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AN OVERVIEW ON FORMULATION OF MOUTH DISSOLVING FILM

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ABSTRACT

Mouth dissolving films are oral solid dosage material that disintegrates and dissolves when put in the mouth without taking water or chewing within a minute. Because of their flexibility and comfort in use, mouth dissolving film is the most advanced oral solid dosage form. Mouth dissolving film has the ability to enhance initiation of action by reducing the dosage and removing the risk of chocking. Such films have the ability to systemically distribute the drug via intragastric, sublingual, or buccal administration pathway. This type of technology offers a convenient way of dosing medication not to specific population groups such as pediatric, geriatric, bedridden patients, mentally ill patients but to the general population as well. Mouth-dissolving film formulations are a revolutionary dosage method for optimizing drug distribution, initiating action, and patient compliance.

KEYWORDS: Mouth dissolving film, bioavailability, solvent casting method.

INTRODUCTION

Oral route is the favored route for the distribution of pharmaceutical products to date, because it has numerous benefits over the other route of medication administration and tablet and capsules are the chosen dosage type, but now they have faced many shortcomings such as startling and swelling discomforts in geriatric and pediatric patients involved with several medical conditions as they are difficult in swallowing or chewing solid dosage forms.[1,2] The most common complaint was tablet size, then surface shape and taste followed. For geriatric and pediatric patients, as well as in traveling patients who may not have immediate access to liquids, the issue of swallowing tablets became more apparent. Therefore, fast-dissolving drug delivery devices came into being in the late 1970s as a 0061n solution to pediatric and geriatric pills, capsules and syrups. Mouth dissolving film drug delivery systems were first developed as based on the transdermal patch technology in the late 1970's.[3-5] This delivery system consists of a thin film, which is placed simply on the tongue or mucosal tissue of the patient, instantly wet by saliva; the film dissolves quickly. It then quickly disintegrates and dissolves to release the oral mucosal absorption medication. Mouth dissolving film is packed with hydrophilic silicone, which dissolves quickly on the tongue or buccal cavity.[1-4]

Special features of oral film

1. Thin elegant film
2. Unconstructive
3. Available in various size and shapes
4. Fast disintegration
5. Rapid release
6. Give a pleasant mouth feel.
7. Have an acceptable taste.
8. Should not leave residues in mouth.

Ideal characteristics for MDF's

1. It should be thin, flexible, and easy to handle
2. The films should be transportable, not sticky and keep a plane form without rolling up
3. It should be easy to administer
4. The film should offer agreeable taste and a satisfying mouth-feel
5. The disintegration time should be as rapid as possible
6. Film surface should be smooth and uniform
7. It should be physically and chemically stable during its shelf life
8. It should be cost effective and ease of commercial production
9. It should have low sensitivity to environmental /atmospheric conditions such as humidity and temperature.[5-10]

Advantages

1. It can be taken without water
2. It disintegrate/dissolve quickly in mouth
3. Flexible and light in weight
4. It is appropriate to all age group
5. Appropriate for patients who are ill or uncooperative
6. Films remain stable for longer time as it is a solid dosage form until its administration.
7. The drug absorbed directly from film formulation into the blood, so it avoids undergoing first-pass

hepatic metabolism which seen in conventional dosage forms
8. Rapid disintegration of film gives quick onset of action; thus, it enriches safety and efficacy profile of active pharmaceutical ingredient (API)
9. Pain-free self-administration is possible.[6-9]

Disadvantages
1. Drug(s) which requires to take in high doses cannot be incorporated into films.
2. Maintaining dosage uniformity is challenging task for the films.
3. Moisture sensitivity.
4. Require special packaging.
5. API's which are unstable at pH of the saliva cannot be designed in the form of film.
6. API's which can cause irritation of the oral mucosa cannot be Administered.[6-9]

Formulation consideration

From the regulatory point of view, all excipients used in oral film formulation and development are considered safe (GRAS listed) and should be approved for use in forms of oral pharmaceutical dosage. The area of oral thin films is 1-20 cm^2(depend on dose and drug loading containing drug).[11-13] Overview on different ingredients employed in formulation of fast dissolving films is given in Table no 1.

