An Introduction to Fast Dissolving Oral Thin Film Drug Delivery Systems: A Review

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Abstract: Many pharmaceutical companies are switching their products from tablets to fast dissolving oral thin films (OTFs). Films have all the advantages of tablets (precise dosage, easy administration) and those of liquid dosage forms (easy swallowing, rapid bioavailability). Statistics have shown that four out of five patients prefer orally disintegrating dosage forms over conventional solid oral dosages forms. Pediatric, geriatric, bedridden, emetic patients and those with Central Nervous System disorders, have difficulty in swallowing or chewing solid dosage forms. Many of these patients are non-compliant in administering solid dosage forms due to fear of choking. OTFs when placed on the tip or the floor of the tongue are instantly wet by saliva. As a result, OTFs rapidly hydrate and then disintegrate and/or dissolve to release the medication for local and/or systemic absorption. This technology provides a good platform for patent non- infringing product development and for increasing the patent life-cycle of the existing products. The application of fast dissolving oral thin films is not only limited to buccal fast dissolving system, but also expands to other applications like gastro-retentive, sublingual delivery systems. This review highlights the composition including the details of various types of polymers both natural and synthetic, the different types of manufacturing techniques, packaging materials and evaluation tests for the OTFs.

Keywords: Film forming polymers, Lycoat, Monoammonium glycyrrhizinate, Oral thin films, Patent non-infringing product development, Solvent casting method.

INTRODUCTION

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms. These systems consist of solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the need of water [1]. Fast dissolving drug delivery systems include orally disintegrating tablets (ODTs) and oral thin films (OTFs). The Centre for Drug Evaluation and Research (CDER) defines ODTs as, "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [2]. USFDA defines OTFs as, "a thin, flexible, non-friable polymeric film strip containing one or more dispersed active pharmaceutical ingredients (APIs) which is intended to be placed on the tongue for rapid disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract" [3]. OTFs are coming into their own as mainstream pharmaceutical products. The first approved prescription OTF was Zuplenz (Ondansetron hydrochloride- 4 mg, 8 mg) which was approved in 2010. The second approved one was Suboxone (Buprenorphine and Naloxone). Statistics have shown that four out of five patients prefer orally disintegrating dosage forms over conventional solid oral dosages forms [4]. These factors, coupled with convenience and compliance advantages, have been (and will continue to) pave the way for ODT and OTF drug product growth.

This review highlights the various types of polymers, the different types of packaging materials manufacturing techniques and evaluation tests for the oral films.

Need for Preparing Fast Dissolving OTFs

Pediatric, geriatric, bedridden, emetic patients and those with Central Nervous System disorders, have difficulty in swallowing or chewing solid dosage forms. Many of these patients are non-compliant in administering solid dosage forms due to fear of choking. Even in the case of ODTs, fear of choking is associated which can be hazardous. Fast dissolving oral thin film drug delivery system is a better alternative to ODTs. OTFs when placed on the tip or the floor of the tongue are instantly wet by saliva. As a result, OTFs rapidly hydrate and then disintegrate and/or dissolve to release the medication for local and/or systemic absorption. ODTs are friable and may break during transport and handling. Thus, fast dissolving oral thin film drug delivery systems are being developed.

Advantages of OTF

1). Ease of administration for mentally ill and non-compliant patients

2). Useful in situations where rapid onset of action is required such as in motion sickness, allergic attack, coughing or asthma

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3). Has wide range of applications in pharmaceuticals, Rx Prescriptions and OTC medications for treating pain, cough/cold, gastro-esophageal reflux disease, erectile dysfunction, sleep disorders, dietary supplements, etc [4].

4). No water is required for the administration and hence suitable during travelling

5). Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, enhancing bioavailability of drugs

6). May offer improved bioavailability for poorly water soluble drugs by offering large surface area as the film disintegrates and dissolves rapidly

7). Leaves minimal or no residue in the mouth after administration

8). Has ability to provide advantages of liquid medication in the form of solid preparation

9). Adaptable to existing processing and packaging machinery

10). Cost-effective

11). Gives accurate dosing as compared to liquids

12). Provides good chemical stability

13). Free of need of measuring, which is an essential drawback in liquids [5].

14). Offers market expansion and product differentiation

15). Can be developed and launched within 12-16 months, thus provides improved product development life-cycle time [4].

