Zibaldone. Estudios Italianos - Vol. XI, issue 2 (2024)
ISSN: 2255-3576

ORODISPERSIBLE FILMS: AN AVANT-GARDE WATER FREE DRUG DELIVERY

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ABSTRACT:

The administration of medication to patients such as geriatric and pediatric patients is difficult because they have difficulty swallowing drugs with water, and there is dysphagia, i.e., fear of choking. Orodispersible films are therefore becoming increasingly popular because they boost treatment adherence and provide targeted patient groups with a water free pharmaceutical delivery system. Orodispersible films (odfs) are a new type of avant-garde formulation prepared with the help of many methods of which the most often utilized technique is solvent casting. However, a number of challenges still exist for odfs and their formulation methods. To address these challenges, a number of scientists and pharmaceutical companies are working together to develop formulations that can deliver a wide range of medications in an efficient way that would be very useful for both patients and the pharmaceutical industries. At present there is exponential growth in the use of odfs because of their ability to avoid first-pass hepatic metabolism, faster absorption, with several advantages. Patents that are filed worldwide for patent approval and the presence of numerous odfs products confirm that the future of odfs has a great potential. This review strives to offer a thorough outline of odfs with various pros and cons along with the formulation approaches as well as evaluation and scope of their future for becoming pioneer water-free medications for the target group of patients.

KEYWORDS: Orodispersible films, Avant-garde, Dysphagia, Water free, Target, Future

1. INTRODUCTION

Oral medication delivery is commonly used technique of medication delivery because of simple use, low technical skills for administration and easy availability[1–4]. The most common examples of dosage forms delivered through the oral route are tablets, capsules, syrups, suspensions and powders. Despite having numerous advantages typically, they aren't preferred by patients such as pediatrics and geriatrics because of difficulty swallowing and fear of choking[5]. Hence, to address this issue, a new type of dosage form known as Orodispersible films (ODFs) was developed in the 20th century with aim of administering the drug via the oral route without water. This type of dosage has numerous advantages over conventional dosages, as it does not require swallowing, is fast to administer, is easy to administer, and is easy to manufacture.

Orodispersible films as the name suggests usually deliver drugs at the site within the mouth. All of the oral cavity is covered by mucosa, with the exception of the tooth region[6]. It is generally composed of carbohydrates and proteins. Its entire surface is covered by squamous stratified epithelium tissue, which is a semipermeable tissue with an avascular and organized structure. The thickness of the stratified squamous epithelium varies from place to place in the oral cavity. The mucosal epithelium generally secretes a gel-like fluid known as mucus which contains up to 90-99 % water and the remaining mucus is composed of enzymes, nucleic acids, and glycoproteins which are generally insoluble in water. The salivary glands secrete saliva into the mouth cavity in addition to mucus secreted by the mucosal epithelium. The main components of the saliva are water, amylase, mucus, lysozyme, etc. Typically, there are three layers that make up the oral mucosa depicted in figure 1, with the *Oral epithelium* (stratified squamous epithelium) being the upper layer. Under this layer, there is a connective tissue called *Lamina propria* followed by last tissue called *Submucosa*. There are two areas in the mucosal epithelium; hydrophilic and lipophilic. Permeation of a drug across the cells of the oral epithelium occurs mainly through basic passive dispersion. Drug's characteristics affect its ability to pass through the epithelium, such as the size of molecule, the charge of the molecule, and the degree of lipophilicity, and these properties also determine the capacity for drug absorption[7].

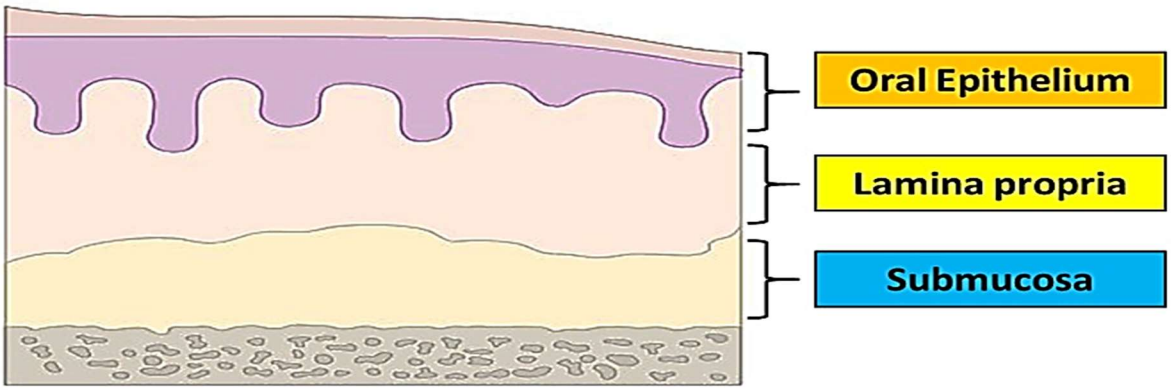

Figure 1: Illustration of the oral mucosa structure.

Compared with the skin and intestine, the oral mucosa is more permeable because of its high vascularization and the presence of a very thin membrane structure which together promote the permeation of drug compounds and thus increase bioavailability. By definition, an orodispersible film is a formulation that dissolves or disintegrates in the mouth after absorbing saliva, hence releasing the active components from the dose when administered in the oral cavity. Another way to describe ODFs are as a medicine dosage forms that patients can get without needing to use water, as they are composed of hydrophilic polymers that cause rapid disintegration of ODFs after soaking saliva; and thus, drug release occurs via dosage forms with rapid uptake by systemic circulation. Hence, the bioavailability of a drug increases as it is absorbed by the highly permeable oral mucosa membrane as portrayed by figure 2.

