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Orodispersible Films - A Future of Modern Drug Delivery System

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Abstract
Orodispersible films (ODFs) have intrigued scientists and researchers in the domain of pharmaceutical formulations and are being looked upon as a novel approach to designing efficient drug delivery systems. ODFs are currently speculated to be an alternative to the conventional solid and liquid oral dosage forms. Orodispersible films are dissolving films or oral drug strips to administer drugs via their absorption in the mouth, ensuring that the drug directly enters systemic circulation It is an alternate platform for molecules that undergo first pass metabolism. Various approaches are employed for formulating ODFs and among which solvent casting and spraying methods are frequently used. Generally, hydrophilic polymers along with other excipients are used for preparing ODFs which allow films to disintegrate quickly releasing incorporated active pharmaceutical ingredient (API) within seconds. Orally disintegrating films have potential for business and market exploitation because of their myriad of benefits over orally disintegrating tablets. This present review reflects information regarding formulation ingredients, to focus on benefits, composition, approaches for formulation and challenges in formulation development of fast dissolving oral films. Additionally, the future scope of this innovative dosage form is also well-positioned. It seems that the value of the overall oral thin films market will grow significantly.

Keywords
Orodispersible films, hydrophilic polymers, formulation challenges, disintegrating dosage form.

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1. INTRODUCTION
Imagination is the capacity to deliver new and interesting thoughts, one such thought is the advancement of Novel Drug Delivery Systems [NDDS]. A vast variety of pharmaceutical research is directed at developing new dosage forms. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally

disintegrating systems have been the favourite of product development scientists Due to their thin size and flexibility they are found to be gaining attention [1, 2].

Thin films aren't a recent formulation rather, they had been initially introduced in late 1970 to beat swallowing difficulties as seen in tablets and capsules. Several other names of these thin films have been appeared, for example orodispersible films [ODFs], oral soluble films, mucoadhesive films, oral strips, oral films [oral thin films], buccal films, wafers, ophthalmic films, and transmucosal films. A film that readily dissolves in the oral cavity is generally named as orodispersible film as indicated by European Medicines Agency or simply soluble film according to FDA. [3,4,5] For the most part, fast dissolving oral films are ultra-thin film [50-150 µm] having size of postage stamp, which dissolves within a few seconds in the oral cavity after being in contact with the saliva leading to fast absorption and instant bioavailability of the drugs. [6, 7] Orally disintegrating films and orally dissolving films, should disintegrate or disperse in oral cavity to be claimed as orodispersible films. [8]

Orodispersible films are defined as single or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly, requiring only a small amount of saliva on the tongue to dissolve within a few minutes of administration. [7] These orodispersible films can be utilized for targeting sensitive site that may not be conceivable with tablets or liquid formulations, hence proving to be a promising candidate for delivery of the drug. [9, 10]

Although orodispersible formulations have particular relevance by improving compliance in special patient populations, such as children, geriatric patients, and dysphasic patients who have difficulty in swallowing tablets or capsules, their convenience, superior dosing accuracy, and rapid onset of action contribute to strong patient preference over conventional solid dosage forms across a wide range of patient groups. [11–13] Rapid dissolution, absorption, and onset of drug action are useful in motion sickness and sudden episodes of allergic attack of coughing, bronchitis, and asthma. Some drugs are absorbed from the mouth, pharynx, and oesophagus: pre-gastric absorption can improve bioavailability with consequent reduction of dosage and unwanted effects. Oral film originally been developed as novelty confection. The first of the kind of orally dissolving film was developed by the major pharmaceutical company Pfizer, who named it as Listerine® pocket packs™ and was used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films [OTF] which contained benzocaine and were used for the treatment of sore throat and in some over the counter medication such as Flu Thin Strip. [14-15]

As the drug is released within seconds into the oral cavity, a rapid onset of action could be achieved. If the drug is absorbed through the oral mucosa, first-pass metabolism can be avoided for some drugs, which may improve bioavailability. Drugs that have potency at low doses are most suitable for orodispersible film administration, as technical considerations limit the incorporation of the drug; generally, between 1% and 30% w/w of the active pharmaceutical ingredient can be introduced in film formulation. [16]

Drug load is limited. Therefore, ODFs are constricted to highly potent low-dose drugs. Moreover, manufacturing typically requires solvents and heat for drying. These factors potentially affect stability of the drug and/or other excipients such as sweeteners and flavours. [17]

1.1 General attributes of oral films

Oral films, also called oral wafers are a group of flat films which are administered into the oral cavity. Dissolving film delivery is vehicle, essentially just a thin flexible sheet of polymer in which active pharmaceutical ingredient [API] incorporated. Oral thin films are loaded with active substances.

Depending on the nature and desired dosage that the film is to deliver the API either dissolved or suspended as crystal or amorphous particles in the polymer matrix of the film. Size and thickness of oral dissolving film product is largely depending on dosage of API that is intended to deliver but the physical attributes are also influenced by disintegrating characteristics that the film is intended to have: a higher surface to mass ratio for a strip of film shows rapid disintegration time than lower one. [18] In general oral dissolving films tends to be few square centimeters in surface area and are typically 50 to 150 um [2-6 mils] thick. These dosage types are usually intended to dissolve as quickly as possible on the order of few seconds. [7] The thickness of a film ranges from 1 to 10 mm and its surface area can be 1 to 20 cm^2 for any geometry. At the same time, the rapid hydration rate facilitates an almost immediate softening of the film upon application in the oral cavity. The wet-tack and mucoadhesive properties of the system are designed to secure the film to the site of application.

