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Orally disintegrating film: A revolutionary new drug delivery system-A review

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Abstract
The propensity toward novel drug delivery technologies over the past few decades has significantly boosted efforts to guarantee efficacy, safety, and patient acceptance. The development of novel drug delivery systems for already existing medications is becoming more popular as the research and development of new chemical agents is a difficult, expensive, and time-consuming process. Orally disintegrating films are a popular drug delivery method in both children and geriatrics. These rapid disintegrating films are better than fast disintegrating tablets because the latter have choking and friability issues. Compared to traditional fast-dissolving tablets, this drug delivery system offers many advantages since it can be used for patients with dysphasia and schizophrenia and because it can be taken without water. One of the most significant oral dose forms for pharmaceuticals is orally disintegrating films (ODFs). It has been observed, nonetheless, that the hygroscopicity of ODFs compromises both their mechanical strength and stability. To investigate the impact of the water content on the mechanical properties of the films and the time it takes for them to disintegrate, we created model ODFs with three different water contents by storing them under various relative humidity conditions. The most used technique for evaluating the mechanical properties of films intended for oral disintegration is the tensile test. The folding endurance (FE) test, which is another accessible test, is more suited for determining the actual strength during manufacture and dosage. However, the FE test is performed manually, and the FE number it generates has not been adequately analysed as an index. These studies aimed to establish an automatic method for determining the FE number and to compare the resulting FE numbers with the tensile properties. Due to the best level of patient compliance, particularly in geriatric and paediatric patients, oral disintegrating systems have established a niche among oral drug delivery systems.

Keywords: ODFs, polymer, plasticizers, surfactants, flavours, sweetening agents

Introduction
Due to its simplicity, non-invasiveness, adaptability, patient acceptance, and convenience of administration, the oral route of medication administration is one of the most popular routes [1]. For patients in the juvenile, geriatric, nauseated, and non-compliance populations, numerous alternatives to the oral route of drug delivery have been consistently provided. The results of technical advancement include bio-adhesive mucosal dosage forms such as adhesive tablets, gels, and patches. [2] When placed on the tongue, oral disintegrating films (ODFs) immediately hydrate by soaking up saliva after disintegrating and/or dissolving, releasing the active medicinal ingredient from the dosage form. ODFs are a class of formulations that are frequently created employing hydrophilic polymers that enable quick dissolution when in contact with saliva. Orally disintegrating drug delivery techniques commonly include oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs). [3] These systems were created in the late 1970 to provide geriatric and paediatric patients who had trouble swallowing traditional dosage forms with an alternative to those forms, such as fast-dissolving tablets and capsules. [4] A typical ODF is usually equal to the size of a postage stamp. In market place, the introduction of ODT was strongly associated with counselling of patients about the appropriate administration by giving instructions like "do not chew/do not swallow". However, despite these instructions, incidents regarding chewing and swallowing were often reported. But, ODFs untied the masses from these adverse events. [5] The management of ODFs has many benefits, some of which are as follows: [6, 7]

1. Convenient transit.
2. Swallowing comfort for young children and older people.
3. Easy and precise dosing.
4. Water is not required for administration.
5. Convenient for people with dysphasia who have trouble swallowing pills and tablets.
6. Stability and a quick start to action thanks to circumventing the hepatic first-pass effect.

The benefits of ODFs include no costly lyophilization, great mechanical strength, quick disintegration, and lower choking concerns. [1] ODFs have become extremely significant in the pharmaceutical sector because they have special qualities and a quick disintegration period of only a few seconds to a minute. The design of ODFs allows for the incorporation of numerous medications for their pharmacological effects, such as anti-tussive, anti-epileptic, anti-asthmatic, and expectorant. [4] One drawback of ODFs is their high temperature and moisture sensitivity, which requires expensive packaging and prevents high-dose loading [9, 10, 11]

Formulation
Pharmaceutical formulation is the multistep process where the active drug is mixed with all other components by considering the factors of particle size, polymorphism, pH, and solubility and becomes the final beneficial medicinal product. ODFs are thin films that quickly dissolve and have an area of 5 to 20 cm2, in which hydrophilic polymer is used to integrate the medicine as a matrix. Up to 15 mg of the active pharmaceutical ingredient may be included with

various excipients, such as plasticizers, colourants, sweeteners, taste-muffling agents, etc. Plasticizer lowers the glass transition temperature of polymers by improving the workability, spreadability, and flexibility of films. [12]