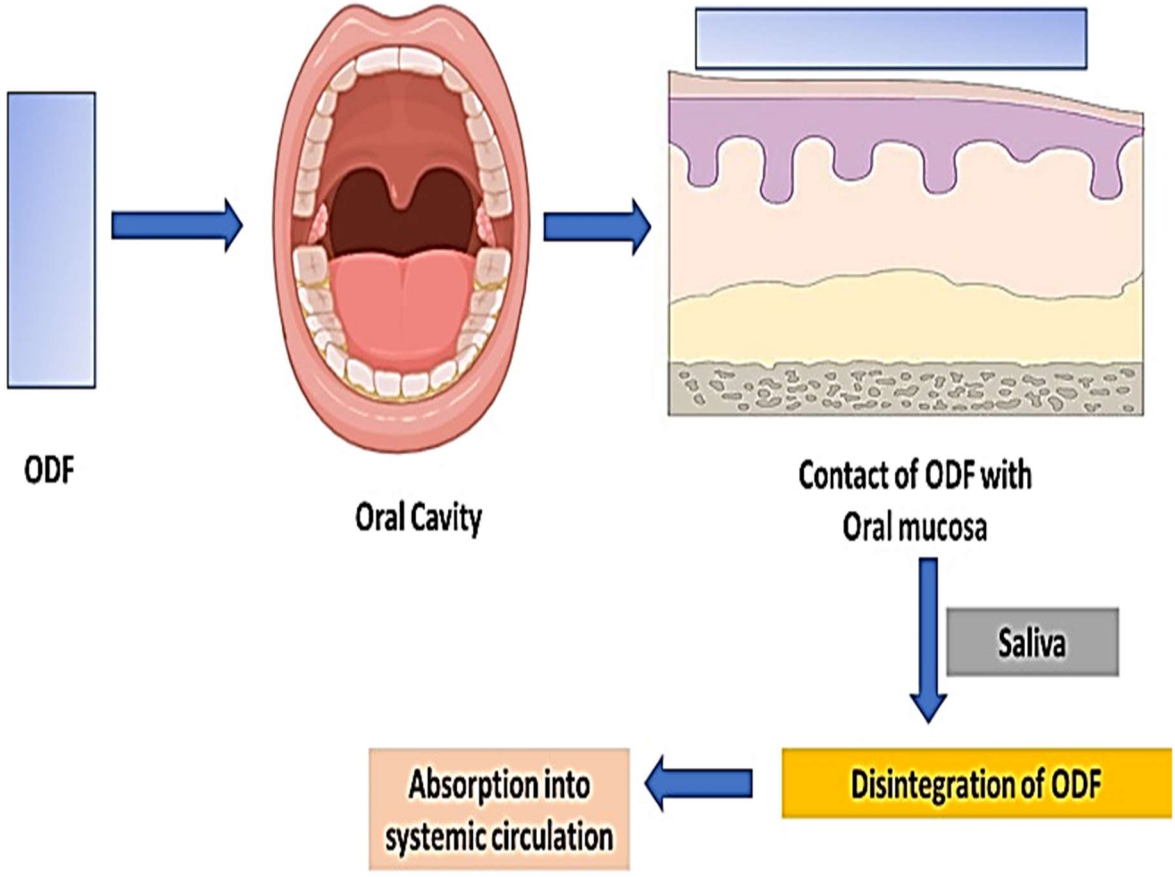

Figure 2: Illustrative diagram of the administration of odfs and their absorption into the systemic circulation.

ODFs are usually postage stamps in size which are meant to deliver the drug through the oral route. They can incorporate low dosages. Orodispersible films are usually widely accepted and can also incorporate various types of drugs, such as antihistaminic, anti-tussive, antiepileptic, and antihypertensive drugs, as shown in Table 1. One of the most important disadvantages of orodispersible films is their moisture and humidity susceptibility as they are composed of hydrophilic polymers that can absorb moisture hence their packaging is somewhat expensive.

Table 1. List of Odfs loaded with different medications along with the target patient group

API	TYPE OF PATIENT	REFERENCE
ONDANSTERON	PAEDIATRIC	[8]
PHENYLEPHPRINE	PAEDIATRIC	[8]
SENNOSIDES	PAEDIATRIC	[8]
DEXTROMETHORPHAN	PAEDIATRIC	[9]
DIPHENHYDRAMINE	PAEDIATRIC	[9]
NICOTINE	PAEDIATRIC	[10]
RISPERIDONE	PAEDIATRIC	[11]
SILICONE OIL	PAEDIATRIC	[8]
PIROXICAM	PAEDIATRIC AND GERIATRICS	[12]
TADALAFIL	GERIATRICS	[13]
GLIBENCLAMIDE	GERIATRICS	[14]
SELEGILINE	PARKINSON'S	[15]
VARSATAN	GERIATRICS	[16]
LORATADINE	GERIATRICS	[17]
KETOCONAZOLE	VARIED	[18]
FUROSEMIDE	VARIED	[19]
MONTELUKAST SODIUM	VARIED	[20]
GRANISETRON HCl	VARIED	[21]

1.1. Advantages of odfs[22,23]:

1. The transportation of ODFs from one place to another is easy.
2. ODFs require no water for administration hence they are easily swallowed by geriatric and pediatric patients.
3. ODFs can be loaded at an accurate dosage.
4. Disintegration and dissolution are rapid in ODFs due to the presence of large surface areas.
5. ODFs are beneficial in emergency cases.
6. ODFs are portable and easy to handle.
7. There is more patient compliance in ODFs.
8. ODFs are very suitable dosage forms for Dysphasic patients.
9. ODFs are available in various dosage forms.
10. ODFs are an unobstructed type of dosage form.

