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(REVIEW ARTICLE)

A review on orodispersible film a novel approach of drug delivery system

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Abstract

The effective distribution of the drug to the body is the main objective of every drug delivery mechanism, but patient compliance must also be taken into consideration. Fast-dissolving drug delivery technologies, such Or dispersible Films (ODFs), make it simple to administer medication to the general public as well as to certain demographic groups with swallowing issues, like youngsters and the elderly. ODFs are cutting-edge dosage forms that dissolve and disintegrate inside the mouth. Intra-oral absorption enables quick action and aids in avoiding first-pass effects, reducing the unit dose needed to deliver the desired therapeutic effect. In comparison to ODTs, or dispersible films dissolve and disintegrate in less than one minute with very little saliva moisture. It can be used safely even if water is not available, as or dispersible films require the use of water.

Keywords: Orodispersible Film; Mouth Ulcer; Solvent Casting; Paediatric; Patents

1. Introduction

The most popular and patient-friendly method of medicine administration is through the oral route. Most patients, including adult, paediatric, and geriatric patients, take their medications in the form of tablets and capsules [1]. However, between 26 and 50 percent of patients have trouble swallowing firm gelatin capsules and tablets [2]. These patients primarily include elderly people who struggle to swallow conventional oral dosage forms due to hand tremors and dysphagia, paediatric patients who frequently avoid taking solid oral dosage forms because of their underdeveloped nervous and muscular systems, as well as mentally ill and developmentally disabled people, as well as uncooperative patients are placed on decreased liquid intake schedules, feeling queasy, or on the go without access to water [3, 4].

The pharmaceutical sector is becoming increasingly interested in orodispersible systems [5]. There is frequently no need for chewing or water, as these systems frequently melt or disintegrate within a minute [6,7]. When compared to oral administration, these technologies provide superior clinical profiles with the possibility of mucosal absorption. Recently, thin films that quickly dissolve or disintegrate into the buccal cavity have been proposed. Innovative dosage forms known as mouth-dissolving films melt or disintegrate in the oral cavity [8]. These are extremely thin medicinal excipients, around the thickness of a postage stamp. These dose forms are applied to any mucosal tissue, including the tongue [9]. The films quickly hydrate and cling to the application site when moistened with saliva. Due to its quick dissolving capabilities, with few modifications, it can also release the drug for oral GIT absorption [10].

2. Orodispersible Film

Orodispersible films are single or multilayer sheets built of the right materials that are intended to swiftly release the loaded active ingredient in the mouth, creating a thin suspension or solution in the saliva without mastication or water intake [11, 12].

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These orodispersible films are designed in such a way that water is not necessary for administration since they immediately break apart within a few seconds, releasing the medication into the mouth. When placed on the tongue, orodispersible films quickly hydrate by soaking up saliva once the dosage form's active pharmaceutical ingredient disintegrates and/or dissolves [13]. These thin films come in a variety of sizes and forms. These have great mucoadhesion and quick release and dissolution [14]. These movies are useful for patients who are bedridden, emetic, experiencing diarrhoea, an allergic attack, or coughing and lead an active lifestyle. They are also useful for children, the elderly, and patients who are paediatric or geriatric. Additionally, it is helpful for localised actions like local anaesthesia for toothaches, mouth ulcers, or teething [15, 16].

2.1. Advantages

- Ease of administration
- Convenient in dosing
- Zero chance of choking
- Increased steadiness
- Better compliance from the patient
- Taste of bitter drugs can be masked
- Site specific and also has local action
- Rapid drug release due to rapid disintegration and dissolution of films

2.2. Disadvantages

- Unlike orally dissolving tablets, these ODFs cannot have a higher dose added to them.
- Because of its hygroscopic nature and the need for specialist packaging, longer preservation is problematic.
- It is prohibited to provide medications that are unstable at buccal pH.
- A lengthy period of no eating or drinking after ingesting ODFs.
- Compared to oral dissolving pills, these films are prepared using pricey methods [3, 4].

