of the films. A large quantity of active pharmaceutical ingredient (API) can be added without drastically altering the film characteristics.

Salivary secretions are enough to disperse/dissolve the films, without the aid of water. Also, the presence of the film will enhance the rate of saliva production; it will help in swallowing without the hazard of choking. Thus the problem of dysphagia is eased.

It is a simple-to-use dosage form which makes it more patient-compliant.

In case of oral mucosal absorption, the APIs go into the systemic circulation directly, bypassing the hepatic first-pass effect.

Oral films are excellent for site-specific delivery of APIs within the oral cavity for local action.

The accessibility of a sizeable mucosal surface area can lead to swift disintegration and dissolution inside the mouth.

Compared to liquid oral dosage forms, oral films have greater dose accuracy[6].

Disadvantages of oral films

APIs that are unstable at oral pH (5.75 and 7.05) are not suitable candidates.

APIs which can cause ulceration of the oral mucosa, such as indomethacin, certain antibiotics, etc., should not be deliveredby oral films.

There is an upper limit to the maximum amount of API

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Table 1: Types of oral films.

Type Property	Soluble films	Mucoadhesive fast disintegrating film	Mucoadhesive non-disintegrating films
Area (cm^2)	2-8	2-8	2-8
Thickness (µm)	20-500	20-500	20-500
Structure	Film: Single layer Foam: 3D structure. Matrix	Single or multilayer system. Matrix	Multi layer system. Matrix
Type of Polymer	Soluble, highly hydrophilic polymer	Soluble, hydrophilic polymer	Low/ non-soluble polymer
Drug phase	Solid solution	Solid solution or suspended drug	Suspension and /or solid solution
Place of application	Tongue, (upper palate)	Gingival or buccal region	Gingival (other region in the oral cavity)
Dissolution	Maximum 60 s	Disintegration in a few minutes, forming a gel which dissolves for immediate release and effect	Maximum 8-10 h for sustained release and effect
Site of action	Systemic or local	Systemic or local	Systemic or local

which can be accommodated in the presented surface area of the oral cavity.

Many drugs have bitter or metallic or unpalatable taste, which makes taste- masking mandatory.

The films are delicate and should be protected from the environment in a sturdy moisture-resistant and tamper-proof packaging[7].

Criteria for an ideal oral film

The API must be stable at oral pH.

The film consumption should be water-free, with only the salivary secretions aiding in disintegration or dissolution.

If the API is unpalatable, it should be compatible with taste- masking excipients.

In case the film is rapidly disintegrating/ dissolving, it must not leave behind any debris in the mouth.

The formulation should be stable throughout the shelf-life[3].

Quality by design (QbD) approach for formulation of oral films

The formulation of oral films can be optimized by QbD approach thus enabling quality assured dosage forms which are validated and reproducible. QbD approach is now favoured and is recommended by ICH guidelines for delivering quality pharmaceutical products. The generalized scheme for any QbD approach including formulation of oral films is to identify the quality target product profile (QTPP) and setting up properly defined critical quality attributes (CQAs) for the ultimate pharmaceutical product. In the scenario of producing ideal oral films, the CQAs are generally, possessing good mechanical properties such as tensile strength, elongation at rupture, appropriate Young's modulus, rapid disintegration time (in case of orodispersible films), excellent mucoadhesive properties (in case of long acting mucoadhesive films), and other attributes specific to the sub-type of the films. A subsequent step of the QTTP is the identification of the critical process parameters (CPPs). CPPs include the process variables, e.g. concentration film forming agents and amount of plasticizer that influence the CQA. By combining the CQA and CPP a design space can be created. As long as the formulation and process variables remain within the design space, a product will be obtained that meets the quality requirements[8].

Films forming agents

Diverse natural as well as synthetic polymers are employed in the formulation of oral films. They can be used either independently or in combination with other polymers so as to attain the required properties of the film. Polymers used must be non-toxic, non-irritant, possess excellent wettability, spreadability and should be economical. They ought to have adequate peel, shear and tensile strengths. Examples are hydroxpropyl methylcellulose (HPMC) E3, E5 and K3, maltodextrin, gelatin, hydroxypropyl cellulose (HPC) and Eudragit®. Polymers are categorized according to strip forming capacity such as very poor, poor, average, good, better and best[3].