1.2. Disadvantages of odfs[24]:

1. High doses cannot be incorporated into the ODFs.
2. Since ODFs are more prone to humidity they require special packaging which is quite expensive.

3. The medications that cause irritation in the oral mucosa cannot be administered.
4. They are highly temperature sensitive.
5. It may have an unpleasant taste due to the presence of other ingredients.

1.3. Ideal characteristics of odfs[24]:

1. Odfs should be stable in nature.
2. The flexibility of odfs should be good.
3. Odfs should be thin in structure.
4. Easy to transport.
5. Odfs should not leave any aftertaste in the oral cavity.

1.4. Challenges of odfs[25]:

1. Low solubility of the drugs.
2. Incorporation of a high dosage of API in the preparation.
3. Increase in palatability of the bitter drug.
4. Drying time.
5. Administration of dual drugs.

2. TYPES OF ORODISPERSIBLE FILMS[26]

Orodispersible films are of the classified into three types:

2.1. Flash release

2.2. Mucoadhesive melt-away wafer

2.3. Mucoadhesive sustained release wafer

2.1. Flash release wafer[26]**:**

Flash release wafers are defined as formulations that dissolve under 60 seconds and upon placement in the oral cavity, the medication is rapidly delivered. Flash release wafers are usually prepared as a monolayer film through solvent casting with a water-soluble hydrophilic polymer and are applied to the tongue.

2.2. Mucoadhesive melt-away wafer[26]**:**

It is a type of mucoadhesive wafer administered on the oral cavity's buccal and gingival mucosa. This wafer sticks on surface of the mucosa because of the mucoadhesive polymers in its composition where it dissolves in a few minutes and releases the drug continuously. They are usually prepared as single or multiple layers through hot melt extrusion as well as solvent casting method.

2.3. Mucoadhesive sustained release wafer[26]**:**

This type of mucoadhesive film remains on the oral mucosa for several hours after which it releases the drug at a sustained rate. Mucoadhesive sustained release wafers are usually prepared from low or non-water soluble polymers as multiple layered structures via solvent casting method.

3. FORMULATION OF ODFs

To formulate good ODFs, a good selection of the excipients is needed as shown in table 2 which overall defines the stability, solubility, permeability, amount of the dose that should be

incorporated in it and also of its taste. The ODFs are usually formulated using active pharmaceutical ingredients along with other excipients like Film forming polymer, Plasticizer, Sweetening agent, Saliva stimulant and Surfactant, etc.

Table 2: List of excipients of ODFs [27,28,24,29,30,31,32,33,34,35,36]

EXCIPIENTS OF ODFs	Concentration (%)	Role
Film forming polymer	40 to 50 %	It gives ODFs its structure, suppleness, and mechanical power
Plasticizer	0 to 20 %	It provides plasticity to the ODFs
Sweetening agent	0 to 10 %	It gives good taste to the ODFs for good patient compliance
Saliva stimulant	0 to 10 %	It is used to promote the secretion of saliva
Surfactant	0 to 10 %	They help in the disintegration of ODFs within seconds
Superdisintegrant	0 to 8 %	Rapid disintegration of the films

3.1. API (Active Pharmaceutical Ingredients)

ODFs has the potential for incorporating various classes of APIs which are as follows: Antihistamine (Chlorpheniramine, Loratadine, Phenylephrine, Diphenhydramine), Antiussives (Dextromethorphan), NSAID (Ketoprofen), SSRA (Sumatriptan, Zolmitriptan), Antidiarrheal (Loperamide), H2 Blockers (Famotidine), Nasal decongestants (Pseudophedrine) and NSAIDS (Rofecoxib) etc. Other than this ODFs have also been formulated using various types of the plants extract, such as Cannabinoids.

Ideal characteristics for an API to be incorporated in ODF[37]:

1. It should be low in dose.
2. It should have good permeability.
3. It should be soluble in saliva.
4. It should not have a bitter taste.
5. Stability in nature.

The main hurdle of loading API in ODFs is that only a small amount of the dosage can be loaded due to the small size of the ODFs.

3.2. Film forming polymers

ODFs require film-forming polymers as a key excipient because they provide shape, elasticity and preserves the films' mechanical qualities. Another aspect that is also important is the viscosity of the polymeric solution, as it directly affects drug release from the formulation. For example, highly

viscous formulations result in the slow release of drugs in comparison to medium or low viscosity formulations. Low viscosity formulations are difficult to handle because of the formation of air bubbles. Hence the choice of polymer type and concentration along with viscosity is of utmost importance in ODFs formulation. ODFs can be prepared with either one or a mixture of polymers. Film forming polymers are generally regarded as the backbone of ODFs formulations and usually constitute about 40-50 % of ODFs mass.

Ideal properties of Film forming polymers are as follows [38]:

1. It should provide good shape to the ODFs.
2. It should provide excellent elasticity to the ODFs.
3. Fast disintegration with enhanced solubility
4. It should provide mechanical strength to the ODFs.
5. It should not irritate the oral mucosa.
6. Inert in nature.
7. It should be nontoxic.