Table 1: Overview on different ingredients in formulation of fast dissolving film.

Composition	Concentration
Drug	1-25%
Water soluble polymer	40-50%
Plasticizers	0-20%
Fillers, colors, flavors	0-40%

1. Pharmaceutical Active Ingredient

Various types of medications can be integrated into ODFs such as antihistamines, anti-diarrheal medicines, anti-depressants, vasodilators, anti-asthmatics, anti-emetic medications etc. You can also incorporate dimenhydrinate into ODFs for taste masking. ODFs include salbutamol sulfate, rizatriptan benzoate, verapamil ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, and so on. [1-3, 8-12]

2. Film Forming Polymer

Water-soluble polymers are used as film formers, as they provide the films with fast disintegration, strong mouth sensation and mechanical energy. The strip's robustness depends on the polymer type and the volume that it uses in the formulations. A variety of polymers are available to prepare films the most commonly used of which are pullulan, gelatin and Hypromellose. Examples of water-soluble polymers include: Pullulan, Gelatin, guar gum, xanthan gum, Hydroxyl propyl methyl cellulose (HPMC), Modified starches, PVPK30, PVA etc. HPMC E3/E5/E6/E15.[6-14]

Ideal properties of the polymers used in the oral film:
1. Polymers should be nontoxic, non- irritant and non-bitter.
2. Polymers should be tasteless
3. It should be devoid of leachable impurities
4. It should be inexpensive and readily available
5. It should not be an obstacle in the disintegration time
6. It should have good wetting and spreadibility property
7. It should exhibit sufficient peel, shear and tensile strength

3. Plasticizers

Plasticizers are the important excipient of the oral film. It improves the flexibility and a mechanical property of the film like tensile strength and elongation and reduces the brittleness of the strip. A plasticizer should be selected so that it must be compatible with the drug, polymers as well as with the other excipients used in the oral film. Plasticizer can improve the flow and enhances the strength of polymer. Film cracking, splitting and peeling take place by the use of inappropriate plasticizer. Plasticizers are used in the concentration of 0–20%w/w of dry polymer weight. Different plasticizers used in the preparation of the oral films are Glycerol, propylene glycol, polyethylene glycol, dimethyl, dibutyl, diethyl phthalate, tributyl, triethyl, actyl citrate, triacetin and castor oil.[8]

4. Sweetening agents

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally, sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. However, it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patient. patients. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second-generation artificial sweeteners. Acesulfame-K and sucralose have more than 200- and 600-times sweetness. Neotame and alitame have more than 2000- and 8000-time sweetening power as compared to sucrose. Aspartame was used for the preparation of oral strips of valdecoxib. Sucralose and neotame was reported to be used in the suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron respectively.[22]

5. Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. E.g. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.[20]

6. Flavoring agent

Flavoring agent are those ingredients which impart flavor to any of the formulation. The perception of flavor varies from individual to individual ethnicity and personal liking. Any US-FDA approved flavor can be added to the formulation according to the choice of the individuals of different age groups. The flavor liking changes with the age as geriatric population like mint or orange flavor while young generation like fruit, raspberry, strawberry flavor. Flavoring agent should be compatible with the drug and other excipients. Flavoring agents are selected depend on their flavor impart in first few seconds and its after taste. Up to 10% of the flavoring agent can be added to the oral strip formulation. Flavoring agent can be extracted from different part of the plant like leaves, flower, fruit, bark, and seeds.[2,7]

7. Coloring agents

FD & C approved coloring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. Eg. Titanium dioxide.[2-7,22]

Method of preparation

One or more of the following process can be used combinly to manufacture the mouth dissolving films.

