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Review on Fast Dissolving Oral Film

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Abstract: ***Over the last few years, interest has been increased in developing innovative drug delivery systems to improve the safety, efficacy and patient compliance. Development of new chemical entity is not only expensive but also time taking process. This is why most of the pharmaceutical companies are now focusing on the development of new and improved drug delivery systems for the existing drugs. One such system is the fast dissolving tablets and films which are gaining popularity now days. These fast dissolving formulations are prepared in such a way that the total time taken by the active pharmaceutical ingredient to disintegrate is very less as compared to other formulations. This technique allows the drug to dissolve at a much faster rate thus reducing the time for the onset of action. These formulations are fast acting and can be administered without water. Therefore, they are very suitable for pediatric and geriatric patients; bed ridden patients; or patients suffering from dysphagia, Parkinson's disease, mucositis, vomiting, migraine, fever, pain etc. Hence these are beneficial for the pediatric and geriatric patients. There are several methods employed for the manufacturing of such dosage forms such as casting, spraying, extrusion etc. the aim of the present investigation is to analyze and review rapidly disintegrating dosage form.***

Keywords: FDIFs – Fast Dissolving Oral Films, OTC –Over - the - counter, HPMC - hydroxypropylmethylcellulose, HA - hyaluronic acid, ANDA - Abbreviated New Drug Application, ODTS – orally disintegrating tablet

1. Introduction

Alternative routes are the most preferred route of drug administration because they have various advantages over other drug delivery routes, but oral drug delivery systems still need improvement due to several disadvantages associated with certain patient classes, including geriatrics, Pediatrics Children and patients with aphasia who have difficulty swallowing or chewing solid dosage forms and are associated with many diseases. Even fast - dissolving tablets present a choking hazard due to their tablet - like shape. Among other factors, the palatability of pediatric oral dosage forms is one of the most important factors influencing adherence. Solid dosage forms are widely used by adults and adolescents, but younger children tend to prefer liquid dosage forms that are easier to swallow.

Recently, several new oral dosing technologies have emerged that can take into account the physicochemical and pharmacokinetic properties of drugs while improving patient compliance. More recently, electrostatic drug deposition and coating, as well as the production of tablets by computer three - dimensional printing (3DP), have become possible. Thus, in the late 1970s, instant dosage forms emerged as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who find it difficult to swallow conventional solid oral dosage form [1]

Oral instant film isa new oral drug delivery system. Developed with transdermal patch technology. The delivery system consists of a very thin oral strip that is simply placed on the patient's tongue or other tissue of the oral mucosa, immediately moistened with saliva, the film is quickly moistened and adheres to the application site. It then rapidly breaks down and dissolves, releasing the drug for absorption in the mucous membranes of the mouth and stomach. Technology Catalyts estimates that the market for oral thin - film drugs was $500 million in 2007 and will reach $2 billion in 2012. based on global growth trends over the past decade, the rapidly disintegrating drug market could generate $13 billion in revenue in 2015 [2]

Characteristics of Oral Film: [2]

- Thin and elegant film
- Various sizes and shapes available
- Non - clogging
- Excellent mucosal adhesion
- Fast absorption
- Fast release

The ideal characteristics of a drug to be selected: [3]

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose upto 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Advantage:

Oral films have some special advantages over other oral dosage forms given as follows:

- Rapidly dissolved and disintegrated in the oral cavity because of large surface area which lowers dosage interval, improves onset of action, efficacy and safety profile of therapy.
- Oral films are more flexible, compliant and are not brittle as ODTS.
- Easily handled, storage and transportation.
- Accuracy in the administered dose is assured from every strip or film.
- Pharmaceutical companies and customers practically accepted OTFs as an alternative of conventional OTC dosage forms such tablets and capsules etc.

- Oral film is desirable for patient suffering from motion sickness, dysphagia, repeated emesis and mental disorders.
- From commercial point of view, oral films provide new business opportunity like product differentiation, promotion etc.

Disadvantages of Fast Dissolving Oral Films:

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Taste masking - Most drugs have bitter taste, and need taste masking.
- Special packaging - OFDFs are fragile and must be protected from water so it needs special packaging.
- Dose uniformity is a technical challenge.
- Expensive packaging of oral film.