ODFs usually employ two types of film forming polymers: natural and artificial. Pullulan, sodium alginate, pectin, starch, etc, are common examples of polymers of natural origin employed in the formulation of ODFs. Pullulan, which is a water-soluble polysaccharide has the best film forming capacity due to its enhanced flexibility and solubility. The physicochemical properties, disintegration time and stability of pullulan based ODFs were very good[39]. Artificial polymers generally include HPMC, Sodium Carboxy methyl cellulose, PVP along with Hydroxy propyl cellulose. With respect to artificial polymers, natural polymers are widely used due to their safety, biocompatibility and superior biodegradability. Odfs formed with high methoxy pectin (HMP) or low methoxy pectin (LMP) show magnificent qualities. HPMC or hydroxypropylmethylcellulose is a cellulose derived polymer used as a film former in ODFs. HPMC is available in various grades, such as Methocel E3, Methocel E5 and Methocel E15 Premium. HPMC is among the widely employed artificial polymers for ODF preparation. Oral thin films containing Montelukast sodium formulated with various grades of HPMC, such as HPMC E15 LV, HPMC E50 LV with Polyethylene Glycol (PEG) as a plasticizer exhibited excellent folding endurance, excellent drug release, and rapid disintegration when HPMC E15 was used as a polymer[20]. Oral thin films containing Diphenhydramine HCl and HPMC E15 with several other plasticizers showed that HPMC E15 is an ideal film former with the best dissolution and excellent disintegration time[40]. The formulation of Bufotenin's buccal films with several types of HPMC showed the best drug release rate with HPMC E5 as a polymer[41]. Prochlorperazine Maleate was loaded on fast dissolving oral thin films that were formulated with HPMC and was found to have good disintegration time as well as excellent drug release[42]. Propanol HCl loaded oral fast dissolving sublingual films formulated with HPMC exhibited good physicochemical properties[43].

3.3. Plasticizer

A plasticizer is mainly used to provide flexibility, tensile strength, plasticity and to decrease the friability of the ODFs. Plasticizers should be a compatible with API and film forming polymers. Examples of plasticizers include Polyethylene Glycol (PEG), Glycerol, Mannitol, Sorbitol, Citric

acid and Propylene Glycol. Plasticizers constitute approximately 0-20 % of ODFs mass. The selection of good plasticizers is important because it can lead to peeling, brittleness and cracking of the film. A study of preparation of low Methoxyl Pectin films with different plasticizers demonstrated that the films that were formulated with plasticizers had better handling and mechanical properties than the films that were formulated without plasticizers[44].

3.4. Sweetener

Sweeteners constitute an important part of the formulation because they are meant to improve the palatability of ODFs. Sweeteners are of two varieties: Artificial and Natural. Glucose, Sucrose, Dextrose, Mannitol, Sorbitol and Fructose are examples of natural sweeteners. Compared with other examples of natural sweeteners, Fructose is mainly used because its sweetness is greater than that of other sweetners such as Sorbitol, and it is also easily perceived. Sucralose, Neotame and Aspartame constitute artificial sweeteners. First class of artificial sweeteners consists of Aspartame and Saccharin, whereas second class of chemical sweeteners includes Acesulfame-K with Neotame. Acesulfame-K is 200 to 300 times more sweet than sucrose whereas Neotame is 2000-8000 times more sweet than sucrose[45]. Compared with natural sweetner, artificial sweetener are commonly used for the following reasons[26]:

1. They do not cause any dental problems such as tooth decay or dental caries.
2. They are more sweet than natural sweeteners.
3. They are ideal for diabetic patients.
4. They can be used at lower concentrations.

However, the main disadvantage of artificial sweeteners is that they leave an aftertaste, to cope with it, their use along with natural sweeteners is preferred.

3.5. Surfactant

Surfactants act as dispersing or wetting agents that help films quickly solubilize and disintegrate, allowing fast oral drug delivery. Sodium Lauryl Sulphate (SLS), Tweens and Poloxamer 80 are common surfactants. Poloxamer is one of the most commonly used surfactants[45].

3.6. Saliva stimulant

Saliva stimulants are acidic in nature because they promote saliva production in the oral cavity. Due to increased saliva, there is more disintegration of the ODFs and hence the drug is quickly released. Ascorbic acid, citric acid, maleic acid and tartaric acid are common salivary stimulants. Citric acid is a commonly used saliva stimulant[45].

3.7. Superdisintegrant

Superdisintegrants are used to provide accelerated or rapid disintegration of the ODF formulation as a combined result of swelling and absorption of water. There is swelling of the superdisintegrant after the absorption of water due to rapid dissolution and disintegration of the formulation. There is a need for strong interactions between superdisintegrants and saliva for good disintegration. Examples of superdisintegrants are Sodium starch glycolate and Crosspovidone[46].

4. PREPARATIONS OF ORODISPERSIBLE FILMS

The preparation of ODFs demands a good amount of knowledge, as the overall characteristics of a film are usually dependent upon various formulation factors such as careful selection of the

approach, polymers and other excipients. Solvent casting, hot melt extrusion, semisolid casting, solid dispersion and rolling methods are commonly employed to prepare orodispersible films [47]:

4.1. Solvent casting method

Solvent casting approach is frequently employed to produce ODFs [48,49]. This method is customarily used for the preparation of thermolabile and thermostable drugs because not a very high range of temperatures is required during the process[50]. In this method as depicted in figure 3 first, a hydrophilic film forming polymer was soaked for several hours in an appropriate solvent. Then, the other solution is formed by dissolving API along with other plasticizers, sweetening agents, surfactants, salivary stimulants and superdisintegrants, in an appropriate solvent. The selection of solvent usually depends upon drug's physicochemical properties like solubility, melting point and compatibility with solvent. After dissolving the drug with other excipients in the solvent, the solution is homogenously mixed with the other prepared solution and carefully casted on Petri dish so that no air bubbles are formed. After drying, the films were separated and sliced into different dimensions. After cutting, it is usually stored in aluminium foil to protect it from moisture which generally disturbs the stability of the films.