The drug is released from the dosage form upon disintegration and dissolution. The disintegration and dissolving times are prolonged as the film

thickness increases. [10] Film texture is the primarily the matter of consumer preference. The physical feel applicability of the film can have an influence on patient compliance. [19]

Taste is an important factor in the development of oral pharmaceutical products to ensure patient acceptability and compliance and is one of the prime factors determining market penetration and commercial success of oral formulations. Palatability and pleasant taste are necessary for fast dissolving films, and various techniques are available to mask drug taste. Flavours, sweeteners, and amino acids can be added to the formulation, generally in association with other taste-masking components. The classical sources of sweeteners are sucrose, dextrose, fructose, glucose, liquid glucose, and maltose. [20]

Furthermore, the solubility of the drug could play a vital role in determination of disintegration vs. dissolution of films in oral cavity. Dissolution of aqueous soluble drugs that belongs to BCS Class I/III in mouth or oral cavity could occur simultaneously with disintegration of films despite they were designed to be absorbed in gastrointestinal tract. This is because of the intrinsic dissolution of drug itself in water [saliva] rather than the impact of formulation component. On contrary, dissolution of poorly aqueous soluble drugs in oral cavity that belongs to BCS Class II/IV could be difficult given their poor solubility and intrinsic dissolution rate, and limited amount of saliva in the oral cavity. The films containing these poorly water soluble drugs are in general orally disintegrating films, whose target site of dissolution and absorption is gastrointestinal tract. Consequently, orodispersible films could either be orally disintegrating or dissolving films depending on the intended site of action and/or absorption. Whatever the intention, when the film is termed as orally dissolving, it should deliver the drug in solution form upon introduction into oral cavity. [8]

Until recently, it was the consent of film formulators that oral films could only be used for delivery of water soluble drugs given their size and thickness. Fascinatingly, recent works have demonstrated the possibility of incorporating poorly water soluble drugs [BCS Class II/IV] into films with faster dissolution. [21-24]

On one hand, although incorporation of poorly water soluble drugs into films seems promising, the dissolution of the poorly water soluble drug particles in *in vivo*, especially in oral cavity, is a matter of concern if the target site of action and/or absorption is oral cavity. On the other hand, as mentioned earlier, dissolution of poorly water soluble drugs in oral cavity might not be crucial for films if the target site of dissolution and absorption is gastrointestinal tract. Hence, the issue of dissolution of poorly water soluble drugs in oral cavity is out of concern, and in fact, these recent findings open a whole new venue of opportunities. In general, like any other drug delivery systems, the rate and extent of dissolution and target site of absorption for oral films could be tailored by its components. The components of film formulation could include, but not limited to, the polymers that form the film matrix, plasticizers that improve the mechanical properties of the film, viscosity enhancers that improve the viscosity of the film precursor solution/suspension, disintegrants that improve the disintegration of the film, stabilizers or surfactants that improve the wetting and/or drug particle suspension, other additives such as sweetening agents, saliva stimulating agents, colouring agents, etc. [13,15,25] Among these, polymers and plasticizers are the major constituent of film formulation and selection of which is very critical given its significant effect on film performance in terms of disintegration and dissolution, and mechanical properties in terms of tensile strength [hardness] and Young's modulus [brittleness]. Among various techniques and technologies available for film manufacturing, solvent casting and hot melt extrusion have been widely used. [11]

1.2 Advantages over conventional dosage forms: [9, 26-28]

Oral mucosa is tremendously vascularized, and it provides elevated absorption, expanded bio availability, quicker onset of activity, and overcomes first pass effect. A thin film dissolves rapidly in contrast to other conventional dosage forms.

Thin films are less friable and provides ease in carrying dosage form in contrast to commercialized orally rapid disintegrating tablets, which need special packing. Moreover, a unit dose of strip can be carried independently without requiring the secondary holder. It is vital to address the poor stability or instability of liquid dosage forms, particularly the aqueous formulations where attention towards the precise measurement of the amount of medicament and shaking the bottle every time before administration may accord to less acceptance by the patients. Bigger surface area provides better platform for quick disintegration and dissolution thereby releasing the drug in the oral cavity. They impart dosage accuracy and quick release with enhanced patient compliance, and there is no danger of choking. These strips on comparing with oral dissolving tablet possess less fragility and have excellent adhesion. The package ODFs in a blister

pack empowers simplicity of transportation and utilization of medication at wherever or time required without water.

1.3.1 Disadvantage of orodispersible films:

- Higher dose cannot be added in these ODFs.
- Longer preservation is troublesome in view of hygroscopic nature and the requirement for specialized packaging.
- Drugs that are not stable at buccal pH cannot be administered.
- Restriction of eating and drinking for quite a while after consuming ODFs.
- Expensive techniques for the preparation of these films in contrast to oral dissolving tablets.

1.3.2 Ideal characteristics of orodispersible films: [29-30]

- Should possess good mouth feel.
- Should rapidly dissolve in sublingual cavity within seconds
- Not require water to engulf.
- Should not leave any residue in mouth.
- Should evince low sensitivity towards certain environmental conditions like temperature and humidity.

1.4 Classification of orodispersible films: [31]

There are three types of oral fast dissolving films:

- Flash release.
- Mucoadhesive melt-away wafer.
- Mucoadhesive sustained release wafers [Table I].

1.5 Technologies used to manufacture oral dissolving films

The technologies used to manufacture ODFs can be classified as given in figure 1 [Arya *et al.*, 2010]

2. MANUFACTURING OF FILM

Formulation of Oral Film involves the intricate application of aesthetic and performance characteristics. From the regulatory perspectives, all excipients used in the formulation of Oral Film should be Generally Regarded as Safe and should be approved for use in oral pharmaceutical dosage forms. [4]

There are different types of ingredients required for the formulation of oral films.

2.1 Formulation ingredients

A typical ODF contains [32]:

- API 1 -- 30%
- Water-soluble film-forming polymers 40 -- 50%
- Plasticizers 0 -- 20%
- Fillers, colours, flavours, and so on, 0 -- 40%.