Table 1

Components	Concentration %
Active Pharmaceutical Ingredient	1-25
Hydrophilic Polymer	40-50
Plasticizer	0-20
Colour, Filler, Flavour	0-40

Active Pharmaceutical Ingredient

ODFs can contain a variety of pharmacological types, such as antihistamines, antidiarrheals, antidepressants, vasodilators, anti-asthmatics, and anti-emetics. For taste masking, dimenhydrinate can also be added to ODFs. [13, 14] Drugs including salbutamol sulphate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc. are frequently included in ODFs. Moreover, an ODF containing a prochlorperazine-like anti-emetic drug was created using microcrystalline cellulose and other film-forming polymers. [13]

Hydrophilic Polymers

The mechanical strength of films is strongly correlated with these parameters, hence the construction of an ODF depends on the rational selection and concentration of polymers. To change the properties of a film, they can be utilised alone or in conjunction with other polymers. When creating an ODF, the concentration of the employed polymers is also crucial. Careful selection of polymer type and concentration is necessary for rapidly dissolving oral films to maintain their integrity. [1] To produce ODFs with the appropriate properties and characteristics, the polymer concentration can be increased up to 60–65% w/w, which is generally around 45% of the total weight of dry thin strip. Certain qualities of the polymer employed in the formulation of thin strips should exist. [14]

Ideal properties of Hydrophilic Polymers [15]

1. Non-irritant
2. shouldn't interfere with the ODF's time for disintegration
3. Affordable
4. It should have strong mechanical qualities, a suitable tensile strength, a good spread ability, and an adequate shelf life.
5. Non-toxic

In recent era, both natural and artificial polymers are used for developing ODF formulation, Most commonly used natural and synthetic polymers in ODFs.

Table 2

Type of Polymer	Examples
Natural	Starch, polymerized rosin, pullulan, sodium alginate, Pectin, gelatin, and maltodextrins
Synthetic	Polyvinyl alcohol, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, polyvinyl pyrrolidone, and hydroxy propyl cellulose

Various polymers are used to modify certain film characteristics. Along with improving flexibility, pullulan has enhanced solubility. Pullulan-containing films also have good tensile strength and temperature stability. The qualities of prepared films are influenced by the molecular weights of the gelatins, and a substantially more pleasing film can be made by utilising polymers with a higher average molecular weight. Excellent strip quality is produced by combining chitosan with high methoxy pectin (HMP) or low methoxy pectin (LMP). Due to their hydrophilic character, the cellulose-derived film-forming polymers hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC), and carboxymethyl cellulose (CMC) produce films with a reduced water vapour barrier. In addition, polyethylene glycol (PEG), whether used alone or in conjunction with other polymers, has effective film-forming capabilities. [16]

Plasticizers

In general, adding plasticizer to the formulations improves mechanical qualities like tensile strength and % elongation. Plasticizer concentrations typically vary from 0% to 20% weight/weight. PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, and other substances are frequent examples of plasticizers.

Surfactants

Surfactants are essential because they act as a dispersing, wetting, and solubilizing agent, allowing films to dissolve quickly and release the medicine they contain. Benzalkonium chloride, tweens, and sodium lauryl sulphate are common surfactants. Due to its many benefits, polaxamer 407 is frequently employed. [17]

Flavours

To disguise the unpleasant or bitter taste of an included medicine, flavours are required. The type and power of the taste determine how much there is. You can use any US-FDA-approved flavour, including mint, sour, and sweet. One study confirmed that a sucralose, liquorice, and mint flavour combination effectively hides the diclofenac sodium's harsh taste. To differentiate between the effects of various taste-masking chemicals, electronic tongues are used (TMAs) [18]

Sweetening Agents

Sweetening agents are made to dissolve or disintegrate in the oral cavity. For making ODFs, artificial and natural sweeteners are both used.

Table 3

Sweetening Agents	Examples
Natural	Glucose, Fructose, Dextose, Sucrose and Isolmaltose.
Artificial	Acesulfame-K, sucralose and neotame.