1. Solvent Casting Method

It is the most popular method of creating fast dissolving video. Firstly water soluble ingredients are combined in water in this process to form a viscous solution. API and other ingredients are dissolved in smaller quantities of water and mixed with bulk with the use of a high shear device. Vacuum is used to expel the dust that is caught there. The formulated solution then casts as a film and pours the solution into a glass mould which helps the solution to dry in a 45-50 ° C oven and is then cut into parts of the desired size.[2-4, 1-14, 17-22]

2. Semisolid casting

Preferably this approach is followed by using acid-insoluble polymers in film preparation. The gel mass is casted onto the films or ribbons using heat-controlled drums in the Semisolid casting process. Gel mass is obtained by adding film forming solution in the ammonium or sodium hydroxide to an acid insoluble polymer solution. The acid-insoluble polymers used to make films include: phthalate of cellulose acetate, butyrate of cellulose acetate. The insoluble acid solvent and solvent shaping material will be used in a ratio of 1:4.[2-4, 1-14,17-22]

3. Hot melt extrusion

In this method the preferred polymers are those with low molecular weight and low viscosity. In the solid form the drug is mixed with the carrier to form granular material. Then, these granules are dried and then inserted into the extruder. The screw speed will be about 15rpm, so that the granules live for around 3-4min within the extruder. Temperatures for the production will be 80° C (zone 1), 115 ° C (zone 2), 100 ° C (zone 3), and 65 ° C (zone 4). Instead, the extrudate (T= 65° C) pressed into a cylindrical calendar to get a picture.[2-4, 1-14, 17-22]

4. Solid dispersion extrusion

In this process, components which are immiscible are extrude with drug and then stable dispersions are prepared. Finally, by means of dies, the solid dispersions are formed into films.[2,4, 1-14, 17-22]

5. Rolling Method

A solution or suspension of product with film forming polymer is prepared in rolling process and is subjected to the roller. Clear rheological attention should be given to the solution or suspension. The solution is primarily water and gas and alcohol blend. On the rollers the film is dried and cut in to the desired shapes and sizes.[2,4,1,14,17-22]

Evaluation

1. Thickness

With the aid of micrometer screw gauge or modified digital Vernier calipers a film thickness can be measured. Film should be measured at five points, i.e. from the center and from all four corners, and then calculated as mean thickness. The uniformity of thickness must be calculated, as it is directly related to the consistency of the dosage in the film.[3,12,15-17]

2. Dryness test/tack tests

Approximately eight phases of the film drying cycle have been established and are set-to-touch, dust-free, tack-free (surface dry), dry-to-touch, dry-to-handle, dry-to-recoat, and dry-free printing. Although these tests are primarily used for paint films, most of the studies can be thoroughly adapted to assess pharmaceutical OFDF. The evaluation details of these parameters can be checked elsewhere and are outside the scope of this review. Tack is the tenacity that the strip adheres to an object (a sheet of paper) that has been forced into strip contact. Instruments for this analysis are available too.[3-5, 17-21]

3. Tensile strength

Tensile strength is the highest force exerted at a point where the material on the strip splits. The applied load at breakup divided by the cross-sectional area of the strip as seen in the equation below is determined by:[3, 12-17]

$$\text{Tensile strength} = \frac{\text{Load at breakage}}{\text{Strip thickness} \times \text{Strip Width}}$$

4. Percent elongation

A strip sample stretches as tension is applied, and this is referred to as pressure. Strain is basically strip deformation divided by the initial sample length. Usually, strip elongation decreases as the output of the plasticizer decreases. [5-8]

$$\% \text{ Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

5. 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 as follows:

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.[5-10]

6. Tear resistance

Plastic film or sheeting tear-resistance is a dynamic feature of its inherent resistance to rupture. It uses essentially very low loading rate of 51 mm(2 in)/min and is designed to test the tearing initiation force. The overall stress or force needed to break the specimen (usually located near the onset of tearing) is reported as the break-resistance value in Newtons.[12-17]

7. Folding endurance

Folding durability is determined by repetitive strip folding at the same location before the stripe splits. The number of times the film is folded without breaking is computed as the folding endurance value Surface pH: The pH value of a film is usually determined by putting the prepared film in Petri dish and subsequently film is made wet by using distilled water and noting pH by touching the film surface with a pH meter electrode. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation.[15-17]

8. Organoleptic evaluation

Special monitored individual taste panels are used for estimation of the product's psychophysical test. To this reason, in-vitro methods of using taste receptors, specially built equipment and drug release are used by updated pharmacopoeial methods. These in-vitro taste assessment apparatus and methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations.[18-22]

9. Surface pH of film

Surface pH of the films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films.

