WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.632
Volume 10, Issue 8, 1630-1643 Research Article ISSN 2278 – 4357

FAST DISSOLVING ORAL STRIPS: A NOVEL TREND OF ORAL DRUG DELIVERY

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Article Received on
26 May 2021,

Revised on 14 June 2021,
Accepted on 3 July 2021,

DOI: 10.20959/wjpps20218-19513

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ABSTRACT

Oral route is most preferred route by medical practitioners and manufacturer due to low cost and highest accepta-bility of patients. About 60% of all dosage forms available are the oral solid dosage form. Fast dissolving oral strips (FDOS) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It is an alternatives platform for molecules that undergoes firstpass metabolism. The present review gives an account of different formulations, methods of preparations and quality control of the fast dissolving oral thin It improve the efficacy of APIs by dissolving within minute in oral cavity after the contactwith saliva without chewing and no need of water for administration strips.

KEYWORDS: First pass metabolism, Hydrophilic polymer, Fast dissolving oral strip, patient compliance

1. INTRODUCTION

Among the drug delivery routes oral route is one of the most convenient, cost effective and preferred route of drugadministration but some patients, especially paediatrics and geriatrics have difficulties in swallowing or chewing some oral solid dosage forms like tablets and hard gelatin capsules.

Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. Fast dissolving oral strips (FDOS) are the most advanced form of oral solid dosage form due to more flexibility and

comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration.

FDOS are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

The OTS place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfills all the need of patients. Eventually, film formulations having drug's will be commercially launched using the OTS technology.[4]

1. Ideal characteristics of a drug to be selected

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose less than 20 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

2. Special features of Fast Dissolving strips

Special features requirements are summarized as follows:

- Thin elegant film
- Available in various size and shapes
- Excellent mucoadhesion
- Fast disintegration
- Rapid release

3. Advantages

- Convenient dosing
- No water needed
- Taste masking
- No risk of chocking

- Enhanced stability
- Improved patient compliance
- Rapid disintegrating and dissolution in the oral cavity
- Flexible and portable nature provides ease in transportation, handling, storage.
- Avoids first past metabolism

4. Disadvantages

- High doses cannot be incorporated
- Dose uniformity is a technical challenge
- Hygroscopic in nature
- Require special packaging for products stability and safety
- High dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight. e.g. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip.

5. Composition of the Formulation

Oral dissolving film is a thin film with an area of 1-20 cm2 (depend on dose and drug loading) containing drug.Drugs can be loaded up to a single dose of 20 mg.

Formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical proper-ties of the strips.

A typical composition contains the following
Drug 5% to30%w/wWater soluble polymer 45%w/w Plasticizers 0-20%w/w Surfactants q.s.

Sweetening agent 3 to 6 %w/wSaliva stimulating agent 2 to 6%w/wFillers, colors, flavors etc. q.s.

5.1 Drugs: Several classes of drugs can be formulated as oral dissolving strips including antiulcer (e.g. omepra- zole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. paraceta- mol, meloxicam, valdecoxib). Less bitter, potent and highly lipophilic drug should be preferred for OTF as in caseof fast dissolving tablets.

5.2 Water Soluble Polymers: Water-soluble polymers are used as film formers. The use of film forming attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouth- feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing themolecular weight of polymer film bases. Some of the water soluble polymers used as film former are Pullulan, carboxmethylcellulose cekol 30, sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and Eudragit RD108,9,10,11,12 Eudragit RL100, HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3,Polyvinylpy-rollidone PVP K-90, Pectin, Gelatin.

5.3 Plasticizers: By addition of plasticizers, the mechanical properties of formulation (tensile strength and elonga- tion) can be improved. Mechanical property is plasticizers concentration dependent property. The commonly used plasticizers are glycerol, di-butylpthallate and Polyethylene glycols etc.

5.4 Surfactants: Surfactants act as solubilizing or wetting or dispersing agent in formulation so that the film is getting dissolved within seconds and release active agent quickly. Some of the commonly used are sodium laurylsulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used assolubilizing, wetting and dispersing agent.

5.5 Superdisintegrants: In many orally disintegrating technologies, the addition of Superdisintegrants principallyaffects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

5.6 Sweetening Agents

Natural Sweeteners: Sweeteners have become the important component for those nutraceuticals as well as phar- maceutical products whose dissolution occurs in the oral cavity. The classical source of sweetener is sucrose, dex- trose, fructose, glucose, liquid glucose and isomaltose. Fructose is sweeter than sorbitol and mannitol and thus usedwidely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are less carcinogenic and donot have after taste which is a vital aspect in formulating oral preparations.

Artificial Sweeteners: The artificial sweeteners have gained more popularity in food and pharmaceutical prepara- tions. The artificial sweeteners can be classified in I generation and II generation sweeteners which are given below in table. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200 - 300 time sweetness.