Composition of mouth dissolving film: [4]

Composition	Concentration
Drug	1 - 25%
Water soluble polymer	40 - 50%
Plasticizers	0 - 20%
Fillers, colors, flavors	0 - 40%

Advance in Formulation Strategies:

Mucoadhesive and orally disintegrating films are suitable bases capable of delivering sufficient amounts of pharmaceutically active ingredients as well as release of these actives at a controlled rate at a site of interest such as the buccal mucosa or sublingual tissue. Materials are needed. The most commonly used base materials are polymers because they can be used to produce a variety of films with properties suitable for a wide range of applications. One of the most important requirements for film formers is that they are non - toxic, non - irritating and do not contain cleaning impurities. In addition, the polymers used must adequately perform the pre - designed function of the oral film, i. e. rapid dissolution and release of the loaded drug or release of the loaded active ingredient in a controlled manner, attached to the mucosa at the desired location and for a certain period of time is extended. Drugs other than basic polymers.

Although natural and synthetic polymers along with the necessary additives can be used to create the desired buccal films, mucoadhesive and orally dispersible films have different properties. In the following section, we present recently published strategies for the preparation of multifunctional oral films and discuss their advantages and disadvantages.

1) Formulation for mucoadhesive films:

A successful mucoadhesive film can adhere firmly to the buccal mucosa for a long time and release the active ingredients in a controlled and controlled manner. To achieve this, formulations containing film - forming polymers and other additives must be carefully selected and evaluated for proper mucosal adhesion as well as controlled drug release. Indeed, natural and synthetic polymers have been studied and used to form oral mucoadhesive films in recent years.

a) Natural polymers:

Recently, many natural polymers have been explored for the preparation of oral mucoadhesive films due to their attractive biocompatibility and biodegradability, as well as attractive molecular structures with active groups that can potentially be used for physical or chemical interaction. mucin It provides desirable mucoadhesive properties in oral mucus and provides significant advantages in drug absorption. In addition, the high molecular weight of this natural polymer may facilitate the integration of mucoadhesive processes through chain interpenetration.

One of the most commonly used natural polymers is hyaluronic acid (HA), also known as hyaluronan. As a natural polysaccharide (anionic, non - sulfated glycosaminoglycan), it is an excellent natural oral material with excellent gelling properties due to its ability to bind water very quickly [5]. A classic example of the use of HA is the controlled release oral mucosal delivery system for the treatment of oral ulcers reported by Abo - shady et al [6], which can overcome the leaching effect of saliva. and food friction. Another example is the mucoadhesive film proposed by Pornpitchanarong and colleagues [7], which uses catechin - functionalized hyaluronic acid (HA dye) with polyvinyl alcohol (PVA) to prepare the oral film for delivery (Figure 2A). Nanosuspension of clotrimazole (CZ) stabilized with Tween 80 and chitosan derivatives.

Starch is a characteristic natural material for the manufacture of oromucose dispersion films due to its excellent disintegration properties, but it can also be used to make mucoadhesive films for sustained release of drugs. Chan and colleagues [8] reported a rice starch - based oral mucosal film (Figure 2B) and investigated the effect of drug loading and plasticizer on the drug release profile. They found that as the loading of the active ingredient increased, the swelling of the rice film played a dominant role in the release of the active ingredient in crystalline form. And the role of the plasticizer is revealed by the plasticizer - starch interaction, and the strong interaction makes the drug more easily soluble in the dissolution medium. Therefore, they concluded that the successful development of excipients as plasticizers could potentially provide the desired drug release profile for rice films partially containing crystalline drugs. This is similar when compared to a completely amorphous dispersion. The results show that rice starch is a promising film - forming polymer with tunable properties and satisfactory drug release profile.

Another typical natural material is guar gum, which has been reported as a film - forming polymer for the preparation of a buccal drug delivery system for PLGA nanoparticles containing antihypertensive peptides for the treatment of periodontitis [9]. The results show that these oral mucoadhesive films successfully increase oral drug bioavailability by increasing drug permeability and preventing first pass effects in the gastrointestinal (GI) tract and liver. Interestingly, Castro and colleagues developed a similar film using PLGA nanoparticles to deliver alpha - casopin [10]. The results showed that this formulation strategy

was successful in increasing oral and intestinal absorption of the delivered bioactive molecules without compromising cell viability. In addition, they combined alginate pellets and guar gum films into a single delivery system to provide more efficient buccal and buccal caffeine delivery with programmed drug release, increased cell viability, and increased buccal permeability.

