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A REVIEW ON ORODISPERSIBLE DRUG DELIVERY SYSTEM

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ABSTRACT

The future of drug delivery holds great promise for orally dispersible dose formulations, which make application simple since no water requirement as compared to conventional solid dosage forms which requires significant volumes of fluids for administration. The objective for development of ODF provides a substitute for pills, syrups, and tablets in treating vomiting as well as nausea, particularly in children. On the basis of transdermal patch delivery system, a novel oral films drug delivery has been introduced. Fast dissolving films disintegrates quickly when come in contact with salivary secretion in the oral mucosa and released the drug fast approximately within 3 mins. ODFs are of different types, like sustained or controlled release, oral patches and fast dissolving films. They can be manufactured using a variety of method including solvent and semi solid casting, hot melt and solid dispersion extrusion, spray drying and rolling. Among them solvent casting method is the most employed method. ODFs comprises of active ingredient, polymer, plasticizer and additives like surfactants, sweetening and coloring agents. ODFs preparation requires hydrophilic polymer which provides quick dissolution in the oral cavity. Hydrophilic polymer act as base for ODFs formulation as they impart mouth feel and mechanical properties of the ODFs also dependent of polymer type. Oral thin-film provide fast drug dissolution precise dosage in a portable, safe, and handy manner that doesn't required water or any special equipment. This review article comprises of different methods for ODFs preparations, ODFs ingredients, ODFs benefits and drawbacks and their packaging.

Keywords: Orodispersible films, Manufacturing methods, Formulation composition, Packaging

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INTRODUCTION

Patients are often more receptive to the oral approach. Roughly 60% of all dose formulations are now available as oral solids **[1]**. Difficulty swallowing, also known as dysphagia, is associated with a wide variety of medical conditions, including Parkinson's disease, stroke, AIDS, radiation treatment of the head and neck, and other neurological problems **[2]**. It is estimated that 25 to 50% of people with mental illness have difficulty swallowing, as do 35% of the general population, 30% of the elderly in nursing homes, and 5% of the general population **[3]**. Further, children, the elderly, and those who are dehydrated owing to sickness, vomiting, or a lack of ready access to water are not good candidates for solid oral dose forms **[4]**. In the late 1970s, the first fast-dissolving drug delivery technique was developed, and in 2001, the transdermal patch and orodispersible film (ODF) were introduced. ODFs are described as. "single or multilayer sheets of appropriate materials, to be inserted in the mouth where they diffuse fast,"

The use of orodispersible films as a dosage form for oral delivery is a recent development. They're like long strips of stamp-sized thin polymeric films that dissolve instantly if put on the tongue. The words used in the literature to describe the same are the orally dissolving film, Wafer, oral film, flash release wafer, thin strip rapid dissolve film, and melt-away film. The films don't melt but rather dissolve or at least disintegrate in the saliva; therefore, the labels "melt-away film" and "melting film" are somewhat misleading **[5, 6]**; the Food and Drug Administration (FDA) prefers the term “soluble film” (sometimes 'buccal or oral soluble film'), while the European Medicines Agency (EMA) is now using 'orodispersible film' (ODF) in their regulations. The first descriptions of what would become known as "oral films" may be found in patent documents from the 1960s **[7]**.

Nonetheless, ODFs took some time to gain ground; in 2001, Pfizer (New York) launched Listerine PocketPaks, small strips for breath refreshing that

was later named one of the top innovations of all time by Time Magazine **[8]**. In 2003, InnoZen (Oxnard) released the world's first OTC ODF (Chloraseptic Relief Strips with benzocaine) to administer an API. Several other over-the-counter films have entered the US market since then. ODF (Ondansetron Rapidfilm,) was the first prescription medicine to be approved in the European Union in 2010. Risperidone ODF was the first prescription medicine product to hit the market.