3. Methods of Preparation

Methods for preparation of oro-dispersible films

3.1. Solvent Casting Method

The century-old technique of filmmaking is solvent casting. It is a method that is frequently used to make orodispersible films. This process is used to produce 2x2 cm and 3x2 cm films [17]. The medication and any essential additions are dissolved in either an organic or an aqueous solvent before being mixed and stirred. A appropriate vehicle is used to dissolve polymers that are soluble in aqueous solutions. After carefully casting, it is dried on a glass, Teflon, or other suitable material petridish or plate [18, 19]. The solution is poured onto an inert basis using specific machinery used in large-scale manufacture with the required rollers. The removal of trapped air is accomplished via vacuum. The last stage involves drying the films and removing any remaining solvent to produce the completed product. The films are cut, stripped, and packaged after they have dried [20].

3.2. Semi-Solid Casting Method

The process begins with creating a polymer film-forming solution that is water soluble [21]. Then, this solution is transferred to an acid-insoluble polymer solution, which can be created by combining either cellulose acetate butyrate or cellulose acetate phthalate with either a sodium hydroxide solution or an ammonium hydroxide solution in a ratio of roughly 1:4. In order to create a gel mass that can be moulded into thin films, plasticizer is carefully added after that [22].

3.3. Hot-Melt Extrusion

This approach can be applied based on expertise from the plastics industry, where formulators can extrude the combinations of drugs, polymers, and other pertinent excipients into desirable final shapes to obtain suitable drug-release profiles [23, 24]. Twin screw extruders have shown to be useful in pharmaceutical formulations because they can mix various formulation materials uniformly and consistently, which improves bioavailability and dissolution rates.

API is blended with additional materials in a dry condition, heated until the mixture becomes molten, and then extruded out to produce thin films. Using the right method, the solvent is fully eliminated [25].

3.4. Rolling Method

This method involves rolling a drug-containing suspension or solution on a carrier. Water or an alcohol-water combination is the primary solvent used. The films are cut into the necessary shapes and sizes after drying on the heated rollers [26, 27]. Additional chemicals, such as API, polymer, plasticizer, and other required substances, are dissolved in small amounts of aqueous solvent using the high-shear processor.

4. Formulations of Orodispersible Films

These are the elements that were employed in the preparation: [11]

- Active pharmaceutical ingredients
- Film shaping polymers
- Plasticizer
- Saliva stimulating vehicles
- Sweetening vehicles
- Flavoring vehicles
- Coloring vehicles
- Surfactant

4.1. Active pharmaceutical ingredients

Any drug class that can be consumed orally or through the buccal mucosa can provide API. The active pharmaceutical ingredient (API) is often included in orodispersible films at a concentration of 1 to 50% w/w; however, for formulation to be successful, the API must be micronized to improve the texture, homogeneity, and speed of dissolving of the orodispersible film [28]. For the creation of orodispersible films, a variety of pharmacological classes can be employed, including antiemetics, neuroleptics, analgesics, antiallergens, sedatives, hypnotics, diuretics, antibacterials, cardiovascular agents, and erectile dysfunction medications [29].

The optimum features for drugs employed in orodispersible films are:-

- The drug ought to taste good.
- The drug used should be in a modest dose..
- The drug needs to be stable and soluble in both saliva and water.
- The medication needs to partially unite at the pH of the oral cavity.
- The medication should be able to penetrate the oral mucosa.
- Drug should leave little to no residue in the mouth after ingestion and should be less sensitive to environmental factors.
- Drug should have an acceptability of taste masking properties.

4.2. Film shaping polymer

As the tensile strength of mouth dissolving films depends on the type of polymer employed, polymer selection is the most crucial and detrimental aspect for the successful creation of mouth dissolving films [19]. The formulation of mouth dissolving films (MDFs) is built on polymers. Since they quickly break down and give the films high mechanical qualities as well as nice mouth feel effects, the entire polymer employed is water soluble [20]. To achieve the necessary film qualities, polymers—both synthetic and natural polymers—can be utilised alone or in combination with other polymers. The following polymers should be used in mouth-dispersing oral films [14].

- No leachable lead ultrations
- Possess good moistening and extending qualities
- Are not poisonous or irritating
- Possess adequate shear and tensile strengths.