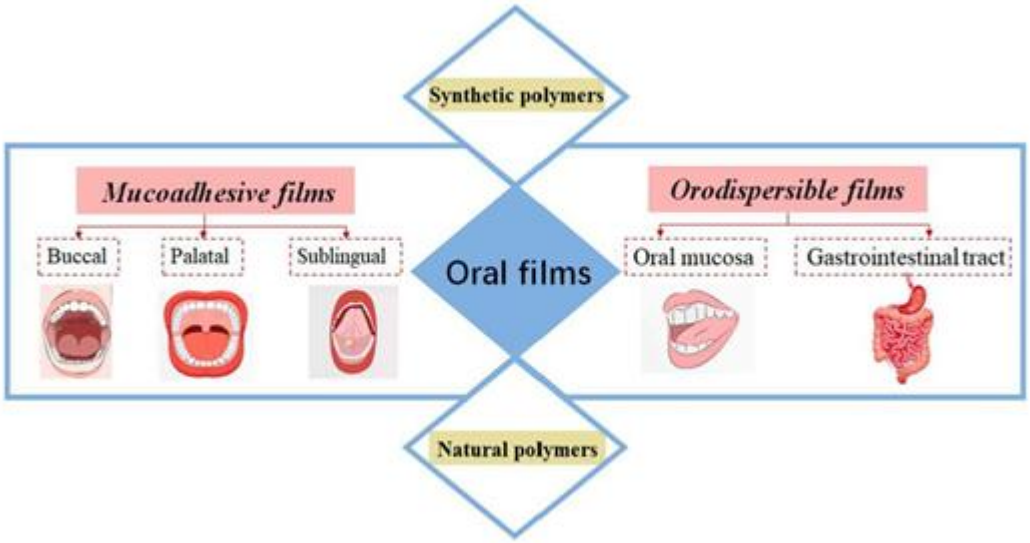


Fig. 1. Typical oral films for drug delivery.

Recently, Prakash and colleagues used another natural polymer, sodium alginate, to produce a film for the treatment of periodontal defects using amoxicillin as a model drug [11] (Figure 2C). The most studied natural polymer for mucoadhesive film formation is chitosan, the only natural cationic polymer with a number of excellent properties such as biocompatibility, biodegradability, and bioadhesion [12]. The molecular weight, the degree of deacetylation, and the amount of functional groups such as amines and hydroxyls present in the molecular structure strongly influence the physicochemical and biological properties, especially cell adhesion and interaction with mucosal proteins, which enhance the bioadhesive properties of the formed oral films [13].

Despite these advantages of chitosan, its low mechanical stability and relatively loose three - dimensional network due to its high water content (especially in acidic solutions) greatly complicate its practical application in the production of buccal films. As an effective strategy for improving mechanical properties and stability, chitosan, usually modified by crosslinking, has been extensively studied as a key mucoadhesive film formulation [14].

An example of using chitosan as a film composition is given by Kilicarslan and colleagues [15]. They designed and developed a drug delivery mucoadhesive film containing clindamycin phosphate for topical periodontal therapy. The results show that the molecular weight of chitosan and the concentration of the polymer mixture affect the viscosity of the composite film, which in turn affects the release rate of clindamycin phosphate. Similarly, Miksusanti and colleagues, created and optimized an oral care film containing Gambier leaf extract using chitosan and tapioca starch as the film composition. The results show that chitosan - based films have good bioadhesive ability with appropriate mechanical properties and can release drugs into the oral cavity in a controlled manner, which makes them practically promising for the treatment of chronic periodontitis [16]. Despite recent advances in mucoadhesive films based on natural polymers, these materials still have some limitations. In general, the physicochemical properties of natural polymers are more complex, such as water insolubility and broad molecular weight distribution, which not only cause additional inconveniences in the manufacturing process, but can also cause complex and unpredictable unstable oral films. property. Therefore, most natural polymers must be modified into derivatives or semi - synthetic polymers with more stable physicochemical properties.