Disadvantages of OTF

1). Dose uniformity is difficult to maintain

2). Only those active pharmaceutical ingredients (APIs) having small dose can be incorporated [6].

3). Research has proven that concentration level of active pharmaceutical ingredient (API) can be improved up to 50% w/w. Novartis Consumer Health's Gas-X® thin strip has 62.5 mg of Simethicone per strip [4].

4). Require expensive packaging

5). Since OTFs dissolve quickly, dose termination is impossible

6). OTFs is not official in any pharmacopoeia

FORMULATION OF FAST DISSOLVING OTFs

Formulation includes consideration regarding mechanical properties, taste masking, fast dissolving, physical appearance, mouth feel. Fast dissolving oral thin films are generally with an area of 5-20 cm^2. APIs can be incorporated upto 50 mg [7]. From the regulatory point of view, all the excipients used should be generally regarded as safe (GRAS) listed and should be used as per Inactive Ingredients Limit (IIG limit). Various components of fast dissolving oral thin films are shown in (Table **1**).

Table 1. Composition of Fast Dissolving Oral Thin Films [8].

Components	% w/w
Active pharmaceutical ingredients	5-50
Film forming polymers	Upto45
Plasticizers	0-20
Surfactants	q. s.
Sweetening agents	3-6
Saliva stimulating agents	2-6
Superdisintegrants	Upto 8
Coloring agents	Upto 1
Flavoring agents	Upto 10

Active Pharmaceutical Ingredients (APIs)

Since the size of the thin films has to be small enough to be conveniently placed on the tongue, those active pharmaceutical ingredients with high dose are not suitable candidates for incorporation into fast dissolving oral thin films [9].

Ideal Characteristics of APIs to be Incorporated into Fast Dissolving OTFs

1). Low dose

2). Palatability

3). Small molecular weight

4). Solubility and stability in saliva

Some of the suitable candidates for incorporation into thin film formulation are given in (Table **2**).

Water soluble APIs exist in the dissolved state or as solid solution and there is no problem of uniformity of distribution. But water insoluble APIs have to be homogenously distributed so as to have an acceptable drug content uniformity. Water insoluble APIs can also be added as milled, micronized or in the form of nanocrystals or microcapsules [10] in order to maintain smooth texture of the film and also for fast dissolution.

- Lou *et al.* formulated Chlorpheniramine maleate microparticles by encapsulating Chlorpheniramine maleate into Eudragit EPO by spray drying of water-in-oil emulsion method. The optimized microparticles were incorporated into OTF with satisfactory weight and drug content uniformity and acceptable physical strength. OTFs disintegrated immediately (in less than 40 seconds) in simulated saliva solutions [11].
- Sievens-Figueroa *et al.* formulated OTFs of hydroxypropyl methyl cellulose (HPMC) by incorporating API in the form of nanosuspension. They transformed nanosuspension produced from wet stirred media milling (WSMM) into polymer films containing drug loaded nanoparticles by mixing with HPMC E15 LV solution containing glycerin followed by film casting and drying [12].

Table 2. Suitable Candidates for Incorporation into Thin Film Formulation.

Active Pharmaceutical Ingredients	Category	Dose (mg)
Levocetrizine Loratadine	Anti-histaminic	5, 10 10
Ketorolac Indomethacin Valdecoxib Piroxicam	NSAIDs	10 25 10, 20 10, 20
Zolmitriptan Sumatriptan succinate	Anti-migraine	2.5, 5 35, 70
Mirtazapine	Anti-depressant	15, 30, 45
Buspirone	Anxiolytic	5, 15, 30
Carvedilol	β-blocker	3.125, 6.25, 12.5, 25
Glipizide	Anti-diabetic	2.5, 5
Galantamine Donepezil	Anti-Alzheimer	4, 8, 12 5, 10
Nitroglycerine derivatives	Vasodilator	0.3, 0.6
Benzocaine		
Buprenorphine/Naloxone	Opioid analgesic	2.5-10
Ondansetron	Antacid	10
d-Amphetamine	Anti-inflammatory	12.5, 25
Clonazepam	Anti-tussive	15, 30
Ondansetron	Anti-emetic	8-24
Loperamide	Anti-diarrheal	2
Buprenorphine Naloxone	Treatment of opioid addiction	2, 4, 16, 24 0.5, 1, 4, 6
d-Amphetamine	Treatment attention deficit hyperactive disorder	10, 20
Clonazepam	Anti-epileptic	0.5, 1, 1.5

As the thin OTF formulation is to be placed on tongue, those drugs having bitter and unpleasant taste may cause vomiting sensation and may be inacceptable by the patient. Hence, various taste masking technologies for bitter drugs like microencapsulation, inclusion complexation with cyclodextrins, complexation with ion-exchange resins are being practiced.