- Excellent film forming capacity
- Long shelf life

Table 1 List of common natural and synthetic polymers

Natural polymers	Gelatin, pectin, sodium alginate, polymerized resin, pullulan, xanthane gum, maltodextrin, starch.
Synthetic polymers	Hydroxyl propyl methyl cellulose (HPMC), methyl cellulose (MC), sodium carboxy methyl cellulose (SCMC), polyvinyl alchol (PVA), polyvinyl pyrrolidine (PVP)

4.3. Plasticizers

Plasticizers are used to make materials more flexible or elastic, which improves automated film holding properties such tensile strength and expansion of the mouth-dissolving film (MDFs). By boosting the polymer's strength, plasticizers make mouth dissolving films (MDFs) less brittle. The choice of plasticizers relies on how well they work with polymers, medications, and other excipients [30]. Plasticizers improve the flow characteristics of polymers and increase their resilience. Examples of plasticizers used in the production of mouth-dissolving films (MDFs) include polyethylene glycol (PEG), low molecular PEG, polypropylene glycol, dibutyl castor oil, glycerol, and diethyl phthalate. [31, 32].Glycerol is a superior plasticizer for PVA-prepared films. Both HPC and PVA films contain polyethylene glycol (PEG).

4.4. Saliva stimulating vehicles

The goal of using a saliva bracing agent entails growing saliva flow because doing so will hasten the rate at which mouth-dissolving films (MDFs) breakdown in the oral cavity [33]. In general, food-grade acids can be used as saliva stimulants; the most often utilised saliva stimulants are citric, ascorbic, tartaric, lactic, and malic acids. The most popular and frequently used of them is citric acid. These vehicles are used alone or in conjunction with other vehicles, occupying between 2 and 6 percent of the strip [34].

4.5. Sweetening vehicles

Pharmaceutical medications that are meant to dissolve or splinter in the oral cavity now include a sweetener as a necessary ingredient, just like food products [35]. The harsh taste of the medications is covered up with sweetening chemicals. To improve the mouth-dissolving formulation's flavour, two types of sweeteners—natural and artificial—are used [36, 37]. In pharmaceutical formulation, artificial sweetening agents have grown in favour. Areribose, glucose, mannose, galactose, sucrose, corn syrups, fructose, galactose, and fructose are examples of natural sweetening agents. Saccharin, Sucralose, and Aspartame are a few examples of artificial sweeteners [38].

4.6. Flavoring vehicles

Depending on the drug's nature, the user's age, and their personal preferences, a flavouring agent is chosen. Vehicles that carry flavours may operate alone or in cooperation with other vehicles. Flavors should ideally be included in the formulation at a 10% w/w ratio. In the creation of pharmaceuticals, the flavours menthol, cinnamon, clove, apple, pineapple, orange, mint, and vanilla peppermint are used. In addition to having anaesthetic effects on taste-related sensory receptors, they work by releasing their own flavours and odours [39].

4.7. Coloring vehicles

Food Drug and Cosmetic (FD&C) has given its approval for the use of colouring agents for creating mouth-dispersing films. The amount of colour used should not be more than 1% weight-per-weight of the preparation, for example. Titanium dioxide is the most frequently used colouring agent.

4.8. Surfactant

Surfactants are used to enhance the films' wettability, solubility, and dispersibility so that they dissolve quickly and release the active medicinal ingredient. Sodium lauryl sulphate, Tween 80, Polaxamer 407, and other surfactants are the most commonly used.

5. Evaluation parameters

5.1. Mechanical properties

Mechanical properties of film can be defined in terms of thickness, tackiness, tensile strength, and Young's Modulus [40]. It has been reviewed in literature that the soft and weak polymers exhibit low tensile strength, low Young's modulus and low elongation at break whereas, the hard and tough polymer have a high tensile strength, high Young's modulus and high elongation at break.

5.2. Thickness test

A micrometer screw gauge, Vernier's caliper, electronic digital micrometer, or scanning electron microscopy (SEM) images can be employed to measure the strip thickness [41]. It has been seen that the amount of plasticizer is known to enhance the thickness of the films. The produced film's thickness is measured five times to ensure uniformity. Less than 5% is ideal.

5.3. Tack test

Tack describes how firmly the film sticks to the attachment after being rubbed against the strip. The dryness is also determined by this test.

5.4. Tensile strength

The highest stress that may be utilised on a strip specimen before it breaks is its tensile strength. A formula is used to calculate it:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness X Strip width}} \text{X } 100$$

5.5. Percentage elongation

Films used as samples can deform under tensile stress, which causes the sample to stretch or lengthen. Using a texture analyzer, it is done to forecast how ductile polymers will be. Formula is used to compute it:

5.6. Young's modulus

It denotes the strip's stiffness or elasticity. Plotting the stress-strain curve allows for the calculation of strip deformation. It can be calculated as the ratio of applied stress to strain in the region of elastic deformation using the formula below:

$$\text{Young's Modulus} = \frac{\text{Slope}}{\text{Strip thickness X Cross head speed}} \text{X } 100$$

5.7. Tear resistance

The intricate relationship between plastic film and sheeting's tear resistance and its ultimate rupture resistance. The tear resistance value is expressed as the highest stress/force (often found close to the Onset of tearing) needed to tear the specimen, expressed in Newtons [42, 43].