Saliva stimulating agent

Salivary stimulants, which are often acidic in nature and stimulate saliva production in the buccal cavity, aid in the breakdown of ODFs. Citric acid, malic acid, tartaric acid, ascorbic acid, and lactic acid are a few of the often-utilised saliva-stimulating substances. [19]

Colouring Agents

Pigments are used as colouring agents. Titanium dioxide is most widely used colorant in ODFs and various other pharmaceutical preparations. Apart from titanium dioxide, a full range of colours are available including FD and C, natural and custom pantone-matched colors.

Conventional approaches for manufacturing of Oro dispersible films

Methods mainly employed for manufacturing ODFs are shown in fig. [20]

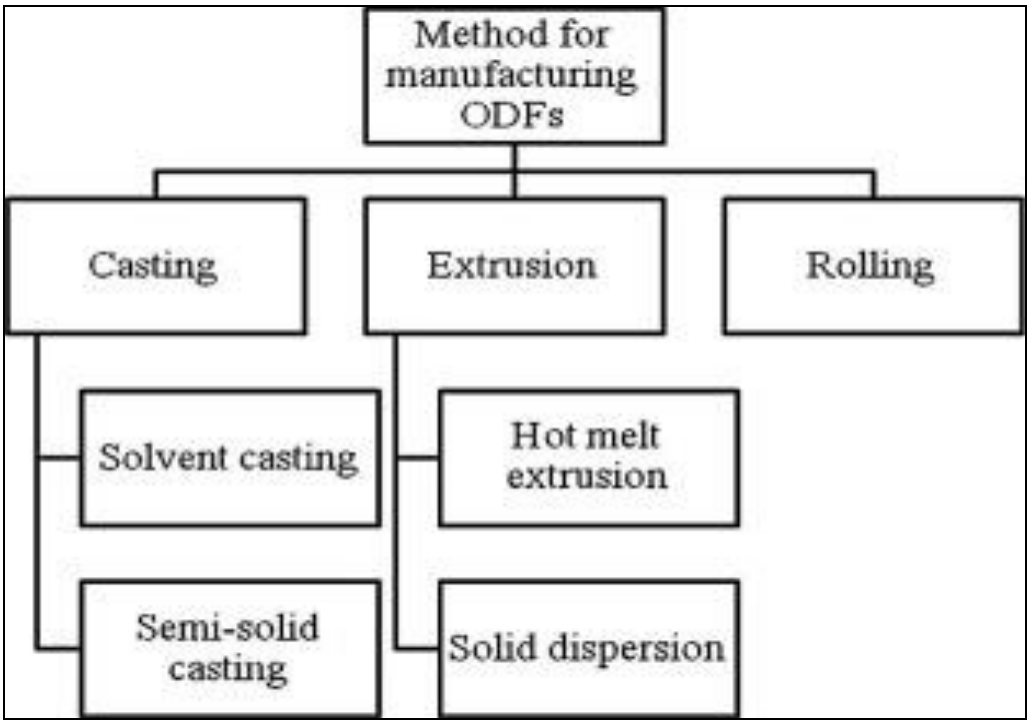

Fig 1

Solvent Casting Methods

The most popular technique for making ODFs involves employing water-soluble excipients, polymers, and drugs that are dissolved in de-ionized water. High shear pressures produced by a shear processor are then applied to the mixture to create a homogeneous mixture. In order to produce high-quality films, the prepared solution is then placed onto a petri plate and the solvent is allowed to dry by subjecting it to a high temperature.