Plasticizer

Plasticizers are usually small molecules in the form of resin or a liquid, that cause a decrease in polymer-polymer chain secondary bonding, resulting in secondary linkages with the polymer chains. They are utilised in oral films because they enhance film forming properties and the morphology of the film, cause a reduction in the glass transition temperature of the polymer, and avert the cracking of film. Plasticizers also improve the flexibility and aid in achieving the required mechanical properties. The frequently used plasticizers include polyethylene glycol, other glycol derivatives, glycerine, glucose, fructose, xylose, glycerol diacetate, etc[9].

Sweetening agent

Sweetening agents are especially used to mask the taste of unpalatable drugs. This also leads to better patient-compliance. Two kinds of sweetening agents, natural and artificial can be used. Sucrose is primarily used as a natural sweetening agent, unless it is contraindicated. Other natural sweeteners include dextrose, fructose, glucose and maltose. The usage of natural sweetener is contraindicated in patients who are diabetic or pre-diabetic, hence artificial

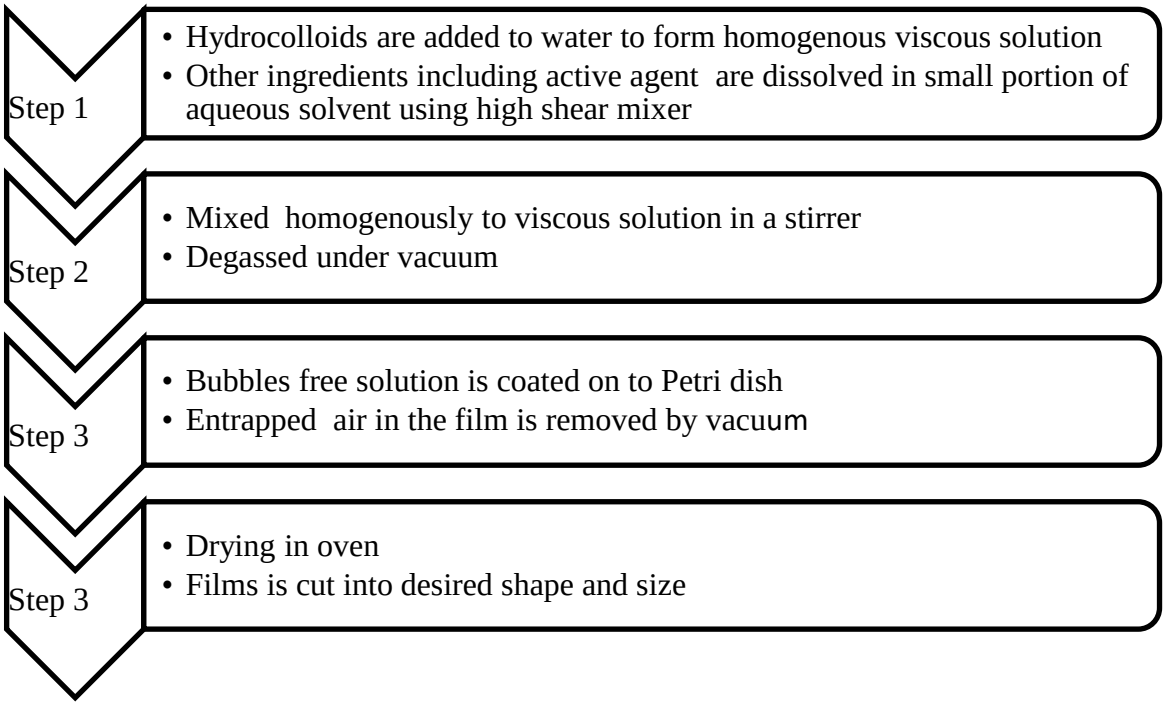

Figure 1: Scheme of preparing oral films by solvent casting method.