Advantages of the Solvent Casting Method[51,52]:

01. In this method there is more uniformity in thickness.
02. It is an easy method.
03. It has more flexibility.
04. A few steps are required in this method.

Disadvantages of the solvent casting method[53]:

01. Involvement of numerous unit operations.
02. Usage of organic solvent.
03. Less uniformity of content.

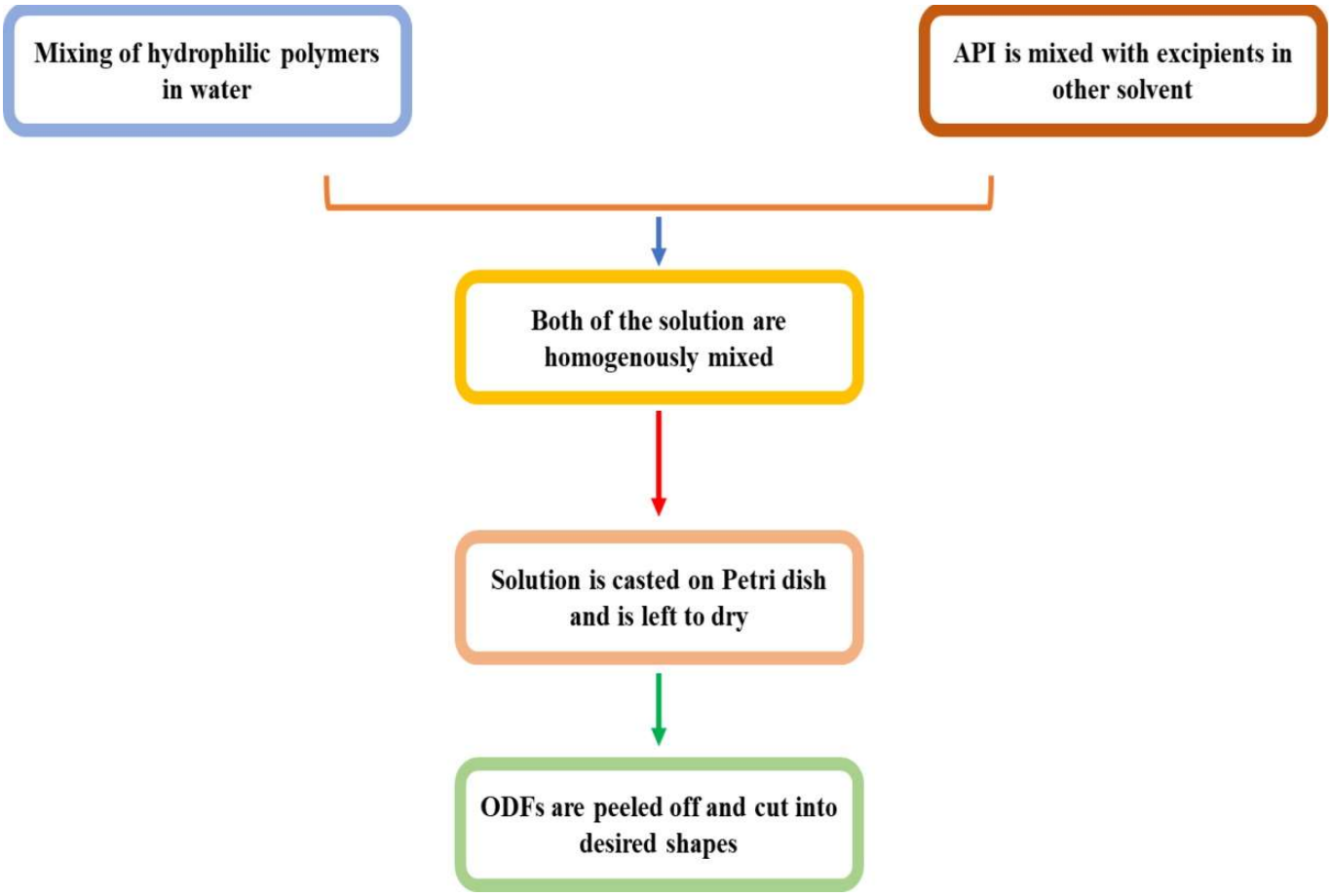

Figure 3: Flowchart of the solvent casting process.

4.2. Hot melt extrusion method

Films prepared via solvent casting approach offers numerous advantages, such as uniformity, increased flexibility and improved drug loading, but they have some disadvantages, such as decreased elasticity and decreased mechanical properties such as decreased tensile strength[54]. In addition, one of the most important disadvantages of solvent casting is that it there is use of volatile organic solvents, which are generally unsafe[53]. To solve the various disadvantages, a new process called the hot melt extrusion was developed, as depicted in figure 4. The pharmaceutical industries frequently use the hot melt extrusion process[53]. Many studies have been conducted for example: thin films of Lidocaine were prepared via hot melt extrusion approach and there was successful extrusion of HPC along with mixtures of HPC:HPMC in the thin film with no degradation of the drug[55].

Advantages of the hot melt extrusion method[53,56]:

01. Few steps are required to achieve extrudes.
02. It is economical.
03. It promotes less use of organic solvents.
04. The formulation is uniform because the drug melted with the polymer.