Acceptability in the context of medication use is described as "the total ability and willingness" of both patients and caregivers to use the medications safely and effectively **[9]**. ODFs are a convenient dose form since they do not need to be taken with water and may be made to hide unpleasant flavors **[10]**. In addition to being more precise than syrups in terms of dosing, they eliminate the danger of choking—their increased surface area facilitates rapid wetting, disintegration, and dissolution as compared to other systems **[11]**. This eliminates the need for the patient to chew or ingest (swallow) the medication. For individuals who have trouble taking their drugs, these characteristics may make them the perfect solution **[12]**. They dissolve quickly in the oral cavity and release the prescribed quantity of the active ingredient, making them an ideal oral form that combines the dosing precision of solid oral forms with the convenience of liquid oral forms **[13]**. These extraordinary features may be employed to increase the acceptability of medications, particularly in youngsters and other patients who have difficulty ingesting solid oral forms of medication. This is especially true in the case of regularly used medication **[14]**.

As a result, this article will conduct a literature review on Oral films only; further details on mucoadhesive and extended-release films are included if relevant.in an effort to elaborate on the role of manufacturing process in orodispersible films.

Oral Films Types

Differentiating between fast-dissolving and sustained-release films, mucoadhesive films, or oral patches seems to be effective depending on the disintegration period and design. In either case, there is no distinct boundary. As buccal sustained-release dose forms, oral patches and mucoadhesive films are widely available. All varieties may be used for either local or systemic drug treatment, with mucoadhesive films, in particular, offering the possibility of systemic therapy via oral mucosal absorption of the active pharmaceutical ingredient **[15]**.

There are a variety of potential uses. When using an ODF, you should put it on your tongue. While the cheeks are the most common location for mucoadhesive films, the palate and sublingual are also viable options. Additionally, ODF technology may allow films to be used in vaginal or rectal applications.

IDEAL CHARACTERISTICS OF ODFS

Ideally, the ODF should be thin, malleable, and sturdy so as to provide a robust production and packaging process, as well as ease of handling and administration **[16]**). It is important that the films be portable, not sticky, and that they maintain a flat plane shape without rolling up and disintegrate the drug within 3 minutes **[17]**. They ought to have a tolerable flavor and a pleasant texture in the mouth **[18]**. The amount of time required for disintegration needs to be minimized. Because of the indirect correlation that exists between mechanical qualities and disintegration time, it is difficult to satisfy all of these requirements **[19]**.

MANUFACTURING PROCESS

The production of ODFs relies primarily on well-established manufacturing processes, such as solvent casting, semi solid casting, solid dispersion extrusion. Rolling method, and hot-melt extrusion. Typically, the production process begins with the formation of a broad web, which is then sliced into the final dosage form. As a result of this, the most important consideration throughout production is the broad web's ability to maintain its consistency.

Solvent Casting Method

The preparation of ODFs is often done via the solvent-casting process since it is uncomplicated, quick, and requires no specialized equipment. Active pharmaceutical ingredients (APIs) and excipients are mixed with water or alcohol, poured onto a surface, dried properly, and cut into suitable dimensions **[20]**. In this method, the suspension of APIs, polymers, sweeteners, flavorings agents, plasticizers and super-disintegrants must be sonicated to get a film with the same thickness and uniform thickness. The suspension is put in a vacuum to get rid of any trapped air bubbles. It is then poured into a mould, like a petri dish, and left to dry **[21]**. For ODFs produced using the solvent-casting technique, there are common CQAs and process variables. The drying temperature must be carefully monitored. When a thermosensitive API is utilized in the process, a low temperature should be used to provide an appropriate viscosity for forming a film. Residual solvent may persist in the ODFs, affecting their stability and mechanical qualities. As a result, the residual solvent in ODFs should be monitored and analyzed **[22]**.

Semi Solid Casting

The semi-solid forming method is well-known for combining the benefits of casting and forging to

manufacture complex-shaped various components **[23]**. Despite being comparable to solvent casting, semi-solid casting needs two primary polymers: hydrophilic and hydrophobic. The process begins with preparing a film-forming polymer solution that can be dissolved in water. An acid-insoluble polymer such as cellulose acetate phthalate in sodium hydroxide is blended with the gel mass of the solution. The acid-insoluble polymer solution must include at least one mole for every four moles of the soluble film-forming polymer. The gel mass is then cast using drums that are kept at a specific temperature. Average film thickness ranges from 0.015 to 0.5 inches **[24]**.