2.1.1 Drug substance:

The API can be incorporated into the films as particles or molecularly dispersed/dissolved. Particularly for dispersed APIs, particle size, particle size distribution and polymorphism become critical quality attributes. It is well known that these factors may affect solubility, rate of dissolution and ultimately bioavailability. As drug load is limited, high potency low-dose drugs are preferred. [33] Maximum drug load depends on the solubility of the API and/or its compatibility with the excipients. [34] A critical drug load can result in recrystallization or excessive influence on mechanical or disintegration properties of the films. [29, 35-36] Typically, drug load is limited to a maximum of 25 mg. Gas-X films [Novartis Consumer Health, Basel] contain a surprisingly high loading of 62.5 mg simethicone. Other challenges may arise from bad API taste, limited API stability resulting from manufacturing conditions or the residual water content of the films as well as potential buccal permeability if only gastrointestinal absorption is targeted. [37]

Wide variety of APIs can be conveyed through rapid dissolving films and suitable drug molecules [Dixit and Puthli, 2009] are listed in Table 2. [25]

Appropriate candidate for ODFs should have following properties:

- Small dose molecules are the best candidates to be incorporated in ODFs.
- Bitter taste of the medication ought to be veiled.
- Dose must be lower than 25 mg.
- Good stability in water and saliva.
- Partially non-ionized at oral cavities pH.
- Ability to permeate oral mucosal tissue.
- The drug should not have unpleasant odor or taste.
- The drug must not cause allergy, irritation and discoloration or erosion of teeth
- Drugs with high molecular weight are not suitable.
- Drug should not affect the natural microbial flora of the mouth.
- Drugs having less oral bioavailability, low biological half and liver extraction ratio more than 0.7 are suitable candidate.

2.1.2 Film-forming polymers:

Film-forming polymers are essential excipients for ODFs. Several polymers have been suggested in the literature. Yet, the selection remains challenging. Although the films should dissolve as fast as possible in the oral cavity, mechanical properties have to remain sufficient for handling, packaging and storage. [38] The robustness of the strip depends on the type and amount of polymer in the formulation. As the strip forming polymer [which forms the platform for the oral film] is the most essential and major component of the film, at least 35% w/w of

polymer should be present based on the total weight of dry film but typically 25 to 45%w/w of polymer is preferred to obtain desired properties. Mainly hydrophilic polymers are used in the oral strip as they rapidly disintegrate in the oral cavity as they come in contact with saliva.

The polymers can be used alone or in combination to obtain the desired film properties. Presently, both natural and synthetic polymers are used for preparation of rapid dissolving oral film. Table 3 represents various natural and synthetic polymers which are nowadays used in ODFs preparation.

Pullulan

Pullulan [Figure-2] is found to be a naturally occurring, fungal polysaccharide produced by liquefied corn starch by *Aureobasidiumpullulans* [originally *Pullulariapullulans*], a ubiquitous yeast-like fungus. It possesses a linear structure consisting predominantly of repeating units of maltotriose units, which are comprised of three α–1, 4-linked glucose molecules bonded with a -1, 6- glycosidic bonds. Pullulan is stable in aqueous solution over a wide pH range [pH 3-8]. It dissolves readily in water but is insoluble in organic solvents. [18] Pullulan when dissolved in aqueous solvents tends be viscous but do not form gels. Upon drying, pullulan forms transparent, water-soluble, fat-resistant, odourless, anti-static, flavourless film.

Pullulan has following properties: [39]

- It and is suitable for protection of readily oxidized fats and vitamins in food. It has been found that pullulan film possesses 300 times stronger oxygen barrier than HPMC film and are several times stronger than gelatin film of the same thickness.
- It can easily be solubilized in cold and hot water to render clear and viscous solution and possess high adhesion and film forming abilities.
- Pullulan are nonionic polysaccharide and is biodegradable, non-toxic, non-immunogenic, nonmutagenic and non-carcinogenic.
- Films crafted from pullulan are thermally stable and possess anti-static and elastic properties.
- The films crafted from pullulan are non-reducing as well as non-hygroscopic.

Starch / modified starches

Biopolymer starch is made out of glucose units and possess two main constituents which are, amylose and amylopectin [Figure-3]. Amylose moiety is a linear one, having long chain of α-D glucose units bonded together by α-1, 4 glycoside linkages and marginally stretched. It is the amylose which is responsible for the film formation using of starch. [39] Starch can be used to craft films which are biodegradable. The films from such polymer are transparent or translucent, tasteless, flavourless and colourless. However, starch film application is restricted due to its efficient barrier against low polarity compound and its poor mechanical strength. Plasticizers like glycerol and sorbitol are commonly required for edible films composed of starch to overcome film brittleness. [40]

Sodium alginate

Alginates [Figure-4] are said to be gums, aqueous soluble biopolymers extracted from brown seaweed. Primarily sodium alginate comprises of sodium salt of alginic acid, which is a blend of polyuronic acids made out of residues of D-mannuronic acid and L-guluronic acid. Alginate is an indigestible biomaterial and is obtained from brown seaweeds [belonging to family-*Phaeophyceae*, mainly *Laminaria*]. Alginates are found in the cell walls of brown algae as the calcium, magnesium and sodium salts of alginic acid. Edible films composed of alginates are appropriate to load antibacterial compounds along with suitable additives. [41]

Maltodextrin

Maltodextrin [Figure-5] is a non-sweet nutritious saccharide polymer obtained from partial hydrolysis of starch and is typically found as a creamy-white coloured, hygroscopic spray dried powder. Maltodextrin [MDX] comprises of D-glucose units bonded in chains of variable length. The glucose units are basically associated with α [1→4] glycosidic bond. [24] It is easily soluble and gets quickly dispersed in water and slightly soluble to almost insoluble in alcohol. The unique feature about the films crafted from MDX is that these are extremely thin, elegant and is accessible in different shapes and sizes. [42] the film modifying properties of MDX on hydroxy propyl methyl cellulose [HPMC E6], polyvinyl alcohol [PVA] and hydroxyethyl cellulose have been investigated in the formulation of a novel verapamil and tianeptine sodium orodispersible films. [42-43]