5.7 Saliva Stimulating Agent: More saliva production helps in the faster disintegration of the fast dissoving film formulations so the formulations may contain acids which are used in the preparation of food as salivary stimu- lants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

5.8 Flavor: Any flavor (US-FDA approved) can be added, such as intense mints, sour fruit flavors or sweet con-fectionery flavors15. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

5.9 Color: Pigments such as titanium dioxide or a full range of colors are available, including FD and C colors, EUColours, Natural Colours and custom Pantone-matched colours.

2. Manufacturing Methods

One or combination of the following process can be used to manufacture the mouth dissolving strips17.

i) Solvent casting.
ii) Semisolid casting.
iii) Hot melt extrusion.
iv) Solid dispersion extrusion.
v) Rolling.

1) Solvent casting method

In solvent casting method water soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried. The most commonly used industrial methods are solvent-casting method and Hot melt extrusion.

Advantages

1) Better uniformity of thickness and better clarity than extrusion.
2) Film has fine gloss and freedom from defects such as die lines.
3) Film has more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 µm, although various thicknesses are possible to meet API loading and dissolution needs.

Disadvantages

1) The polymer must be soluble in a volatile solvent or water.
2) A stable solution with a reasonable minimum solid content and viscosity should be formed.
3) Formation of a homogeneous film and release from the casting support must be possible.

2) Hot Melt Extrusion

In this method the mass is prepared first under the control of temperature and steering speed. Afterwards, the film is coated and dried in a drying tunnel, once again the temperature, air circulation and line speed are con- trolled. Then follows a slitting and in the last step the films are punched, pouched and sealed. Ex. F. Cilurzo etal. formulated Piroxicam film with Maltodextrin plasticized by glycerin by using Hot-melt extrusion method.

Advantages

1) Without use of any solvent or water.
2) Fewer processing steps.
3) Compressibility properties of the API may not be of importance.
4) Better alternative for poorly soluble drugs.
5) More uniform dispersion because of intense mixing and agitation.
6) Less energy compared with high shear methods.

Disadvantages

1) Thermal degradation due to use of high temperature.
2) Flow properties of the polymer are essential to processing.
3) Limited number of available polymers.
4) All excipients must be devoid of water or any other volatile solvent.

3) Semisolid Casting

In this method solution of water soluble film forming polymer are mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate, cellulose acetate butyrate). After sonication it is coated on non-treated casting film. On drying. The thickness of the film is about 0.381-1.27 cm. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

4) Solid Dispersion Extrusion

Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped in tostrips by means of dies.

5) Rolling Method

In this method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mix-ture of water and alcohol. The film is dried on the rollers and gives desired shape and size.

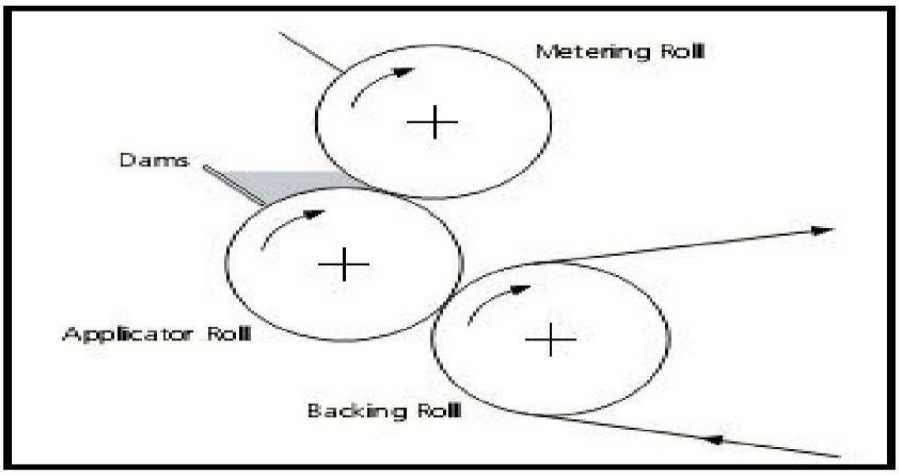

Fig.1.1: Rolling method for manufacturing of Oral Film.

3. Evaluation Parameters

- **Mechanical properties**

➢ Thickness
➢ Dryness/tack test
➢ Tensile strength
➢ % elongation
➢ Young's modulus
➢ Tear resistance
➢ Folding endurance

- Organoleptic test
- Surface pH test
- Swelling test
- Transparency
- Assay/content uniformity
- Disintegration test
- In-vitro dissolution test
- Contact Angle Measurement

1) Mechanical properties

Mechanical properties of strips are evaluated Instron using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Strips are held between two clamps positioned between 3cm. During measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks. Three mechanical properties namely tensile strength, elastic modulus and % elongation are calculated.