Disadvantages of the hot melt extrusion method[57]

01. It requires a thermal process.

02. There is a use of a limited number of polymers.
03. Heat sensitive molecules cannot be used.

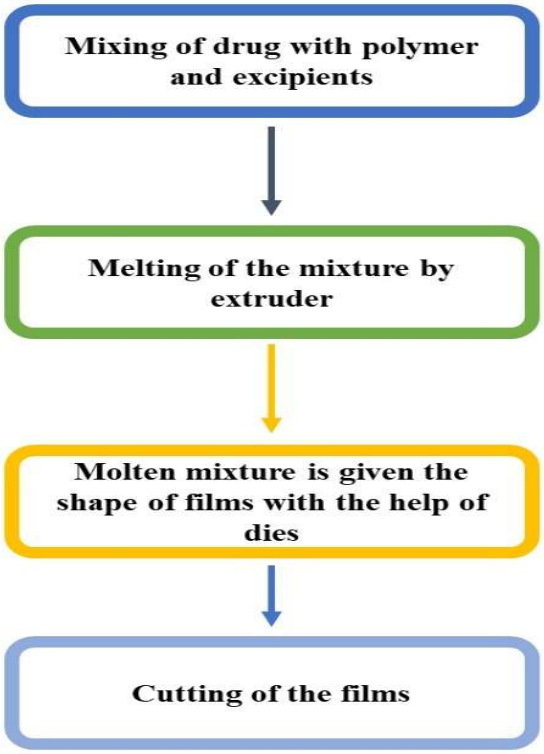

Figure 4: Flowchart of Hot melt extrusion approach.

4.3. Semisolid casting

It is another type of method employed to prepare ODFs, in which film former solution is introduced to acid insoluble polymeric solution. After this, a gel is created by adding plasticizers and then moulded into odfs with the help of heated controlled drums. In the last step, the films are cut into the desired steps[58]. The uniformity of films with good mechanical properties is advantageous because of the need for sophisticated procedures.

4.4. Solid dispersion method

This method involves mixing of drug with an appropriate solvent to obtain solution, and after this mixture is mixed with melted polymers without removing the solvent, as a final step, the solid dispersion is moulded into films of the required size[30].

Advantages of solid dispersion method[59]:

1. Drug's solubility increases.
2. Dissolution of drug also increased.
3. Amelioration of drug's bioavailability.
4. Reduction of drug's adverse effect.

Disadvantages of solid dispersion method[59]:

1. There is a tackiness problem.
2. Instability is one of its major limitations because it involves the use of hydrophilic polymers that absorb moisture.

3. Recrystallization of the drug occurs.

4.5. Rolling method

This process involves dissolving the medication in an appropriate solvent, loading the roller with a premix solution that has the API, solvent along with the film forming polymer and then drying the films with cutting into the required shape[60]. It is an advantageous method because it produces a film with uniform thickness however the main disadvantage is that it makes use of hydrophilic polymers that absorb moisture and create instability.

5. CHARACTERIZATION OF ODFs

Characterization is performed to assess and evaluate the desired objectives and properties of the prepared odfs.

5.1. Organoleptic evaluation

In organoleptic evaluation, taste is assessed. There are two types of organoleptic assessments: in-vitro as well as in-vivo. In in-vitro test, there is assessment of prepared orodispersible film's taste with the help of electronic taste sensors[61] whereas in-vivo evaluation is carried out with the help of controlled taste panels of humans. The organoleptic evaluation is performed with the aim of evaluating the taste masking effect and the level of sweetness produced by the taste masking agents. In-vitro tests are commonly used because they provide fast and high throughput taste sensing results for odfs compared to in-vivo evaluations[62–64].

5.2. Visual inspection

Visual inspection of odfs provides details about the prepared odfs' surface morphology. It is done with optical microscopy[65] along with scanning electron microscopy[66]. Visual assessment performed with a scanning electron microscope is more advantageous than that performed with an optical microscope because of the more sophisticated and advanced technology through which the study of odfs is performed in the ultramicroscopic range compared to simple microscopic studies.

5.3. Mechanical evaluation

To determine the desired mechanical parameters of the created odfs, the mechanical attributes of the odfs, including hardness, tensile strength, thickness, and folding endurance, is assessed[67].

5.3.1. Film thickness

In order to determine the uniformity of dosage forms, the thickness of developed odfs is often measured via calibrated digital micrometer[68]. The thickness of each manufactured batch was measured five times using a digital micrometer to assess the homogeneity of the odfs and mean is computed. The thickness of the developed odfs is a measure of the consistency of the dose strength and is directly correlated with the dosage strength.

5.3.2. Dryness evaluation

The purpose of the dryness evaluation is to determine how well the odfs adhere to the paper when placed in between the prepared strips[21]. Dryness evaluation or tack tests generally define the extent to which prepared odfs adhere to the paper when squeezed between the strips. In actuality, films may be dried to eight various levels: dust free, dry thorough, tack free, dry print free, set to touch, dry to recoat, dry hand, and dry to tough. Dryness assessment of odfs is done to evaluate the dryness of the prepared odfs.

5.3.3. Tensile strength

To gauge the prepared odf's flexibility, tensile strength is measured[69]. It is described as the maximum stress tolerated by odfs before resulting in a crack or break in the film[30]. It is calculated with the help of the equation:

Tensile strength = (maximum load/thickness of film x film width) x 100

5.3.4. Percent elongation

The change in a material's dimensions under stress is called elongation. The percentage of elongation aids in assessing the ductility exhibited by the polymer utilised in the formulation as well as the quantity of stretching the film experiences prior to breaking down. The percent elongation is measured with help of the following equation[70]:

Percent elongation = change in length at break / initial length x 100

5.3.5. Young's modulus

Degree of stiffness in relation to hardness as indicated by the odfs is often reflected in the Young's modulus. It is computed using the linear component of the stress-strain curve[71].