Polymerized rosin

Rosin [Figure-6] and its esters are accounted to have exceptional film forming properties and can be utilized for enteric coating and delayed release of drugs. [44] Rosin, formerly called colophony or Greek pitch [*Pixgraeca*], is resin which is yellow translucent irregular solid obtained from pines and some other plants, usually conifers. It has many brilliant properties, for example, anti-oxidation, non-crystallizing and good compatibility with film-forming agent. [45]

Chitosan

Chitosan [from chitin] [Figure-7] is a promising biomaterial. It is natural, safe and nontoxic. Pure

chitosan films are generally compact, cohesive and the surface of the films obtained from it has a smooth contour without pores or cracks. Films composed of chitosan, tend to show fat and oil resistance and specific penetrability to yet need imperviousness to water transmission. [46]

Hydroxypropylmethyl cellulose [HPMC]

HPMC also known as Hypromellose [Figure-8] is a typical excipient commonly utilized as a vital part of orodispersible films. The process of developing formulations of HPMC to obtain films that meets the high-quality requirements can be a demanding procedure. Jaime F.C et al., explored the impact of hydration conditions and polymer dispersion on hypromellose film properties, such as clarity, strength, oxygen permeability and water vapour transmission. Its results demonstrated that physical properties of the films were generally unchanged by the range of conditions explored, optical properties were contrarily influenced by high hydration temperatures [50°C]. Also film clarity was not influenced by film thickness. [47]

Hydroxypropyl cellulose [HPC]

Hydroxypropyl Cellulose [HPC] [Figure-9] is a non-ionic water soluble-cellulose ether possessing a versatile combination of properties. Literature research revealed that disintegration time of HPC film tends to be increased in proportion to film thickness stating that the increasing is dependent on HPC content and the tensile strength was independent.

Kollicoat

It is a novel graft copolymer of polyvinyl alcohol-polyethylene glycol [Figure-10] that is freely soluble in water. Structurally it consists of 75% polyvinyl alcohol units which is the major component and the remaining 25% consisting the polyethylene glycol units. Films formed from kollicoat are clear, colourless, not tacky, having high pigment binding, immensely flexible and dissolve very quickly in water. In contrast to pure polyvinyl alcohol films, the flexibility is maintained in storage due to the fact of rearrangement of the molecules to a high level of order ["crystallization"] is restricted. Relative humidity in the range of 30–75 % has practically no influence on the mechanical properties of the Kollicoat films. [49]

Polyvinyl pyrrolidone [PVP]

Polyvinyl pyrrolidone [PVP] [Figure-11], also known by other names such as Polyvidone or Povidone. Among the abundant polymers, the PVP has great film-forming and adhesive behaviour on several solid substrates and films produced from PVP exhibits the good optical quality and mechanical strength which is essential for applications. The amorphous structure of PVP additionally provides a low scattering loss, which makes it as a perfect polymer for composite materials for various applications. PVP tends to easily solubilize in water, hence it is preferred to bypass phase separation in the reactions. [50]

Poly [ethylene oxide]

Poly [Ethylene Oxide] [PEO] [Figure-12] is a non-ionic polymer. It has numerous properties such as, binding, water retention, gelling, lubricity and film formation. In a study, different grades of Polyox were evaluated for mechanical properties. It was found that the increment in molecular weight causes an increment in mechanical strength rendering it suitable as a film former. [51]

2.1.3 Plasticizers

Plasticizer is a crucial ingredient impelling the strength of the orodispersible films. They tend to reduce the brittleness of the strip by lowering glass transition temperature [Tg] of polymers thereby improving the flexibility of the films. The choice of plasticizer will depend on upon its compatibility with the polymer and also nature of the solvent employed in the casting of the strip. The flow of polymer will be improved when used along with plasticizer and additionally the strength of the polymer also gets improved. Glycerol, propylene glycol, sorbitol, low-molecular-mass macrogols, phthalates, citrates or combinations thereof are commonly used. [17,35,42,52-53] Citrate derivatives which are eco-friendly such as tributyl, acetyl citrate, triacetin and phthalate derivatives like diethyl, dimethyl and dibutyl phthalate, are some of the generally employed plasticizer reducing the elastic modulus. are used normally in the concentration of 0-20% w/w of dry polymer weight. [54]

2.1.4 Taste masking

Numerous APIs have an unpleasant taste. The use of taste masking excipients is often essential. Depending on the physical state of the API in the film [dissolved or dispersed] and its solubility in saliva, different taste-masking techniques have to be used. They range from the simple addition of flavours, sweeteners and bitter-blockers to particle coating, encapsulation or complexation with ion exchange resins, where the larger particles may cause scrapes during casting and may give an unpleasant gritty mouth-feel. [2,6,30,55] Research showed that taste and mouth-feel are more important for the acceptability of orally disintegrating dosage forms than short disintegration times. [58]

All drugs that are even partly soluble in saliva will be accessible to taste sensation. Suitable sweeteners

include natural molecules such as glucose, maltose or stevioside, artificial sweeteners such as acesulfame-K or Saccharin-Na, dipeptide based sweeteners such as aspartame and protein-based sweeteners such as thaumatin. [17] The sweetness has to be perceived on the tongue before onset of the bitter taste and during the bitter aftertaste sensation. Therefore, often combinations of different sweeteners and flavours are incorporated in ODFs.

Sprinkling flavours or sweeteners on the film surface has been mentioned as another improvement. [24] All commonly applied taste-masking techniques can greatly affect maximum drug load. [1] Further, stability, disintegration time and mechanical properties may be influenced by the type and amount of taste-masking agents.