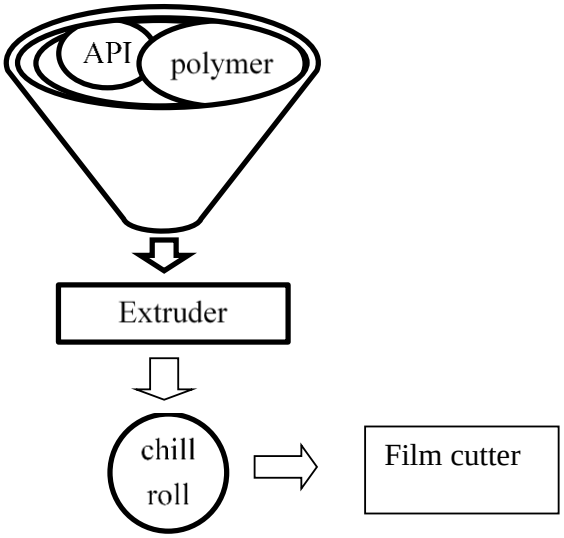

Figure 2: Hot-melt extrusion technique for preparing films.

sweeteners are substituted in their place. Examples of artificial agents are cyclamate, aspartame, sucralose and neotame etc[3].

Flavouring agent

Flavours enhance the palatability and feel of the films. Flavouring agents are usually derived from extracts of oleo-resin and herbal extracts. Examples include cinnamon oil, peppermint oil, caraway oil, dill oil, Stevia extract, etc. Artificial flavours include ascorbic acid, vanillin, benzaldehyde, etc[10].

Surfactant

Surfactants enhance the solubility and wettability of poorly aqueous soluble drugs and help in releasing the drugs in the span of a few seconds. Examples include sorbitan derivatives, sorbitol derivatives, esters of sucrose, fatty acid esters, alkylbenzene sulfonates, poloxamers, etc. Generally, their usage in the formulation varies between 0.5-6% by weight of the formulation. Polaxamer 407 is one of the most widely surfactant used in oral film formulation[11].

Thickening agents and stabilizer

Thickeners are added to increase the consistency and viscosity of the formulation. Thickening agents stabilize the formulation by creating a steric hindrance. They are especially used if the drug particles are in the form of suspension. Examples include xanthan gum, carrageenan,

Table 3: List of some marketed product available as oral films [19-23].

S.N	Brand name	API	Use
1	Listerine Cool Mint ®	Menthol	Mouth freshener
2	Melatonin fast dissolving strips	Melatonin	Jet lag
3	Orajel® Fil forming gel	Benzocaine, Menthol	Mouth-ulcer
4	Vitamin B_{12} fast dissolving strips	Vitamin B_{12}	Energising
5	Niqutin Strips	Nicotine	Smoking cessation

cellulosic derivatives, etc., up to a concentration of 5 % w/w[10].

Saliva stimulating agent

Salivary secretions aid in the quick disintegration of films. The concentration used is in the range of 2-6% w/w of the formulation. Examples include citric acid, ascorbic acid, etc[10].

Colouring agent

Colouring agents which are certified and permitted according to Food, Drug and Cosmetics (FDC) can be used. Examples include, naturally occurring fruit colours, pigments, for instance, titanium dioxide, zinc oxide are the most frequently employed colouring agents for oral film[10].

Oral films manufacturing method

The oral films manufacturing process includes:

Solvent casting method

Hot melt extrusion

Semi solid casting method

Solid dispersion extrusion

3D Printing

Solvent casting method

Preparation of oral film by using different steps in solvent casting method is explained in fig. 1[12].

Hot melt extrusion

In this method, drug is mixed with carrier or polymer in the solid form (refer fig. 2). Then extruder having heaters melt the mixture and finally the melts are shaped into films by the dies. Some benefits of hot melt extrusion include[13]:

Fewer operation units

Better content uniformity

Anhydrous processing.

Semi solid casting

In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to forms homogenous viscous solution. After sonication it is then coated on non-treated casting film. On drying, the thickness of film should be 0.015-0.05 inches[14].

Solid dispersion method

This method involves the dispersion of one or more active ingredients in an inert carrier in solid state in the presence of amorphous hydrophilic polymers[14]. For example, solid dispersions (SDs) of felodipine were prepared using poylvinylpyrrolidone K 30 as an inert hydrophilic polymer by solvent evaporation method. The SDs were then made into oral films via solvent casting technique[15].