1.1 Thickness

The thickness of film is determined by screw gauge or micrometer at different points of the strips. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy ofdose in the strip.

1.2 Dryness/Tack test

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack- free (surface dry), dry-to-touch, dry-hard, dry through (dry-to-handle), dry-to-recoat and dry print-free. Alt-hough these tests are primarily used for paint strips, most of the studies can be adapted intricately to evaluate phar- maceutical orally fast dissolving film. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are available for this study.

1.3 Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks

It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given inthe equation below:

Tensile strength = Load at breakage/ Strip thickness × Strip Width

1.4 Young's modulus

Young‟s modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation. Hard and brittle strips demonstrate a high tensile strength andyoung‟s modulus with small elongation. Elastic modulus is calculated by formula

$$\text{Young's modulus} = \frac{\text{force at corresponding strain}}{\text{Cross sectional area } (mm^2)} \times \frac{1}{\text{Corresponding strain}}$$

1.5 % Elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer.

% Elongation = Increase in length ×100 / Original length

1.6 Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The num-ber of times the film is folded without breaking is computed as the folding endurance value.

1.7 Tear resistance

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basi-cally very low rate of loading 51mm (2 in)/min is employed and is designed to measure the force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton‟s (or pounds-force).

2) Organoleptic evaluation

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmaco- poeial methods are being used for this purpose. These in-vitro taste assessment apparatus methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations.

3) Morphology Studies

Scanning electron microscopy (SEM) study refers the differences between upper and lower side of the strips. It also helps in determination of the distribution of API. Near-infrared chemical imaging (NIR-CI) study helps in determining the difference between drug distributions in drug loaded strips and recrystallization.

4) Surface pH

The surface pH of the strips was determined in order to investigate the possible side effects due to change in pHin vivo, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibratingfor 1.0 min.

5) Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in apre-weighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml mediumin a plastic container. Increase in the weight of the film was determined at preset time interval until a con- stant weight was observed.

The degree of swelling was calculated using parameters

$$S.I = Wt - Wo/Wo$$

Where S.I is the swelling index, Wt is the weight of the film at time‟t‟, and Wo is the weight of film at t = 0.

6) Transparency

The transparency of the strips can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of strips at 600 nm. The transparency of the strips was calculated as follows:

$$\text{Transparency} = (\log T600)/b = - €c$$

Where T600 is transmittance at 600 nm and b the film thickness (mm) and c is concentration.

7) Assay/ Content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmaco-poeia. Content uniformity is determined by estimating the API content

in individual strip. Limit of content uni- formity is 85–115 percent.

8) Disintegration time

The disintegration time limit of 30 sec or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating strips strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharma-copoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 sec.

9) Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus. The dissolution me- dium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolutiontest can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

10) Contact Angle Measurement

Time dependent contact angle is measured by an optical contact angle meter. The Contact angle measured by dif-ferent methods like the two tangential methods, a height width ratio, the circle fitting and sessile drop fitting. It's prediction for wetting behavior, disintegration and dissolution of oral strips.

4. RESULT AND DISCUSSION

Preformulation studies

A) Analysis of Amlodipine Besylate

1) Organoleptic Properties

Drug powder was white in colour and found odourless.

2) Description

It was found to be fine, non-hygroscopic powder.

3) Melting Point

The melting point of Amlodipine Besylate was found between the range of 177-1790C, within the reported range, in the certificate of analysis. The drug was considered as pure. The melting point determination is first good indica-tion of purity since the presence of small amounts of impurity can be detected by decrease as well as widening in the melting point

range. Any particular behavior of the substance undergoing melting, such as drastic change in volume, crystallization, gas evolution, color change or any other physical change could be indicative of significant changes such as polymeric transition, desolvation, oxidation or decarboxylation.

4) Solubility

Freely soluble in Methanol, DMSO and water.

5. CONCLUSION

The conclusions educed form present investigations are as follows:

a. Preformulation studies of Amlodipine Besylate were carried out. FTIR studies implied that there were no in-teraction between drugs and polymers.
b. Six batches of oral fast dissolving film of Amlodipine Besylate were prepared successfully using HPMC E6 as polymer and PEG 600 as plasticizer were prepared by Solvent casting method.
c. The prepared strips were evaluated for visual appearance, thickness, Weight variation, surface pH, % drugcontent, In vitro disintegration time, and In vitro release.
d. The optimized formulation was compared with conventional tablet which shows 90.21% release of Amlodi- pine Besylate in 60min. These results concludes that optimized formulation of oral fast dissolving film is su-perior over conventional tablet in achieving better release pattern.

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