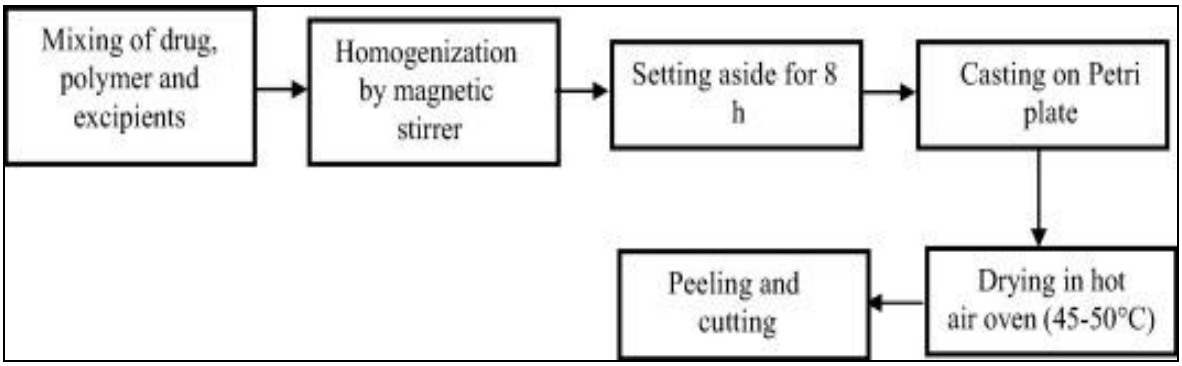

Fig 2

With the use of various grades of Lycoat and HPMC, the solvent casting technique was effectively used to create an Oro dispersible film of tianeptine sodium. Film-forming polymer is typically steeped in a suitable solvent for an entire night when using the solvent casting technique. The type of API that must be included in ODF determines the best solvent to use based on important physico-chemical characteristics of the API such melting point, shear sensitivity, and polymorphic form. Before deciding on a formulation, the compatibility of the medicine with the solvent and other excipients is also taken into account. Entrapment of air bubbles during formulation can reduce the homogeneity of manufactured films. Hence, the mixture is deaerated with the aid of a vacuum pump. [21]

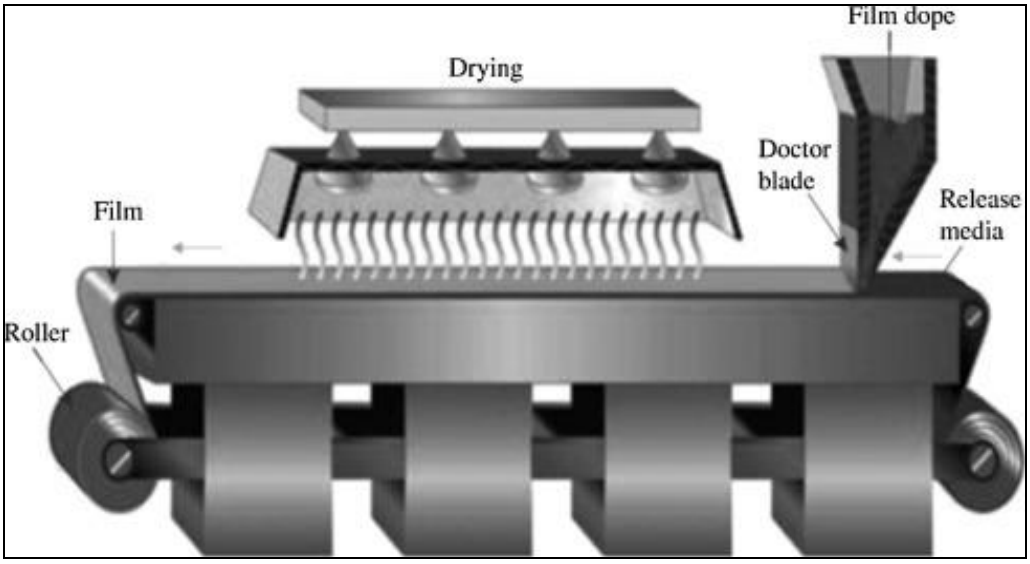

Fig 3

Solvent casting was also used to successfully create mosapride's orodispersible film composition. The viscosity of the solution to be poured is crucial to the casting process. Pullulan solutions with concentrations between 2% and 8% produce low viscosity solutions, making it possible to cast film with ease. With the aid of the solvent casting approach using HPMC (E5) and polyvinyl alcohol, fast disintegrating films of anastrozole were also successfully created (PVA). [21]

Hot Melt Extrusion

A medication, polymer, and excipient mixture is extruded at a high temperature using a process called hot melt extrusion to create a homogenous mass that is subsequently cast to create smooth films. Despite the fact that this is a solvent-free method, processing thermolabile materials is a significant disadvantage because extrusion takes place at a high temperature. [22]