5.8. Folding endurance

A section of film is cut, and it is folded repeatedly at the same spot until it breaks, in order to measure folding endurance. The folding endurance value is calculated by how many times the film could be folded at the same spot without breaking. A film's typical folding endurance falls between 100 and 150.

5.9. Swelling index

Studies of the films' swelling indices are carried out in simulated salivary fluid at an appropriate pH. The prepared film is meticulously preserved in a pre-weighed stainless steel wire strainer after being precisely weighed. A pestle and 50ml of pH 6.8 simulated salivary medium are used to immerse the sieve containing the film. Up until a consistent weight is seen, the film's weight growth is calculated at each time interval. Using the following formula, the swelling's degree is assessed:

$$SI = \frac{Wt - Wo}{Wo}$$

Where,

SI = Swelling Index,
Wt. =weight of the film at time "t",
Wo = weight of the film at t = 0

5.10. Organoleptic evaluation

In-vitro techniques, such as taste sensors and specialised equipment, are being employed to assess the orodispersible films' organoleptic qualities. Utilizing these in-vitro taste evaluation methods, oral pharmaceutical formulations are subjected to high throughput taste testing.

5.11. Surface pH

The film is placed on a layer of 1.5% w/v agar gel to measure the surface pH, and then a pH paper with a pH range of 1 to 11 is placed on the film. It is noted and reported that the pH paper's hue has changed.

5.12. Contact angle

At room temperature, a goniometer is used to measure contact angle. A drop of distilled water should be placed on the dried film's surface [44]. Following that, a digital camera is used to capture photos of the water droplets within 10 seconds of their deposition. On each side of the drop, the contact angle is calculated as an average.

5.13. uniformity of drug content

The homogenization process can be used to dissolve a known weight of film for 30 minutes while aggressively shaking the container in 100 ml of simulated saliva with a pH of 6.8. The drug content of each film is then estimated in order to determine the consistency of the content. 85-115% is the maximum level of content uniformity.

5.14. Moisture content

The produced films are first weighed and placed in desiccators with cadmium chloride or another appropriate dessicant. The films are reweighed three days later to determine the % moisture loss, which is computed using the formula:

$$\%\text{Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X } 100$$

5.15. Disintegration test

The duration, in seconds, at which a film disintegrates when exposed to moisture or saliva is known as the disintegration time. A CDER guidance paper that applies to ODFs describes the disintegration time limit for orally disintegrating tablets as 30 seconds or fewer [45]. It is possible to do this examination using pharmacopoeial disintegrating test equipment. The average time for film to dissolve is 5 to 30 seconds.

5.16. *In-vitro* dissolution studies

The cumulative proportion of drug retained and cumulative drug release are computed in these investigations. Using USP paddle-type equipment, these studies are carried out. The investigations are conducted in 900 cc of simulated saliva at 37 °C and 75 rpm of swirling speed. At predetermined intervals of 2, 4, 6, or 10 minutes, required sample amounts were taken out and refilled with the same volume of buffer [46]. By utilising a UV-visible spectrophotometer and a suitable wavelength to assess the concentration of the samples, it was possible to confirm that ODFs were being dissolved.

6. Packaging

It is crucial for the pharmaceutical sector that the chosen package adequately protects the product's integrity [31]. For the purpose of safeguarding the dosage of other rapidly dissolving dosage forms, specific processing, pricey packaging, and special attention are advised during production and storage [47]. Before packing, converters may decide to print

information directly onto the film unit dosage for branding reasons and to comply with industry rules. Unit dose packaging, barcode labelling, the content of usage instructions, child-resistant closures, and packaging that is senior-friendly are some of the requirements that need special consideration [48].

The chosen material needs to fulfil the following requirements

- The FDA must have approved them.
- They must safeguard the preparation from the elements.
- They need to adhere to the relevant tamper-resistant standard.
- They must not react with the substance used to prepare films.
- They cannot impart flavours or scents to the product.