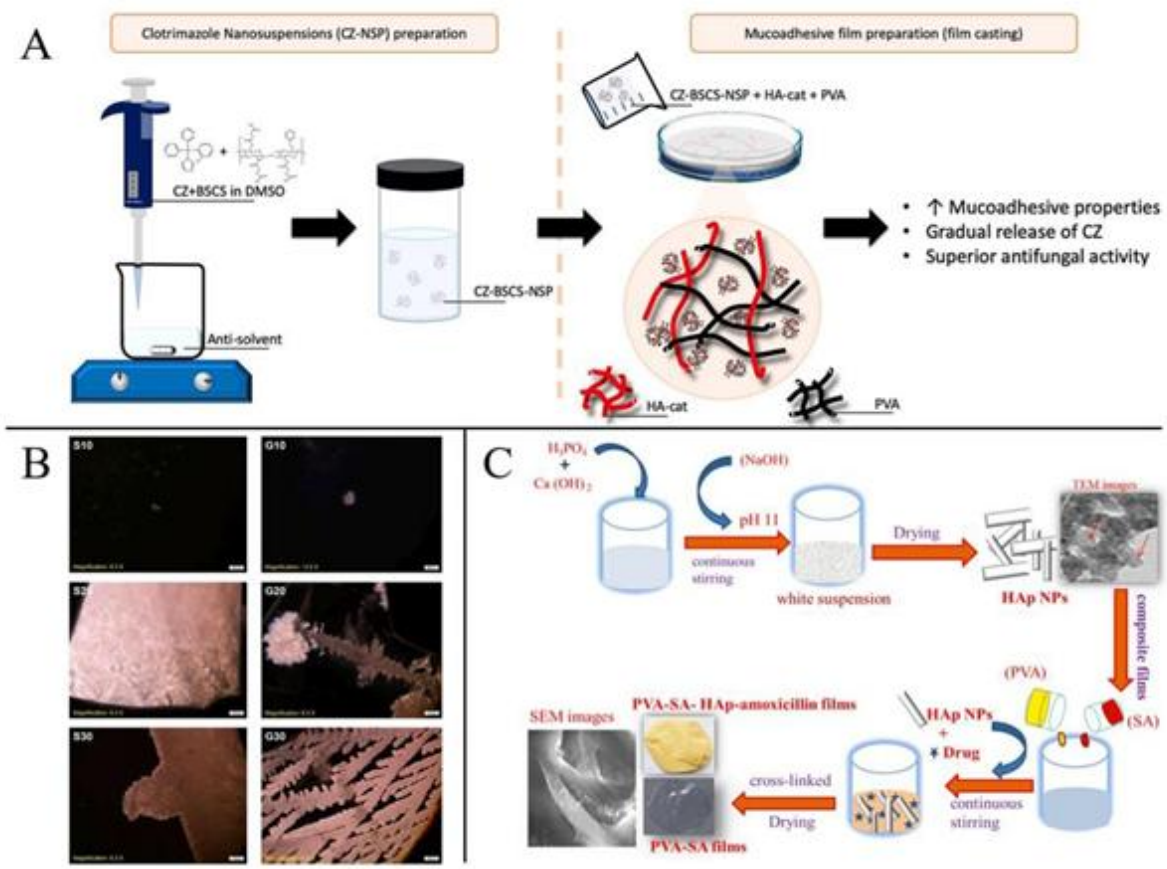


Figure 2: (A) Schematic diagram of clotrimazolenanosuspensions - loaded HA - cat/PVA film fabricates technique. (B) Microscopic images of different rice films containing paracetamol. (C) Schematic diagram of PVA - SA - HAp - amoxicillin film fabricates technique [17]

b) Synthetic and semi - synthetic polymers:

Semi - synthetic and synthetic polymers commonly used to make mucoadhesive films include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and polyvinyl alcohol (PVA), polyethylene glycol (PEG) and carbopol (KP). The physico - chemical properties of these polymeric materials are stably controlled with appropriate biocompatibility and biodegradability. In addition, these polymers are known to have excellent film - forming properties along with fantastic post - film mechanical properties.