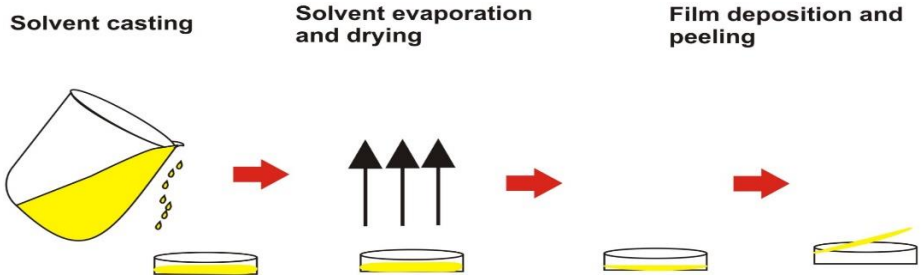

Figure 1: Solvent casting method.

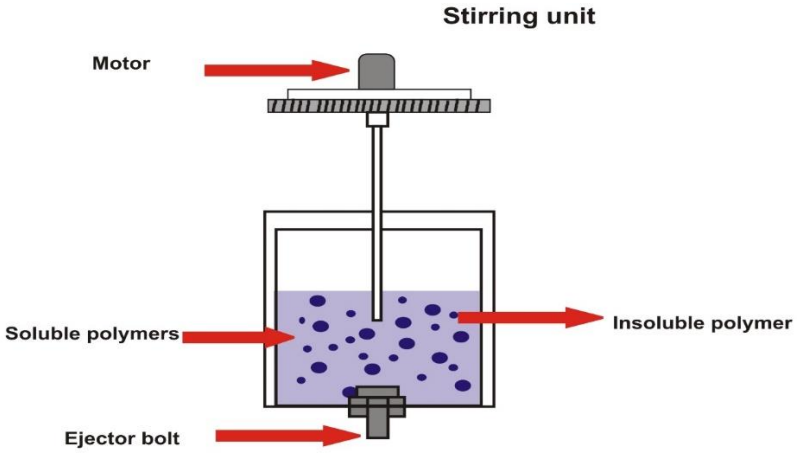

Figure 2: Semi-solid casting apparatus.

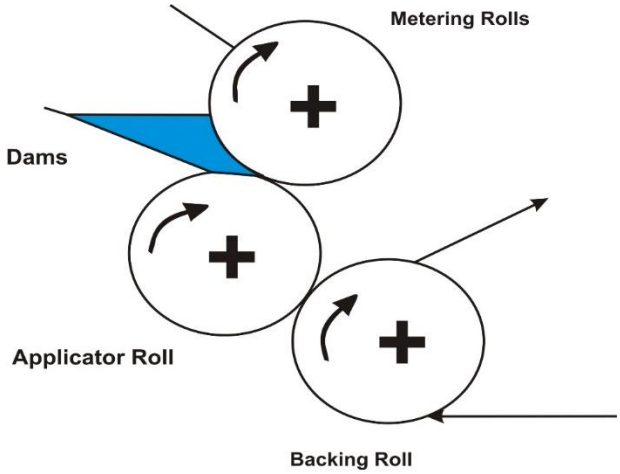

Figure 3: ODFs roller apparatus.

Rolling Method

First, a suspension with the desired rheological characteristics is generated, which includes film-forming polymers, water, a combination of water and alcohol, and additional excipients (except APIs). A metering roller is used to regulate the amount of suspension used. A metering pump and control valve are used to regulate the suspension's quantity before it reaches the mixers. In a mixer, the APIs are combined with the suspension to create a uniform matrix that is fed via the metering pumps. The applicator roller applies the film once the metering roller has determined its thickness. Finally, the film is created on the substrate and removed using the backing roller (**Fig. 3**). Controlled bottom drying is then used to dry the wet film; ideally, there are no external air currents or heat sources on the film's top surface **[25]**.