2.1.5 Saliva stimulating agent

Since dry mouth impedes the rapid dissolving of films therefore it is necessary to include saliva stimulating agents to increase the rate of production of saliva that would cause the faster disintegration of the orodispersible strip formulations. Generally, those acids which are used in the preparation of food can also be use as salivary stimulants. citric acid, lactic acid, ascorbic etc. are few examples of salivary stimulants. On combination of organic acid and saccharin a synergistic saliva stimulating effect can be produced. Saliva stimulants can be used 2 to 5%w/w of the strip. [56]

2.1.6 Others

Further excipients for ODFs include fillers, opacifiers, cooling agents, colours, lubricants or antitacking agents, preservatives and stabilizers. [6,17,34] To increase mucoadhesion, appropriate polymers can be added [57]. If absorption through the oral mucosa is desired, penetration enhancer and buffering agents may improve buccal bioavailability. Enzyme inhibitors can inhibit drug degradation. For some ODFs solubility enhancers may be necessary. Surfactants can improve spreading of the coating mass on the intermediate liner as well as wetting by saliva in the oral cavity. [32] Stabilizers and thickening agents may be needed to avoid particles sedimentation. Natural gums such as xanthan or guar gum can improve viscosity and film-forming capacity. [25]

3. MANUFACTURING METHODS

The manufacturing of orally dissolving films is done by various methods such as:

1. Solvent casting method
2. Hot melt extrusion method
3. Semisolid casting method
4. Rolling method
5. Solid dispersion extrusion

One or a combination of the following process can be used in the manufacturing of ODFs.

3.1 Solvent casting method

Solvent casting is the century old film making process. It is a generally applied technique for preparing orodispersible films. This technique is employed to manufacture films of size 2x2 $cm^2$and 3x2 cm^2. Polymers that solubilizes in aqueous solvents are dissolved in suitable vehicle and the drug along with other required additive are dissolved either in aqueous or organic solvent and finally both are mixed and stirred. It is then carefully casted on petri dish or plate made up of glass, Teflon or suitable material and dried. Specific types of equipment which is used at large scale production with the appropriate rollers are utilized for pouring the solution on an inert base. Entrapped air is eliminated utilizing vacuum. The final step concludes by drying the films and remove the trace of solvent to obtain the finished product. After the films are dried, the cutting, stripping and packaging is done. [16]

Advantages

- Better uniformity in thickness and better clarity.
- Films possess fine gloss and free from defects.
- Films possess more plasticity and better physical properties.

Disadvantages

- The polymer utilized must possess property of solubilisation in volatile solvent or water.
- The stable solution with a suitable minimum solid content and viscosity must be formed.
- Formation of a homogeneous and release of films from the casting support must be possible.

3.2 Semi-solid casting method:

Primarily a solution of water soluble film forming polymer is prepared. This solution is then further moved to acid insoluble polymer solution which can be obtained using either cellulose acetate butyrate or cellulose acetate phthalate in sodium or ammonium hydroxide solution in approx. ratio of 1:4. Then carefully plasticizer is added to get a gel mass which is casted into thin films using temperature controlled drums.

3.3 Solid dispersion extrusion

In this technique the immiscible components are extruded along with the drug, and then solid dispersions are prepared. Solid dispersions are shaped in suitable thin sized films with the use of dies.

Advantages

- Lesser processing steps.

- Better uniformity in dispersion of the fine particles due to intense mixing and agitation.

3.4 Hot-melt extrusion

This technique can be employed based on knowledge from the plastics industry where formulators can extrude the combinations of drugs, polymers, and other suitable excipients into desire final forms to achieve appropriate drug-release profiles. In pharmaceutical formulations twin screw extruder has proved to be beneficial due to homogenous and consistent mixing of multiple formulation ingredients leading to improved dissolution rate and bioavailability. The API and other ingredients are mixed in dry state, subjected to the heating process where the mixture gets molten and then extruded out producing thin films. The solvent is completely removed by suitable technique. The produced strips are further cooled and cut to the desired sizes. [15,20]

Advantages

- Need not require the use of solvent or water.
- Cost effective process because it requires less processed time and unit operations.
- Better uniformity in dispersion of the fine particles because of less intense mixing and agitation.
- Good dispersion mechanism and bioavailability for poorly soluble drugs.

Disadvantages

- Thermal degradation may occur due to high temperature.
- Lower melting point binder is not suitable in a situation where melting/softening of the binder can occur during handling and storage of agglomerates.
- Higher melting point binders needs high melting temperature which adds a problem of volatility particularly for thermolabile materials.

3.5 Rolling method

In this technique suspension or a solution containing drug is rolled on a carrier. The solvent utilized mainly is water or a mixture of water and alcohol. The films are dried on the heated rollers and sliced into desired shapes and sizes. Other ingredients such as API, polymer, plasticizer and other required ingredients are dissolved in a small quantities of aqueous solvent utilizing the high-shear processor. [15]

4. PACKAGING [55]

In the pharmaceutical industry it is vital that the package selected should adequately protect the integrity of the product. Specific processing, expensive packaging, and special care are recommended during manufacturing and storage for protection of the dosage of other rapid dissolving dosage forms. Criteria that require special attention includes the need for unit dose packaging, barcode labelling, and the content in guidelines for use, child-resistant seals, and senior-friendly packaging. The material selected must have the following characteristics:

- They must be FDA approved. They must protect the preparation from environmental conditions.
- They must meet applicable tamper-resistant requirement.
- They must not be reactive with the material utilized in preparing films.
- They must not bestow to the product odours or tastes.
- They must be non-toxic.

5. FUTURE SCOPE

Oral drug delivery technologies form an important part of the pharmaceutical industry. From the conventional tablets/capsules to modern-day fast disintegrating and rapidly acting tablets / films, the market has come a long way. Lower bioavailability of oral solid drugs, inconvenience of administering injections, inaccurate dosing by liquid formulations have turned the focus of pharmaceutical companies to develop novel oral dosage forms that eliminate several known limitations. Oral thin films are able to meet most of these challenges. The concept isn't new and several over the counter oral thin films are readily available. Good acceptance from the users and an increasing demand of over the counter oral film products has led to the development of prescription drugs into oral thin films. These films not only offer a range of benefits to specific patient population segments but also provide a number of additional benefits to other stakeholders in the industry. The emerging area has gained attention from both established and start up pharmaceutical firms. Companies are utilizing their oral thin film technologies to develop different types of oral thin films [e.g. oral dispersible, sublingual, buccal]. In addition to the drugs, several hormones and vaccines are also being formulated into oral thin films with the aim of providing improved patient compliance. Some of the key players in this area include MonoSol Rx, Applied Pharma Research/Labtec GmbH, Bio Delivery Sciences and NAL Pharma. Many companies are collaborating with these technology providers and utilizing oral thin films as a life cycle management tool for their branded drugs that have lost patent in other dosage forms.