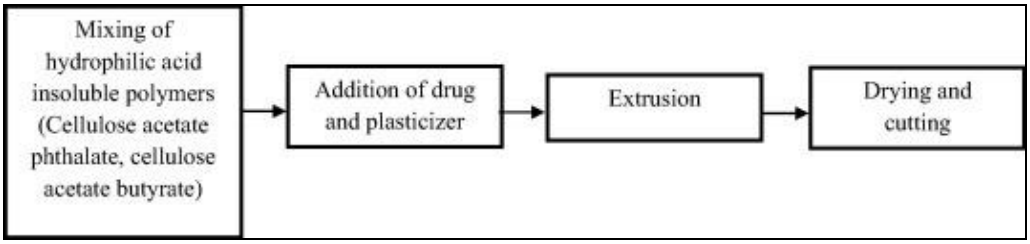

Fig 4

Characterization and Evaluation

For this, specialised, regulated human taste panels are employed. Human participants are used in this in-person taste study. Using taste sensors for screening, ODFs are in-vitro taste evaluated. For high-throughput taste sensing of such dosage forms, *in vitro* methodologies and technologies are suitable and sufficient. Both *in vivo* and *in vitro* methods are used to evaluate the sweetness and taste-masking effectiveness of taste-masking substances.

Mechanical properties

Thickness test

With a calibrated digital micrometre, the thickness of a film is measured, and the mean average is then computed. Typically, the average of three readings from all the batches is calculated. By cutting the film and calculating the weight of each individual film, weight variation of a film is calculated in triplicate. Uniformity in thickness is vital to verify as it is directly proportional to dose accuracy of the film. [23]

Dryness test/Tack test

This test is performed to find out the ability of a film to get adhered to a piece of paper pressed between strips. Obstinacy with which the film adheres with the piece of paper or any other accessory pressed in between the films is known as tack. Almost there are eight stages of film drying process which are identified *viz* dry-to touch, dry-to-recoat, dry hard, set-to-touch, dust-free, dry-through, tack-free and dry print-free. Primarily these tests are used to evaluate dryness of films in paint industry but are also adoptable for assessing orally fast disintegrating films. Dryness or tack test can also be performed by with the help of some newly invented instruments. [24]

Tensile strength

The maximum stress at which a film will break is referred to as its tensile strength. In essence, this test is done to assess the mechanical durability of films. It can be calculated using the equation below by dividing the applied load at rupture by the strip's cross-sectional area.

Tensile Strength = (load at failure/strip thickness × strip width) ×100

Percent elongation

A film stretches when stress is applied, which is referred to as strain. The length of the film divided by its initial/original length of the film specimen is known as the strain. The

amount of plasticizer used in the formulation of the film has a quantitative relationship with percent elongation. The strip often stretches farther when the plasticizer concentration in the film is higher. It is determined by the following formula [25]

Percent elongation= (change in length/initial length) ×100

Young's Modulus

It is the measure of film stiffness. In the elastic deformation region, it can be calculated as the ratio of applied stress to strain. It is determined by the following formula

Young's modulus= (slope/strip thickness × cross head speed) × 100

It also can be written as= force at corresponding strain/cross sectional area × corresponding strain

Young's modulus and tensile strength are two properties of films that are related to their hardness and brittleness. With little elongation, a hard, brittle film exhibits higher values for tensile strength and Young's modulus. [26]

Packaging of orally disintegrating film

Storage, protection, and stability of the dosage form depend heavily on packing considerations. Barrier films, single pouches, aluminium pouches, blister packaging with multiple units, foil paper or plastic pouches are among the packaging options for oral thin films. For drugs that are extremely moisture sensitive, barrier films are most frequently used. Primary packaging made of a sealing pouch that has enough room for logos, codes, instructions, or other information is described by rapid film technology developed by Labtec GmbH. The films are created through a laminating process, and the cost of packaging is similar to that of tablets. [27]

Conclusion

The current review demonstrates that one of the unique techniques in the world of pharmaceutical sciences is the use of oral fast dissolving films. In comparison to conventional dose forms, they have higher acceptance and patient compliance, no risk of choking, and superior safety and efficacy. The main motivation for developing ODFs was to address the issue of paediatric, geriatric, and psychiatric patients with dysphagia finding it challenging to swallow traditional oral dosage forms. ODFs are currently widely accessible, which reflects their significance for conditions like hypertension, acidity, allergies, pain, etc. The administration of such a dosage form without the need of water satisfies the desire of the target population for convenience in medication administration while also avoiding hepatic metabolism, thereby improving therapeutic response.

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