3D Printing

Myriads of printing technologies are generating awareness as promising techniques for production of drug delivery systems. Printing when incorporated with oral film preparation techniques can yield formulations which offer a high degree of reproducibility and precision. Among these, inkjet printing is popular because of ease of automaticity and efficiency. Inkjet printing works on providing liquid droplets based on thermal or piezoelectric sensors. It is compatible with different substances and surfaces. Thermal inkjet printing was utilized to formulate salbutamol sulphate as an oral film using potato starch as a polymer for pediatric purpose. Flexographic printing has shown promising for incorporating appropriate doses of drug into placebo oral films. In a research paper, rasagiline mesylate and blue colorant were added to polymers such as hydroxypropyl cellulose in ethanolic solvent, and this ink was printed flexographically by rollers[16].

Evaluation parameters of oral films:

Uniformity of dosage units of the preparation

It should be tested by using 20 preparation of oral films and contain of drug were determine by analytical methods. The acceptance value (AV) of preparation is less than 15% according to Japanese pharmacopoeia (JP 15). It has been calculated according to following equation [17].

AV= (M-X)+ks

Where M= label claim

X= average

k= acceptability constant

s= standard deviation

Thickness

It should be measured by micrometer screw gauge at various positions on the films. It can be critical to establish the uniformity in the thickness of the films which is correlated directly to the accuracy of dose in the film[3].

Tensile strength

Tensile strength is the measure of maximum stress applied to a particular place on the film at which at which the film sample ruptures It can be calculated by the formula given below [3].

$$\text{Tensile strength}=\frac{\text{load at failure}\times 100}{\text{strip thickness}\times\text{strip width}}$$

Percentage elongation

It can be calculated by the formula given below[3]:

$$\%\text{Elongation}=\frac{\text{increase in length of strip}}{\text{initial length of strip}}\times 100$$

Elastic modulus

It can be calculated by the formula given below[3]:

$$\text{Elastic modulus}=\frac{\text{force at corresponding strain}}{\text{cross section area}(mm^2)}\times\frac{1}{\text{corresponding strain}}$$

Swelling studies

The degree of swelling can be calculated in terms of % weight gain by the film. The swelling index can be calculated using following formula[3].

$$\text{Swelling index (S.I)} = \frac{W_t - W_o}{W_o}$$

Where, S.I = swelling index

W_t = weight of tablet at time t

W_o = weight of tablet before placing in the beaker

Young's modulus

Young's or elastic modulus can be measure stiffness of films. It should represent as the ratio of applied stress over strain in the region of elastic deformation[3].

$$\text{Young's modulus} = \frac{\text{slope} \times 100}{\text{films thickness} \times \text{cross - head speed}}$$

Disintegration test

Disintegration time ranges from 5-30 s. USP disintegration apparatus is stated in the official pharmacopeia to find out disintegration time of the films. The two techniques for determining disintegration time are:

Slide frame method

A drop of distilled water is dispensed over the film fastened into slide frames and placed on Petri dish. The time taken by the film to disintegrate is recorded.

Petri dish method

A film is kept in Petri dish having 2 ml of distilled water. The time taken to disintegrate is recorded[17].

Dissolution test

Dissolution testing is carried out by using simulated saliva solution or pH 6.4 phosphate buffer employing a standard basket or paddle apparatus at 37±0.5° C. The samples are taken out at periodic time intervals and analyzed by UV-visible spectrophotometer, or any other appropriate technique[17].

Stability testing

Accelerated stability study can be done under common stress conductions like temperature, humidity, and light. A strip of film is kept in an aluminium packing at 25° C with 50-60% relative humidity (RH) or at 40°C at 75 ±5 % RH for 4-24 weeks. Then, periodically, the assay, morphology and other critical attributes are checked[3].

For the list of some marketed products available as oral films[18-22], refer table 3.

CONCLUSION

Oral films have come of age and have the potential to be marketed as popular oral dosage forms which are known for efficient, patient-complaint drug formulations. The limitations which hampered it mass production have been given an impetus by using new age technologies such as HME and 3D printing. With further developmental studies, oral films may become as ubiquitous as tablets and capsules.

ACKNOWLEDGMENT

The authors would like to acknowledge the support of the management and Principal of Krupanidhi College of Pharmacy, Bangalore.

AUTHOR'S CONTRIBUTION

Dr. Arshad Bashir Khan has contributed 60% and Mr. Bikash Pandey 40%.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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