HPMC is a semi - synthetic polymer with excellent bioadhesive properties and is therefore widely used as a film - forming polymer [18]. Sim Yi Lim and colleagues have presented an example of the manufacture of mucoadhesive films using HPMC [19]. They explored the possibility of combining HPMC with Carbopol 917 to obtain an acceptable mucoadhesive film that would successfully allow the simultaneous delivery of antiseptic and anti - inflammatory antibiotics. The results show that mucoadhesive films are an effective drug delivery system for the treatment of periodontal disease. Another typical example of the use of HPMC for the preparation of mucoadhesive films containing buprenorphine hydrochloride (Fig.3A) was proposed by Zahra and colleagues [20]

They found that the properties of the final product, including flexural strength, tensile strength, modulus of elasticity, swelling index and time to maximum swelling, are highly dependent on the composition and composition of the film. In addition, researchers have found that incorporating particle systems such as nanoparticles and liposomes into oral films can effectively increase buccal permeability, effectively increasing drug absorption and bioavailability. Okafor and colleagues reported a similar mucoadhesive film (Fig.3C) made from HPMC, CP, and Pluronic F127 (PF127) copolymers, in which efavirenz liposomes were embedded to increase buccal permeability of the drug. They study the effect of film composition on film properties. Interestingly, their results show that the bioadhesiveness of films composed of SR is higher than that of HPMC [21]

However, the persistently temperature sensitive nature of HPMC films makes it difficult to deliver poorly water soluble drugs. To overcome these limitations, Salehi and colleagues [22] proposed the creation of a mucoadhesive buccal film using Kollicoat® IR, a polyvinyl alcohol (PVA) - polyethylene glycol (PEG) graft copolymer (Figure 3C). Simultaneous delivery of rizatriptan benzoate (RB) and propranolol hydrochloride (PRH) was achieved. Similar work was proposed by Alopaeus and colleagues, who also improved the drug loading as well as the mucoadhesive properties of the final buccal film using a graft copolymer (Soluplus®) (Figure 3B) as a film former [23].

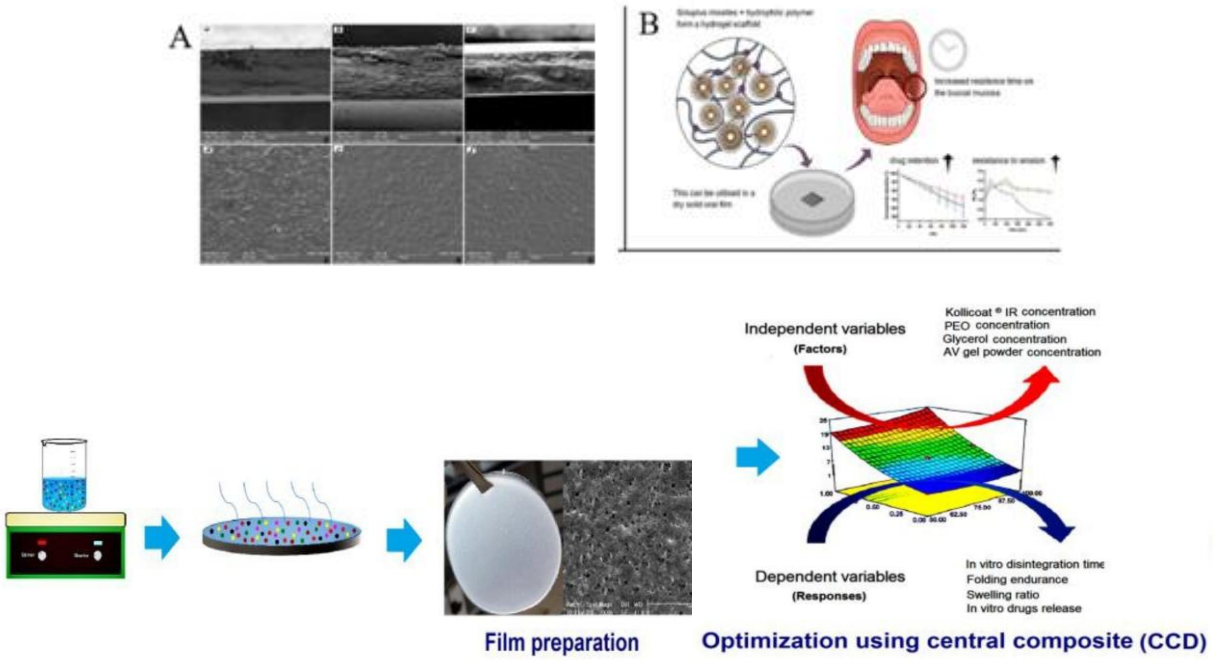


Figure 3: (A) Schematic diagram of scanning electron microscopy images. (B) Schematic diagram of mucoadhesive buccal films based on a graft co - polymer. (C) Schematic diagram of kollicoat ® IR based mucoadhesive buccal film for co - delivery of rizatriptan benzoate and propranolol hydrochloride [20] [22] [23]