There are not many prescriptions for oral thin films currently available in the market; however, the

pipeline holds a wider promise. Despite the uncertainties related to the development, approval and penetration rate, the market is likely to witness stable growth in the coming decade.

6. APPLICATIONS OF ODFS IN DRUG DELIVERY SYSTEM

- To date, the commercial launch of ODFs is primarily in OTC products inscribing therapeutic categories such as cough/cold, antacid/gas relief, sore throat and mouth fresheners as well as a number of nutritional supplement applications.
- Nausea and Vomiting: Various anti-emetic drugs have been formulated in form of ODFs such as Metoclopromide, Domeperidone, Granisetron, Ondansetron etc.
- Transdermal application: The feasibility of active agents such as antimicrobials or analgesics in wound care and other applications could be highly promising approach towards innovation due to its ease of application and better cosmetic appearance. [58]
- The development of thin strip that dissolves in the mouth for delivery of life-saving rotavirus vaccine to infants can aid in curing the primary source of severe diarrhoea and vomiting in children.
- Gastroretentive drug delivery: The drug can be released by dissolving the film via triggering by pH or enzyme secretion in gastrointestinal tract [GIT] helping in treating GI disorders. [59]
- Asthma: Asthma is a disorder in which patient get attack in which bronchi constricts making it difficult to swallow a solid content. In such condition patient need to take medicine for preventive measure daily therefore dosage form which don't need water and which can be consumed anywhere without water will make it easy for patient. In market, various anti-asthmatic agents in form of tablets, inhalation, injection and syrups are available. Rapid dissolving film have got all advantages of tablets, but in addition to it, it is easy to swallow and preferable for paediatric and geriatric patients [ease of application]. It leads to precise dosing, rapid bioavailability, easy application [no need of water], easy to carry.

7. CHALLENGES IN FORMULATION DEVELOPMENT OF FAST DISSOLVING ORAL FILMS

Technology catalysts give an idea of the market for drug products of oral thin film formulation which is valued at $ 500 million in 2007 and will be reached to $ 2 billion in future. Oral thin film technology is still in the beginning stages and will be the first preference of patient in future. Since 2003, North America is having more than 80 oral thin films brands but, the market remained limited when compared to oral dissolving tablets. In US market, the OTC films of pain management and motion sickness are commercialized. Now, prescription oral films have been approved in three major countries i.e. US, EU and Japan. These approved films have a potential to dominate over other dosage forms of same drugs. It seems that value of oral film market will grow significantly [58].

Today, huge literature is available on formulation, development and evaluation of oral fast dissolving or fast disintegrating tablets and films. However, formulator comes across with some challenges while development of such dosage forms. There is need to address such challenges which may help in future to explore the particular area in research and that may help in overall formulation and development. These challenges are directly related to patient compliance. Hence, preference should be given to them in formulation and development.

Following are some of the challenges in formulating fast dissolving oral film and trying to elaborate and solve these problems. These include

7.1. Insolubility of drug

Solubility plays a rate limiting factor to get desired concentration of drug of orally administered formulation in systemic circulation. Problem of solubility is a main challenge for formulation of oral film of BCS class II drugs having low solubility and high permeability. [20]

7.2. Taste masking of bitter and obnoxious drug

Taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the pediatric and geriatric population. Taste is an important parameter in case of fast dissolving oral film. Oral film has to remain in contact with oral mucosa until it completely dissolves in saliva in oral cavity. For this, taste of bitter drugs should be masked. So, taste masking becomes a prerequisite for bitter drugs used in fast dissolving oral film to improve the patient compliance especially in the pediatrics and geriatric population [59].

7.3. Reduction in drying time of film

Drying time plays an important role in oral film formulation and also in case of rate of production of oral film in industries. Generally, hot air oven is not used for drying of oral film of thermolabile drugs. So, oral film is dried at room temperature. But, it takes more time to dry [about one day].

7.4. Dose incorporation in film

Dose of drug in oral film formulation can be increased by increasing area of container. Only area should be increased keeping thickness of formulation solution constant so that volume of solution needed for formulation is also increased which help in incorporation of high dose and reduction in drying time also. [61]

7.5. Co-administration of drugs

Use of more than one drug i.e. co-administration of drugs is a very difficult task in oral film formulation. Because, it may affect disintegration time as well as dissolution rate of formulation. [61]

7.6. Stability of film against humidity and temperature

Fast dissolving oral film consists of about 45% of polymer which is hydrophilic in nature. In the humid atmosphere, film will absorb water and get liquefied due to dissolution of film in water. So, the stability of film against humidity is very difficult and challenging task. [62]

7.7. Need of special packaging

In the pharmaceutical industry, it is vital that the package selected adequately preserve the integrity of the product. A variety of packaging options are available for fast dissolving films. An aluminum pouch is the most commonly used packaging material. APR- Labtec developed the Rapid card, patented packaging system designed for the Rapid films. The rapid card has same size as a credit card and holds three rapid films on each side. Every dose can be taken out individually. [63]

7.8. Dose uniformity

Film which is to be made in a container has to cut into desired area containing required dose of drug. So, to get a uniform dose in all films which cut into desired area is a challenging task.