The stiffness as well as hardness of the odfs are directly correlated with Young's modulus as high Young's modulus suggests that films have a reasonable level of stiffness and hardness.

5.3.6. Tear resistance

The tear resistance is evaluated to determine the resistance to rupture shown by the film. The maximum force at which the rupture of odfs occurs is called the tear resistance value[72]. It is a crucial parameter since it affects the mechanical characteristics of odfs.

5.3.7. Folding endurance

An essential metric for evaluating the mechanical characteristics of odfs produced is folding endurance[69]. In this evaluation odfs are folded repeatedly at a place until it breaks. Both mechanical characteristics and amount of plasticizer employed are directly related to the folding endurance. Odfs with high folding endurance show the best mechanical properties and are also preferred compared to films with lower folding endurance.

5.4. Swelling studies

Swelling studies are done to evaluate the swelling ability of the odfs in the simulated salivary solution[38]. Swelling studies are important because odfs are prepared with the help of hydrophilic polymer. In general, the pace and extent of swelling displayed by the odfs control the release of medications from them. The percentage of hydration can also be evaluated with the help of swelling studies.

To carry out swelling studies, the prepared odfs were first weighed (W_1) and subsequently placed in stainless steel wire mesh and at a preset time, they were submerged in artificial salivary fluid. After a certain period of time, the samples were removed with excess water and weighed (W_2) and the degree of swelling was computed with the help of the following equation[73]:

Degree of swelling = $W_2 – W_1 / W_1$ x 100

5.5. Surface pH

It is done to evaluate pH range in which the odfs were prepared. The Surface pH is an important parameter as the pH of an odf generally determines its ability to release a drug in the oral cavity in

the pH range of 5.5-7.4. A thermal Fischer tabletop pH meter was used to test the pH after the film has been dissolved in 5 milliliters of distilled water for the purpose of evaluating the surface pH[74].

5.6. Moisture loss

It defines the hygroscopicity of odfs. Moisture loss evaluation is done by placing the film initially weighed as W_1 and then placing it in a desiccator with calcium carbonate for three days. Following this, odfs were taken out of the desiccator and weighed as W_2. The following formula is then applied to determine the amount of moisture lost[75]:

Moisture loss = Initial weight (W_1) – final weight (W_2) / Initial weight (W_1) x 100

5.7. Disintegration time

It defines amount of time in which the odfs disintegrate to release the drug in the buccal cavity. Disintegration time evaluation is performed with the help of two methods i.e., Petri dish and Slide frame method[76].

5.7.1. Petri dish method

In this process, odfs with a 2 cm^2 area were submerged into a Petri dish that had been filled with 10 ml water and the time at which odfs diminished or disintegrated is noted. It is conducted 3 times for good results[77].

5.7.2. Slide frame method

This evaluation involves clamping odfs to the slide frame, adding droplets of distilled water, and noting the timing of disintegration of the film[78].

5.8. In-vitro dissolution test

In-vitro dissolving experiments of odfs have been conducted using two standardized official paddles and a basket device. Most importantly sink conditions must be maintained during dissolution studies. During in-vitro dissolution studies there is a usual floating of film over the medium in the paddle apparatus due to which basket method is preferred. The media used in the in-vitro dissolution test of odfs are Phosphate buffer (6.8 pH) and 0.1 N HCl. In in-vitro dissolution studies media was sustained at 37±0.5ºC with a rotation speed of 50 rpm[79]. Six aliquots of 5 ml were drawn at specific times and are analysed with UV-Spectrophotometer.

5.9. Transparency

The evaluation of the transparency of odfs is usually performed with an UV-spectrophotometer for studying the visual appearance of odfs[80]. During this assessment, the film specimens were initially sliced into rectangle shapes and adhered to the inside of the photometer cell. The following was calculated via equation:

Transparency = (log T600)/b – ϵc

Where,

T600 = Transmittance of the film worked at 600 nm wavelength, b = thickness of odfs in mm, ϵ = Molar absorption coefficient and c = concentration.

5.10. Content uniformity

Content uniformity of odf is usually assessed with the help of standard assay methods provided by pharmacopeias for individual drugs[81]. In this evaluation odfs with a 1 cm^2 area were dissolved in 100 ml of buffer solution, and then 2 ml of an aliquot was removed and diluted with 10 ml of

buffer solution. After this dilution, the solution's absorbance was evaluated via UV-vis spectrophotometer which provides the value of the absorbance from which the amount of drug can be calculated thus the uniformity of the content of the odfs can be evaluated.

6. NEED OF ORODISPERSIBLE FILMS

The Greek philosopher Aristotle identified three factors: *Ethos*, *Logos* and *Pathos*, that can be used to advocate the importance of an idea infront of people[82]. These three factors can be used to support the current need for orodispersible films. They are depicted as the main pillars for the necessity of orodispersible films in figure 5.