2) Formulation of Ordispersible Film:

Unlike mucoadhesive oral films, the key to the success of orally disintegrating films (ODFs) is the rapid dissolution or disintegration of the formulation and the immediate release of the active ingredient to the mucosa of the target site. Accordingly, the applied composition, including the film - forming polymer and other additives, must have sufficient solubility in water to achieve a rapid dispersing action. At the same time, the drug must be bioadhesive to ensure proper adhesion to the mucosa to achieve high absorption and bioavailability of the drug. In addition, the thickness of the mucosal dispersion is also important for acceptable drug delivery efficiency. Generally, an orally disintegrating film should be thick enough to adequately contain the drug, but not so thick as to interfere with the orally disintegrating properties. Like mucoadhesive buccal films, natural and synthetic polymers have recently been studied and used to make orally disintegrating films.

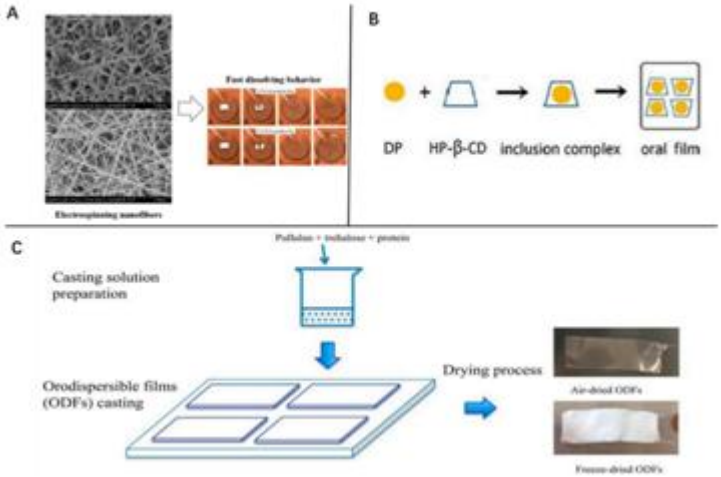


Figure 4: (A) SEM images of different electrospinning nanofibers and Schematic diagram of fast dissolving behavior of fast dissolving oral films (FDOFs). (B) Schematic diagram of DP/HP - β - CD ODF. (C) Schematic diagram of preparation of Orodispersible films based on blends of trehalose and pullulan. Reprinted with permissions from [24] [25] [26]

a) Natural Polymer

An increasing number of natural materials have been applied to manufacture ODFs due to their excellent film forming properties and biocompatibilities. One typical example is maltodextrin, which is a polysaccharide that is produced from vegetable starch by partial hy - drolysis. Initially, a mixture of maltodextrin/glycerin was utilized by Musazzi and co - workers to prepare ODF [27]. More recently, Elbl and co - workers (Elbl et al., 2020) also used maltodextrin as the film forming agent to produce ODF and it is interesting to note that they adopted the 3D printing technique with semi - solid extrusion method to print the predesigned ODFs. Natural oligosaccharides such as trehalose, pullulan and chitosan could also be applied to prepare ODFs to orally

deliver macromolecules by utilizing the excellent ability of stabilizing proteins of some oligosaccharides. Wang and colleagues proposed a fast ODF using composite nanofibers of chitosan and pullulan [24] (Fig.4A). The results show that the resulting film quickly dissolves in the oral cavity and can successfully release the encapsulated aspirin. In addition, reported ODFs prepared using okra biopolymer, an inexpensive polymer with excellent biodegradability and biocompatibility. As a result, ODF prepared from okra biopolymer and HPMC K15 has been proven to have excellent mechanical properties, which can be practically used for oral administration of citalopram for the treatment of depression. The delivery of drugs with an unpleasant taste and smell in the ODF is also a disadvantage. A practical solution is to combine perfume and film polymer into an inclusion complex [28].