Property/Sub Type	Flash Release Film	Mucoadhesive Melt Away Film	Mucoadhesive Sustained Release Film
Area (cm2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure of Film	Single layer	Single or multilayer system	Multilayer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, highly hydrophilic polymers	Low/non-soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspension and/or Solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival,(other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Table 1: Classification of orodispersible films

Molecule	Therapeutic category	Dose (mg)
Nicotine	Smoking cessation	1-15
Zolmitriptan	Antimigraine	2.5
Sumatriptan	Antimigraine	35-70
Loratidine	Antihistaminic	5-10
Oxycodone	Opoid analgesic	2.5-10
Ketoprofen	Anti-inflammatory	12.5-25
Acrivastine	Antihistaminic	8
Cetrizine	Antihistaminic	5-10
Famotidine	Antacid	10
Omeprazole	Protonpump inhibitor	10-20
Flurazepam	Anxiolytic, Anticonvulsant	15-30
Dextromethorphan HCL	Cough suprassant	10-20
Azatidine maleate	Antihistaminic	1

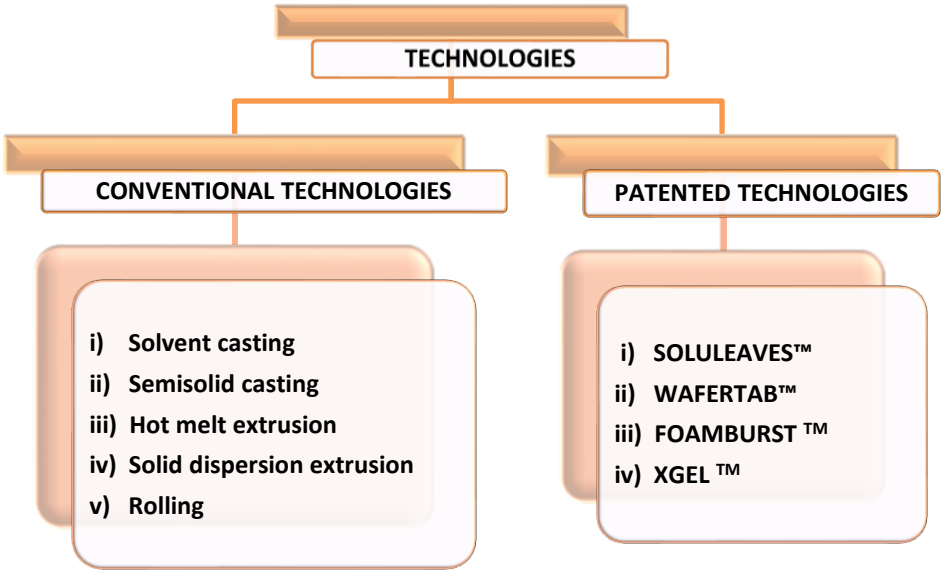
Diphenhydramine HCL	Antihistaminic	25
Nitroglycerin derivatives	Vasodilator	0.3-0.6
Chlorpheniramine maleate	Anti-allergic	4

Table 2: Potential candidates eligible for incorporation in ODF

Polymers employed in the preparation of ODFs.	Polymer	Examples
1	Natural Polymer	Pullulan, Starch, Gelatin, Pectin, Sodium alginate, Maltodextrins, Polymerized , Rosin
2	Synthetic Polymer	Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Poly ethylene oxide, Hydroxy propyl cellulose, Poly vinyl pyrrolidone, Poly vinyl alcohol.

Table 3: Polymers employed in the preparation of ODFs.

Figure 1: Technologies used to manufacture oral dissolving films



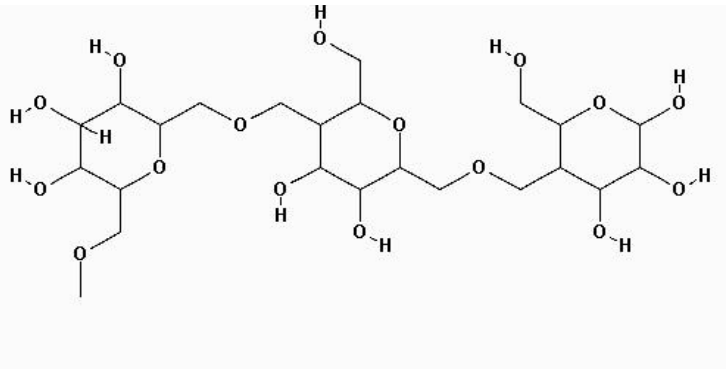


Figure 2: Structure of pullulan.

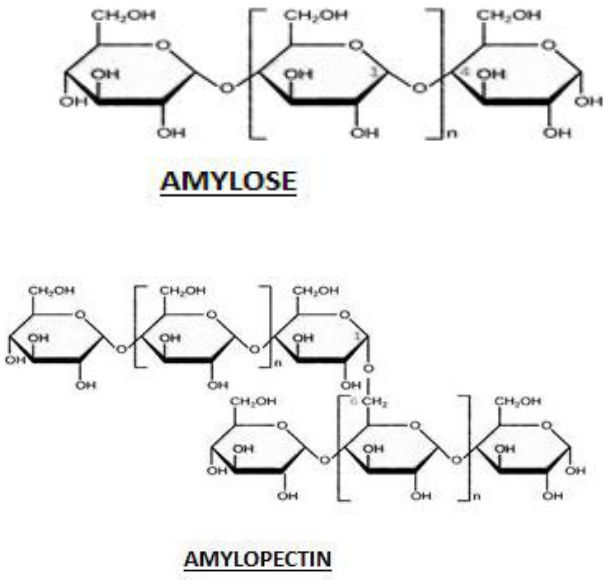


Figure 3: Structure of amylose and amylopectin.