6.1. Applications of ODFS in drug delivery system

- ODFs have primarily made their commercial debut in over-the-counter (OTC) medications for therapeutic purposes such cough/cold, antacid/gas relief, sore throat, and mouth fresheners, as well as a few nutritional supplement applications, to date [49].
- The development of a thin, dissolve-in-the-mouth strip for administering the rotavirus vaccine to infants could aid in treating the major cause of severe diarrhoea and vomiting in kids, which results in approximately 600,000 fatalities each year.
- Vomiting and Nausea: Several anti-emetic medications, including metoclopromide, domeperidone, granisetron, etc., have been developed as ODFs [35].
- Transdermal application: Due to its simplicity of use and superior cosmetic appeal, the possibility of active substances such as antibiotics or analgesics in wound care and other applications could be a highly promising way to innovation [48].
- Gastroretentive drug delivery: Dispersible films can thought to be a delivery system for poorly soluble molecules and water soluble drugs in film form. The medicine can be released by breaking down the film by being triggered by pH or the secretion of enzymes in the digestive tract (GIT), helping to treat GI diseases [36].
- Asthma: A patient with asthma will experience attacks during which their bronchi will tighten, making it challenging to swallow solid foods [37]. It will be simpler for the patient if the medication is in a refore dose form that may be ingested anyplace without water and doesn't require water to be consumed [38]. There are many anti-asthmatic products on the market, including tablets, inhalation devices, injections, and syrups [49]. Rapidly dissolving films are preferred by paediatric and geriatric patients because they are simple to swallow and have all the benefits of tablets (ease of application). It results in accurate dosing, quick absorption, simple application (no need for water), and ease of transport [50].

Table 2 List of Few Patents of Orodispersible Films

S.no.	Patent number	Title of invention
1	EP2632443B1	Preparation of orodispersible films
2	WO2014/076117	Orodispersible film compositions
3	EP2886103A1	Pharmaceutical orodispersible film comprising buprenorphine particles with a particular size
4	WO2011124570	Oral film formulations
5	US20200360461	Orodispersible film composition comprising enalapril for the treatment of hypertension in a pediatric population
6	2199/MUM/2015	Stabilized orodispersible film and its preparation
7	KR20200069611	Orodispersible films using fermented extract of SparassisCrispa
8	US20200108011	Structured orodispersible films [SOFTs]

9	WO2019198105	Composition of active ingredient loaded edible ink and methods of making suitable substrates for active ingredient printing on orodispersible films
10	2008/0200452	Oral, Rapidly Disintegrating Film, Which Cannot be Spat Out, for a Neuroleptic
11	2012/0149713	Oral films comprising 7-[4-[4-(2,3-dichlorophenyl) piperazin-1-l]butoxy]-3,4-dihydro-1h-quinolin-2-one base or salts or hydrates thereof
12	WO2008040534	Non-mucoadhesive film dosage forms
13	WO2020014431	Rapidly disintegrating oral film matrix
14	US10092651	High-content fast dissolving film with masking of bitter taste comprising sildenafil as active ingredient
15	2008/0213343	Oral, Quickly Disintegrating Film, which cannot be Spit Out, for an Antiemetic or Antimigraine Agent
16	US20090047350	Perforated water soluble polymer based edible films
17	US7425292	Thin film with non-self-aggregating uniform heterogeneity and drug delivery systems made from there from
18	US20110136815	Solid oral film dosage forms and methods for making same
19	US9301948B2	Instantly wettable oral film dosage form without surfactant or polyalcohol
20	EP2741737A1	Orodispersible films for manufacturing of individualised medicine or for large scale production
21	WO2016009001A1	Orodispersible films
22	WO2015092811A3	Oral films

7. Conclusion

In recent years administration of drug via orodispersible film has been very popular, as it offers advantage over conventional dosage form like patient compliance, convenience of administration, enhanced bioavailability as the drug avoid hepatic metabolism. In comparison to conventional dose forms, they appear to be a self-administerable and practical drug delivery platform, improving patient compliance and adherence. ODFs have been included in monographs for the pharmacopoeias, but there are no unique guidelines or procedures for their quality assessment. ODF's recent growth in popularity and success on the international market makes it essential owing to consumer desire. In the case of paediatric and geriatric patients in particular, it ensures patient compliance.

Compliance with ethical standards

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