Fang Liang and colleagues [25] incorporated donepezil hydrochloride/cyclodextrin (DP/HP - β - CD) inclusion complexes (Fig.4B) into HPMC ODF and glycerol. The results show that this ODP not only dissolves quickly, but also successfully masks the characteristic odor of the drug. This study provides a satisfactory formulation strategy for the design and development of ODFs requiring taste masking. Interestingly, this natural polymer can also be used to make ODF for macromolecular delivery. Visser and colleagues [26] investigated the composition of trehalose/pullulan - based ODF for oral protein delivery using a lyophilization/air - drying method (Fig.4C). Using several representative proteins as model drugs, including ovalbumin, lysozyme, and β - galactosidase, we concluded that formulation (drug - to - polymer ratio) and processing method (lyophilization/air - drying method) have a strong influence. One of the main limitations that significantly slows down the practical application of ODF is its short residence time on the mucosa. Jasjeet et al [29] increased mucosal residence time using chitosan, an excellent mucosal polymer, as a film former along with HPMC. The results show that the model drug, frovatriptan succinate monohydrate (FSM), was successfully delivered to the sublingual mucosa after intimate contact, resulting in higher bioavailability.

Method of Preperation of Fast Dissolving Oral Film: [4]

Following are the manufacturing methods of the mouth dissolving film

1) Solvent Casting.
2) Hot - melt Extrusion.
3) Semisolid Casting.
4) Solid Dispersion Extrusion.
5) Rolling.

1) Solvent Casting

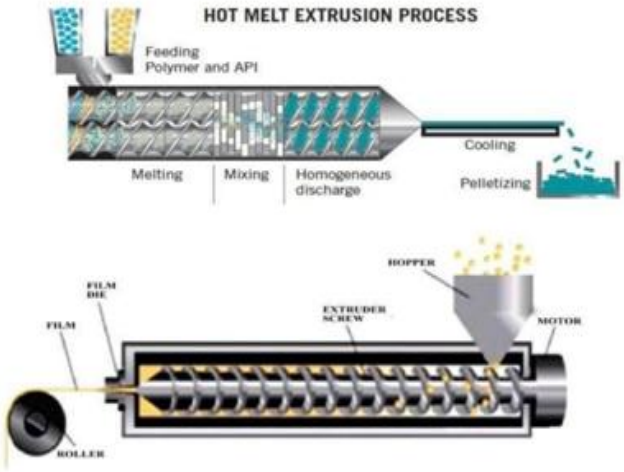
Solvent casting is the most commonly used method for producing ODF using deionized water - soluble fillers, polymers, and water - soluble drugs. Therefore, a homogeneous mixture is obtained by applying a high shear force generated by the shear processor. The prepared solution was poured into a Petri dish and dried by exposing the solvent to high temperature until a good quality film was obtained. Tianeptine sodium dispersible film has been successfully prepared by solvent casting using various grades of Lycoat and HPMC.

In solvent forming technology, film - forming polymers are typically soaked overnight in a suitable solvent. The type of API to be included in the SRF determines the choice of an appropriate solvent based on the important physicochemical properties of the API, such as melting point, shear sensitivity, and polymorphic form. Compatibility of the drug with other solvents and excipients was also considered before finalizing the formulation. Air bubbles introduced during formulation can affect the uniformity of the resulting film. Thus, the mixture is removed using a vacuum pump.

Orodispersible film formulation of mosapride was additionally effectively ready by utilizing dissolvable projecting strategy. Thickness of the answer for be poured is an basic angle in projecting technique. The convergence of pullulan differing from 2% to 8% outcomes into low consistency arrangement, therefore, empowering simple projecting of movies. Quick deteriorating movies of anastrozole were likewise actually ready with the assistance of dissolvable projecting strategy utilizing HPMC (E5) and polyvinyl liquor (PVA).

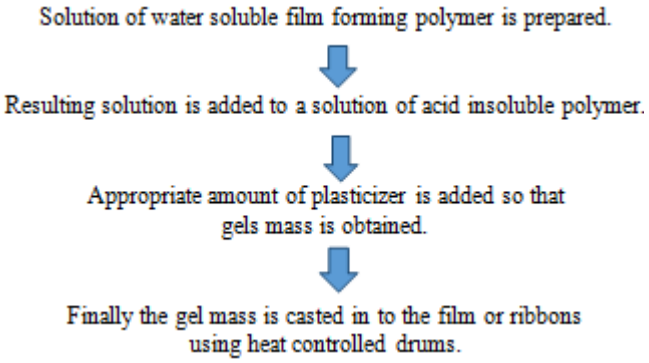
2) Hot Melt Extrusion:

A mixture of a medicine, polymer, and excipients is extruded at a high temperature using a process called hot melt extrusion to create a homogenous mass that is then coasted to create smooth films. Although this is a solvent - free technique, processing thermolabile materials is a significant disadvantage because extrusion takes place at a high temperature.