Hot Melt Extrusion

Since the early 1980s, the pharmaceutical sector has used hot-melt extrusion (HME). Granules, sustained-release pills, and transdermal buccal and transmucosal drug delivery devices are often made using HME. Pharmaceutical HME makes use of a continuous processing technique that enables API-polymer mixes to produce the required drug release patterns (**Fig. 4**). The method's crucial process variables are the settings for temperature, feeding rate, pressure and speed **[26]**. ODFs formulated via the solvent-casting process may have low production levels, environmental risks, and instability due to uncontrollable variables such as polymer chain relaxation, moisture uptake or loss, and interactions between the polymer and plasticizer during storage **[27]**. HME techniques, on the other hand, include benefits such as ease of shape, reduced operating units, low wastage, scalability, appropriateness for pharmaceuticals that are sensitive to moisture, and effectiveness of solubility improvement for APIs that are poorly soluble. HME techniques, however, are expensive and require specialized tools **[28]**.

Solid Dispersion Extrusion

Solid dispersion extrusion as a method for increasing the bioavailability and dissolution rate of hydrophobic drugs, solid dispersions in hydrophilic carrier systems have gained significant attention **[29]**. Solid dispersions can be produced from an appropriate dispersion without removing the liquid solvent. The solid dispersion extrusion is often composed of mixing one or more APIs that have been dissolved in a suitable solvent with polyols, such as melted Polyethylene glycol **[30]**.

INGREDIENTS

A typical ODF contains following ingredients

An active pharmaceutical ingredient up to 30%, film forming water soluble polymer around 40-50%, plasticizers in the range of 0-20%. Beside these ODFs also contains fillers, disintegrants, sweeteners and flavourants.

Since ODFs are a viable option for dosing children and elderly patients, therefore it is imperative that safe excipients must be used.

Active Pharmaceutical Ingredient

Particles or molecularly dispersed/dissolved API may be added into the films. Particle size, particle size distribution, and polymorphism are critical quality factors for dispersed APIs. It's widely known that these variables may alter a drug's solubility, dissolution rate, and bioavailability. Considering the limitations of the drug loading, low-dose drugs with good efficacy are a suitable choice **[31]**. The API's solubility and excipient compatibility determine the maximum drug loading. Recrystallization or overwhelming effect on the mechanical or disintegration characteristics of the films might occur at a critical drug loading **[32-33]**. Drug loads are typically restricted to a maximum of 25 mg **[34]**. API stability depends upon manufacturing parameters or residual water content of the films, as well as possible buccal permeability if solely gastrointestinal absorption is desired **[35]**.

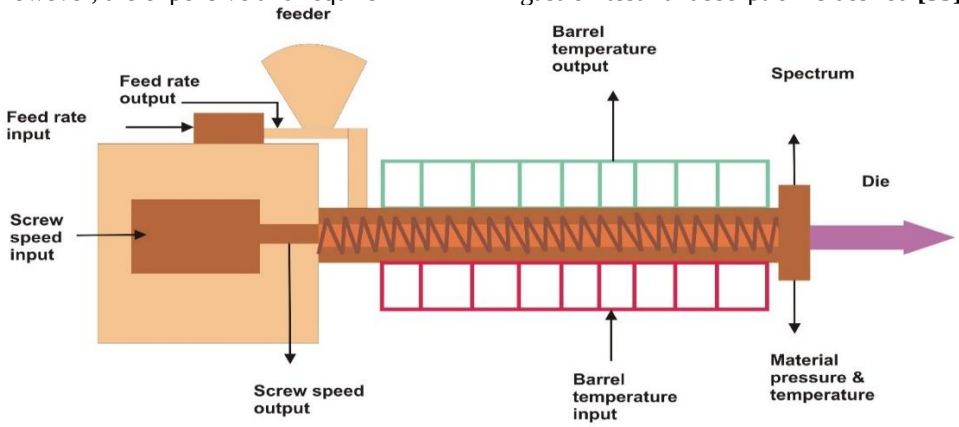

Figure 1: Hot melt extrusion apparatus.