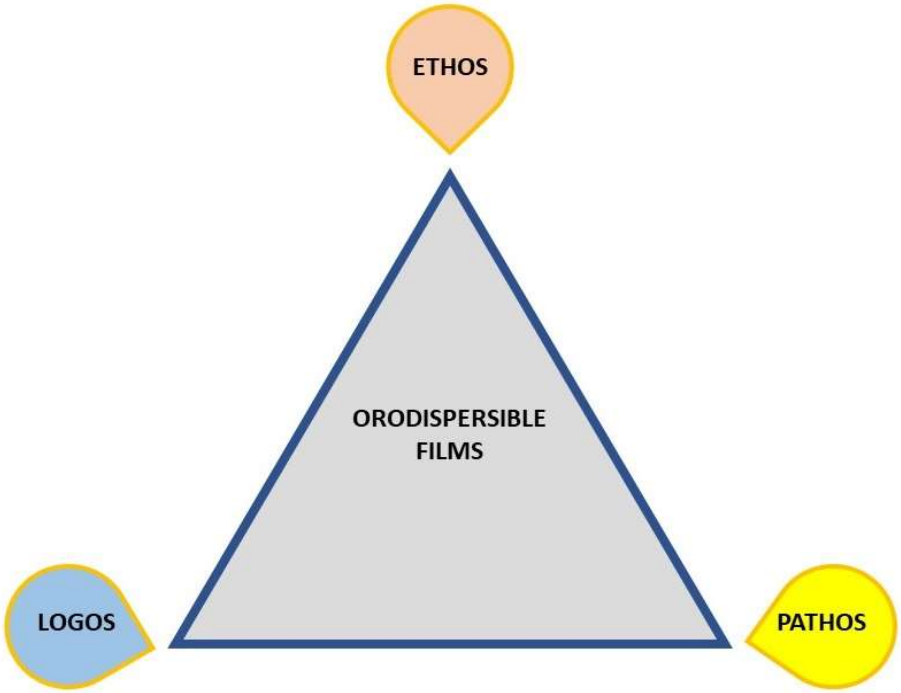

Figure 5: Aristotle's 3 factors supporting need of Orodispersible films.

These factors help to explain why orodispersible films are necessary in the modern era for patients experiencing dysphagia. *Ethos* refers to ascendancy; in the context of orodispersible films, this indicates that doctors prescribe them to patients who are suffering from dysphagia[83]. *Logos* denotes rationality, since orodispersible films provide the medication through the oral route[83] via oromucosa, they are undoubtedly the greatest substitute for conventional methods. *Pathos* are sentiment and orodispersible films act as pioneer water-free medications that provide relief to dysphagia patients and thus win their trust[84]. Hence, in a collective of three pillars given by Aristotle, orodispersible films are necessary for patients suffering from dysphagia since they find difficult to administer the medications.

7. FUTURE OF ODFs

The confluence of the art of finding new drugs with the sustained aim of improvement, forms the core of the pharmaceutical industry as it opens a new way for overcoming obstacles and odds in the formulation and development of new drugs which generally make collective therapy for patients more efficient. Both the quantity of research and the number of ideas for patents have increased in recent years[85] , which clearly shows that ODFs are now becoming an area of interest

for many researchers who are continuously working in the field of formulation development. The future of odfs has two sides, similar to two faces of coins, one is promising and the other is challenging. The first aspect of the future of odfs is the obligatory shift in the manufacturing of odfs from small to large scale so that there is access to odfs in a large community and the other aspect is to make odfs ideal for drug delivery for common people, who stills think that the conventional drug delivery system is good and inexpensive. This dual faced future of odfs at first sight may seem to be challenging but when it is successfully solved it will create new opportunities for development of the odfs. At present, odfs are mainly formulated via a solvent casting process which is easy and simple but has one major issue, namely, the susceptibility of the formulation to humidity degradation as water-loving polymers can absorb the moisture. There are many approaches that overcome this issue, such as the semisolid casting and solid dispersion method. The other aspect that needs attention is the small loading of drugs on the odfs as such they are unable to deliver the drug over wide ranges of dosage strengths. It has been confirmed that the future of odfs is secure and bright, as many patients such as pediatrics, geriatrics and several others, have difficulty taking the drug with water and they find odfs to be ideal, as they can take it without water. A search for fully customizable doses along with formulations that can be administered easily is needed for future development and progress.

CONCLUSION

A novel class of oral dosage forms known as orodispersible films (ODFs), distributes medication through the oromucosa. Compared with conventional dosage forms which have low bioavailability, are difficult to swallow, have slow action at non-uniform dosage, odfs have better bioavailability, and uniform dose strength with fast action; therefore, they are among the most accepted dosage forms for patients, including geriatrics, pediatrics, paralyzed, bed-ridden patients and all others, who have found difficult to swallow medications with water. The Orodispersible films can be easily utilized by placing them on the tongue, with quick absorption. Odfs are often created using a range of techniques, including rolling, solvent casting, hot melt extrusion, semi-solid casting, and solid dispersion. Among the numerous methods of formulation, the solvent casting approach is the first preferred option as it is easy and the development of the formulations can be achieved quickly; however, the susceptibility of the formulations to moisture degradation is the greatest disadvantage, which overall decreases the shell life as well as the stability of the odfs owing to the use of water-loving polymers in the process. This disadvantage is overcome by other methods such as Semisolid casting and Solid dispersion. The most important properties of odfs are their mechanical strength, tensile strength, folding endurance and disintegration, which are usually evaluated to assess their physical properties so that efficient and stable formulations can be confirmed. Orodispersible films are one of the fields of drug research that is moving at one of the quickest rates, as seen by the sharp rise in the applications for patent awards filed in recent years. It brings new ideas and innovations together under one roof. The future of orodispersible films is very bright as they are receiving increasing amounts of attention from scientists, and as such, there is great potential for odfs in the near future owing to the advent of newer technologies and ideas.

CONFLICT OF INTEREST

The authors confirms that there is no conflict of interest related to the manuscript.

ACKNOWLEDGEMENTS

Declared none.

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