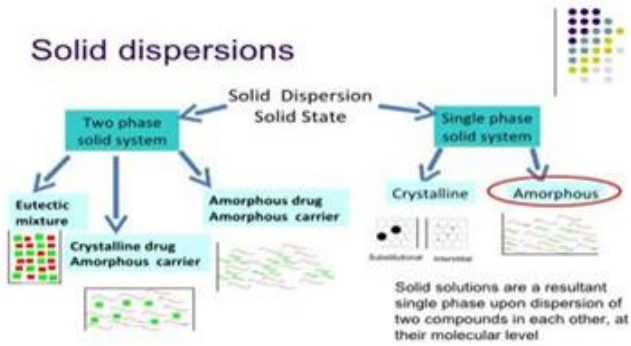
3) Semi Solid Casting Method:

When acid - insoluble polymers are to be employed in the creation of the films, the semi - solid casting process is preferred. Acid among the insoluble polymers used to make films is cellulose. Cellulose acetate butyrate, phthalate of acetate. Insoluble in acid the usage of polymer and film - forming polymer in the 1: 4 ratio.



4) Solid Dispersion Extrusion Method:

Domperidone was effectively produced as a solid dispersion using beta - cyclodextrin, PEG400, and HPMC E15, and films were formed utilising the solid dispersion extrusion process.



5) Rolling Method

Solution should have specific rheological properties in order to roll onto the drum according to the planned rolling method preparation of medication and polymer suspension in water or alcohol Suspension is rolled about by rollers. Suspension is rolled about by rollers. Solution evaporation Solution evaporation.

2. Result & Discussion

In the pharmaceutical industry, great advancements have been made in oral drug delivery technologies. The market has come a long way from the conventional tablets/capsules to modern - day fast disintegrating and rapidly acting tablets/films. Various limitations such as lower bioavailability of oral solid drugs, the inconvenience of administering injections, inaccurate dosing by liquid formulations are keystone which has turned the focus of pharmaceutical companies to develop novel oral dosage forms that eliminate these limitations. Fast dissolving oral thin films are designed 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. This emerging area is gaining 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 (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, BioDelivery Sciences and NAL Pharma. Many companies are collaborating with these technology providers and utilizing oral thin films as a lifecycle 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. According to the clinical and regulatory aspects in the US Food and Drug Administration (US FDA), if the product is bioequivalent to that of the existing oral product the drug, an Abbreviated New Drug Application (ANDA) route is followed. There are no clinical studies associated with this generic approval processes (section 505 (j) of the Food, Drug, and Cosmetic Act). The example of such case would be a comparative bioequivalence between an orally disintegrating tablet (ODT) formulation and orally dissolving film (ODF) product. However, developed oral film product may exhibit different pharmacokinetic profile compared to the existing marketed product. The ODF is categorized as "new dosage form" and the section 505 (b) approval processes needs to be followed. In this case, a new clinical study would be required. The advantage of new clinical study is that it would award 3 years of marketing exclusivity to the product. Preclinical toxicity studies are not required if the molecule is the same as that of the approved product. Safety, tolerability, and efficacy features are to be demonstrated in such trials. Oral mucosa - irritation testing is carried out in both animal models and humans. The future looks very promising for the film technology in the time to come as new technologies are rapidly introduced to prepare thin films.

3. Conclusion

FDOFs have better patient compliance and may improve biopharmaceutical properties, improve efficacy and better safety, compared with conventional oral dosage forms. After the FDTs, the new products as FDOFs are intended for the application in the oral cavity and they are innovative and promising dosage form especially for use in elder patients. The development of fast dissolving drug products also provides an opportunity for a line extension in a marketplace, for a wide range of drugs (e. g. NSAIDS, antiulcer, antihistamine, Hypnotics & sedatives, antipsychotics, antiparkinsonism, antiemetic, antimigraine and in future, this system is most acceptable and prescribed due to its quick action i. e. within a minute. Because of increasing patient demand, the popularity of these dosage forms will expand the study in future.

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