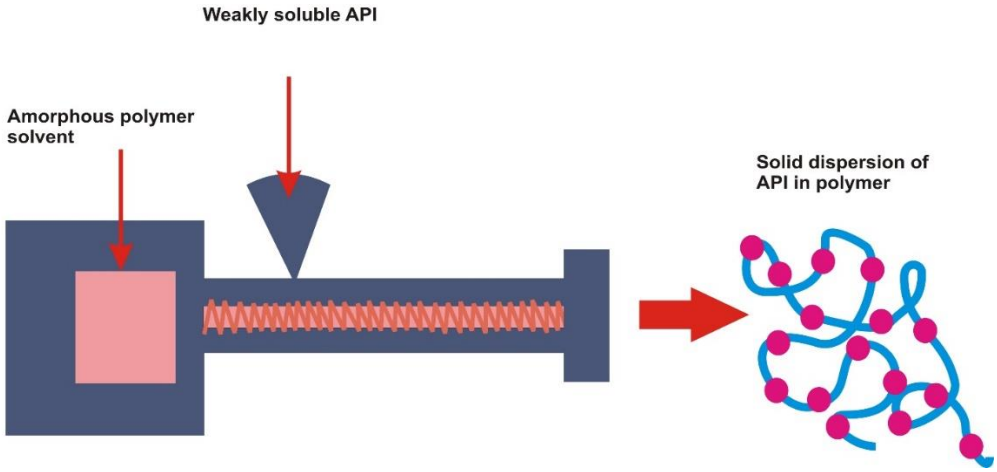

Figure 2: Solid dispersion extrusion apparatus.

Film Forming Polymers

ODFs need film-forming polymers as key excipients. Several polymers have been described in the existing literature. However, the selection remains tricky. Although the films must dissolve quickly in the oral cavity, their mechanical characteristics must be sufficiently suitable for handling, shipping, and storage **[36]**. The characteristics of polymers rely on their molecular mass. In general, polymers with a low molecular mass dissolve faster, while polymers with a larger molecular mass have superior mechanical qualities. Hypromellose grades with increasing molecular weight (E3, E5, and E15). They determined that E3 is preferable to E5 and E15 for the production of ODFs containing levocetirizine hydrochloride **[37]**. The influence of maltodextrin molecular weight (mw) on film characteristics. Maltodextrin films with a higher molecular weight were more rigid than maltodextrin films with a low molecular weight. They exhibited superior tensile strength, elastic modulus, and elongation at break. Additionally, these films were less sticky than those produced using a lower molecular mass of maltodextrin **[38, 39]**.

Cellulose derivates, polyvinyl alcohols, and pullulan are more popular. Typically, cellulose derivates with low viscosity grades of hypromellose, methocel or carmellose are employed **[40]**. Polymers such as polycarbophil, polymethacrylic, thioglycolic acid or polyacrylic acid might be added to the formulation to produce sustained-release or bio-adhesive films **[41, 42]**.

Plasticizers

Generally, a plasticizer is required to generate flexible, non-brittle ODFs. Combinations of glycerol, propylene glycol, low-molecular-mass macrogols, phthalates, sorbitol and citrates are often used **[43]**. As ODFs retain a relatively high-water content after drying, water serves as a natural plasticizer. Plasticizers interact with polymers that form films by reducing their glass transition temperature, hence enhancing the films' flexibility and elasticity **[44]**. Most of them have additional effects that must be addressed, such as sorbitol's usage as a sweetener. Plasticizers may impact the API's solubility and medication absorption **[45]**. High plasticizer concentrations may reduce a material's resistance to moisture, resulting in instability issues or sticky films **[46]**. Due to their incompatibility with maltodextrin, Macrogol 400 and citric acid esters cannot be used to plasticize maltodextrin films. Increasing the glycerol or propylene glycol concentration in maltodextrin ODFs lowered the elastic modulus and increased the elongation at break. Concentrations over 18% w/w resulted in blooming and adhesion. The flavor of ODFs plasticized with glycerol was better than that of films plasticized with propylene glycol.