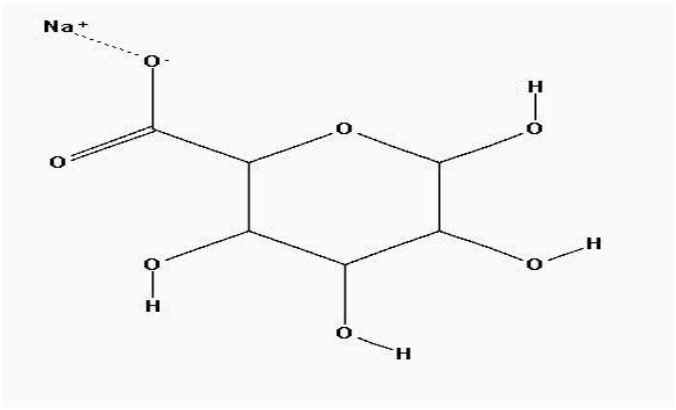


Figure-4: Structure of sodium alginate

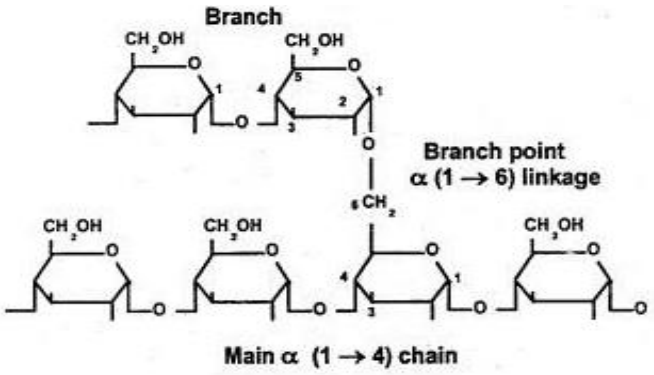


Figure-5: Structure of maltodextrin.

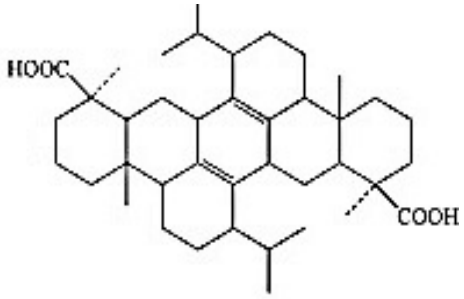


Figure-6: Structure of polymerized rosin.

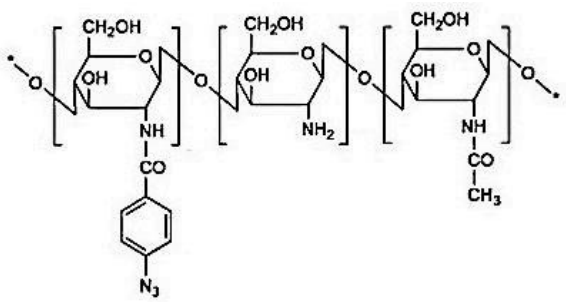


Figure 7: Structure of chitosan.

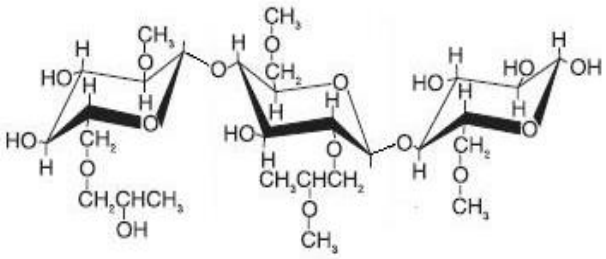


Figure 8: Structure of HPMC.

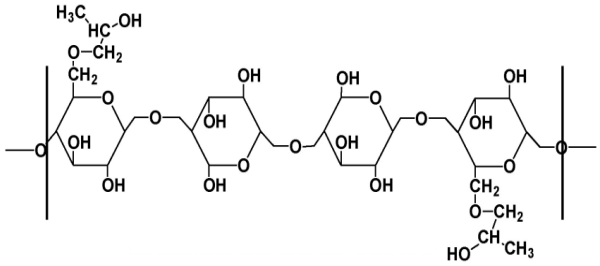


Figure-9: Structure of HPC

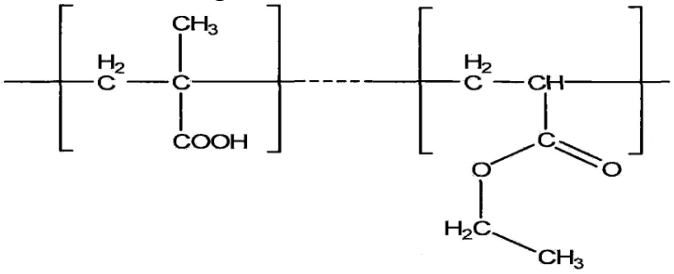


Figure 10: Structure of Kollicoat.

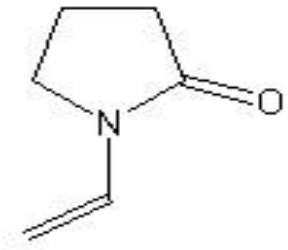


Figure 11: Structure of PVP

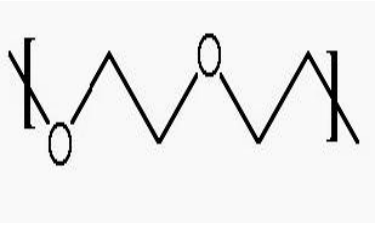


Figure 12: Structure of PEO

CONCLUSION

From above, this can be concluded that fast dissolving oral films are beyond doubt emerging as platforms for drug delivery, for all groups of population or patients with problem of swallowing. They have improved acceptance and patient compliance with no risk of choking associated with better safety and efficacy in comparison with conventional dosage forms. Currently oral thin films target only a limited section of the consumer market. ODFs are currently costlier to develop and manufacture as compared to tablets. ODFs could be alternatives to the convenient dosage forms. Orodispersible films are used as a good tool for product line extension of the existing product by getting patent of same product as fast dissolving oral films. Though at present the ODF technology is confronted by many challenges, optimizing the research, formulation and manufacture shows a promising picture and huge scope for ODFs in the future.

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