The change in the color of pH paper was observed and reported.[21]

10. Swelling property

Reports of film swelling are performed using synthetic solution of saliva. Growing film sample is measured and mounted in a pre-weighted wire mesh constructed from stainless steel. The mesh containing film sample is dipped in a plastic container into a 15ml medium. Change in the film's weight was measured at predetermined time intervals before a steady weight was recorded.

The degree of swelling was calculated using parameters.[22]

$\alpha = wt - wo/wo$

wt- is weight of film at time t, and wo is weight of film at time zero.

11. Transparency

You can determine the clarity of the films using a basic UV spectrophotometer. Cut the images of films into rectangles and position them on the inner side of the spectrophotometer. The decides film transmission at 600 nm. The transparency of the films was calculated as follows:

Transparency = (logT600)/b = - €c

Where T600 is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.[14]

12. Assay/ Content uniformity

It is calculated by the specific assay procedure listed in either of the specific pharmacopoeia for the particular API. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.[7,14]

13. Content uniformity

For various pharmacopoeias, the quality of a film is calculated by the specific assay procedure defined for individual drugs. This research is rendered using analytical methods on 20 samples. The test's approval rating according to Japanese pharmacopoeia is less than 15 per cent. According to USP27, the contents should range from 85% to 115% with the standard deviation of less than or equal to 6% Content uniformity is worked out for estimating drug contents in individual film.[21-22]

14. Disintegration time

Disintegration apparatus listed in official pharmacopoeias is used to assess the duration of a film's disintegration. The disintegration time is usually the function of film structure, since it varies with the formulation and typically ranges from 5 to 30 s. In this test the USP disintegration system is often used. There are no formal recommendations available for evaluating the duration of orally rapid disintegrating films to disintegrate. Movie disintegration time is calculated by two processes.[3,14]

15. Slide frame method

A drop of purified water is poured onto the film, clamped in slide frames mounted on the petri platter. The time the film took to break noted.[2,7]

16. Petri dish method

In Petri dish a film is put in 2 ml of distilled water. The time the film takes to fully dissolve is known as the disintegrating one [21-22]

17. In-vitro dissolution test

To perform film dissolution tests, regular official basket or paddle system is used. Conditions for sinking should be preserved before dissolving. Sometimes film floats over the medium when conducting this process, which makes it difficult to execute the test properly. This problem is more likely to occur in case of paddle method thus the basket apparatus is mostly preferred. Media used are 6.8 pH phosphate buffer (300 ml) and 0.1 N HCl (900 ml). Temperature is maintained at 37 ± 0.5 C and rotation speed of 50 rpm is usually adjusted. Dissolved drug samples are obtained at pre-determined intervals and analyzed using UV-spectrophotometer. Despite its common use, the dissolution test is often vulnerable to notable inaccuracy and let down results.[7-13, 21-22]

CONCLUSION

The present analysis reveals that one of the new strategies in the pharmaceutical sciences is the oral quick disintegrating films. In contrast with traditional dosage methods, they have increased acceptance and patient compliance with no chance of choking along with greater protection and efficacy. The key concept behind ODF formulation was to cope with the difficulties of swallowing traditional oral dosage types for pediatric, geriatric, and psychiatric patients with dysphagia. Presently, ODFs are commonly available for hypertension, acidity, inflammation, discomfort, etc. that indicate their significance. Significant benefits of such a dosage type are their administration without the use of water that fulfills the need of target population seeking ease in drug administration along with bypassing the hepatic metabolism, resulting in enhanced therapeutic reaction.

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