Polyvinyl alcohol-based ODF composition with glycerol and mannitol as a plasticizer and a filler. A high proportion of polyvinyl alcohol increased tensile strength, decreased drug release, and increased cumulative points. The glycerol addition decreased tensile strength and drug release and increased the overall score. An increased concentration of mannitol decreased tensile strength, increased drug release, and increased total score **[47]**. Stabilizers Fillers, pigments, opacifiers, preservatives, and anti-tacking agents are additional excipients for ODFs **[48, 49]**.

BENEFITS AND DRAW BACKS

ODFs are designed to be put on the tongue, where they dissolve quickly in saliva. It is not necessary to swallow the entire thing. As a result, they are ideal for children and geriatric patients, as well as bedridden patients and those suffering from dysphagia, nausea or vomiting and Parkinson's disease **[50]**. Because of the fast wetting, oral films may stick to the mucosa or break down quickly,

making them difficult to spit out **[51]**. Some people are so concerned that they won't even take orally disintegrating pills because of the risk of choking or accidentally breathing them in **[52]**. Because ODFs are relatively thin and may be taken without the need of water **[53]**, they are an excellent option for travel patients or travelers who do not have constant access to water.

The use of orally disintegrating tablets, often known as ODTs, has become more common in recent years. Many ODTs are designed to be fragile so that they may disintegrate quickly. This creates challenges throughout the production process as well as storage, handling, and administration. On the other hand, ODFs are not only flexible but also resistant to the effects of mechanical forces **[54]**. Lyophilization is a typical procedure that is used in the production of ODTs. On the other hand, the technology that is used to produce transdermal patches is used in the production of ODFs. This method is cost-effective as compared to lyophilization **[55]**. ODFs provide the simplicity of correct dosage, which makes them preferable to liquid formulations such as drops or syrups **[56]**. It is possible to obtain a rapid onset of action of the drug since it is delivered into the oral cavity in a matter of seconds. For certain medications, the elimination of the first-pass metabolic step is possible if the drug is absorbed via the oral mucosa. This results in increased bioavailability. For instance, patients who suffer from migraines may find that absorption via the buccal cavity is especially helpful. Due to the rapid onset of action, however, some patients can feel drowsiness after taking the medication **[57]**. The drug load is restricted. As a result, ODFs are limited to potent low-dose medicines. Furthermore, solvents and heat are often required for drying in the industrial industry. These variables may have an impact on the drug's stability or the stability of other excipients such as sweeteners and flavors. Taste is a crucial disadvantage of orodispersible dose forms in general. Taste masking may further limit the maximum medication dosage. Taste masking may even be tricky for excessively bitter APIs **[58]**.

PACKAGING

Since ODFs are sensitive to water uptake, they shouldn't be stored unpacked. Most of the time, ODFs are sealed in pouches. There needs to be a barrier against moisture in packaging. Visual inspections and weigh variation could be measured. Single and multiple dose packaging can be done, but multiple dose packaging offers sticking issues resulting overdose. Personalized medication use can be achieved using roll dispenser that provide desired sized cut film. Modern packaging methods like the Rapidcard (Labtec GmbH), which is the equal to credit card and each side contained three films, provide a new technique for ideal drug delivery for transport. Packaging should be safe for children and easy for older people administration. Before packaging, the necessary information should be labelled in film package for comply industry standards.

CONCLUSION

ODFs can be prepared using a variety of methods but the best and most commonly employed methods are solvent casting method and hot melt extrusion. ODF formulated using high concentration of plasticizers may reduce a material's resistance to moisture, resulting in instability issues or sticky films. A high proportion of polyvinyl alcohol increased tensile strength and decreased drug release. Polymers such as polycarbophil, poly-methacrylic, thioglycolic acid or polyacrylic acid might be added to the formulation to produce sustained-release or bio-adhesive films. Among different grades of Hypromellose, E3 is preferable to E5 and E15 for the production of ODFs. ODFs provide the simplicity of correct dosage, which makes them preferable to liquid formulations and also overcome dysphagia related with solid dosage form.

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