- Prednisolone drug particles were masked by ethyl cellulose and Eudragit E by emulsion solvent evaporation technique and incorporated into ODT. This technique can be further extended to OTF formulation [13].
- In fast dissolving OTF formulation for treating erectile dysfunction, hydroxylpropyl-beta-cyclodextrin (HP-β-CD) was used as a taste masking agent [14].
- Preis *et al.* developed taste masked orodispersible film containing Dimenhydrinate using HP-β-CD as a taste masking agent [15].
- Ion exchange resin like Amberlite IRP 69 was used to formulate taste masked fast dissolving orally consumable films of Dextromethorphan [16].

Film Forming Polymers

Since the film formulation rapidly disintegrates and dissolves in oral cavity, the film forming polymers used must be water soluble. The polymers can be used alone or in combination with others in order to obtain the desired film which should be tough enough so that there won't be any damage while handling or during transportation and at the same time showing fast dissolution in the mouth. The robustness of the film depends on the type and amount of polymer used in the formulation. The disintegration time of the polymers is increased by increasing the molecular weight of polymer film bases [17]. Since polymers are the major components of the film formulation along with the APIs, their proportion related to each other is governed by 2 factors:

a). Minimum % w/w concentration of polymer required to form matrix which incorporates APIs and other excipients with desirable mechanical and viscoelastic properties.

b). % w/v concentration of polymer in solution to be casted as film which is governed by the desired viscosity. Viscosity should be optimum enough to prevent suspended solids from settling and to form a smooth spreadable film [18].

Ideal Properties of Polymers

1). Non-toxic
2). Non-irritant
3). Bland
4). Good mouth feel
5). Should be stable for long period
6). Should not alter properties of the active pharmaceutical ingredient or other excipients of the formulation
7). Inexpensive
8). Should have good wettability and spreadability
9). Should not retard the disintegration time of the film
10). Should have optimum peel strength and tensile strength

NATURAL POLYMERS

Gum Polysaccharides

Gum polysaccharides like gum arabic, κ-carageenan, and sodium alginate are some of the potential polymers for film formation. They can be used in combination with others so as to provide primary film structure and rapid dissolving characteristics. Some examples are shown in (Table **3**).

Advantages

a). Addition of these can improve can improve dissolution of films in mouth

b). Reduces tensile strength only to a minimal extent

Table 3. Film Composition and the Resulting Dissolution Time [19].

Film Composition	Dissolution Time (Seconds)
Gum arabic (1.25%) along with sodium alginate (2.5%) and low viscosity carboxy methyl cellulose (1.25%) and water	20
κ-carageenan (1.25%) along with sodium alginate (2.5%) and low viscosity carboxy methyl cellulose (1.25%) and water	28
Polydextrose (1.25%) along with sodium alginate (2.5%) and low viscosity carboxy methyl cellulose (1.25%) and water	12.60

Gelatin

Gelatin consists of a mixture of purified protein fractions obtained either by partial acid hydrolysis which is called as type A gelatin or by partial alkaline hydrolysis which is called as type B gelatin of animal collagen. Gelatin is prepared by the thermal denaturation of collagen isolated from animal skin, bones and fish skins [20]. It is readily soluble in water above 40º C and it forms viscous solution of randomly coiled polypeptide chains. Mammalian gelatins have better physical properties and thermostability than most of the fish gelatins due to their higher amino acid content. The properties and film forming ability of gelatin is directly related to the molecular weight of the gelatin, i.e., the higher the average molecular weight, better the quality of the film. The molecular weight distribution depends mainly on the degree of cross-linking of collagen fibers and the extraction procedure used. Gelatin films could be formed from 20-30% gelatin, 10-30% plasticizer (glycerin or sorbitol) and 40-70% water followed by drying the gelatin gel [21].

Advantages of Gelatin Films

a). Dissolve rapidly

b). Films are excellent carriers for flavors

c). Films produce a smooth mouth feel [22].

- Ghorwade *et al.* formulated Montelukast sodium fast dissolving films using gelatin as a film base (3.54% w/w). It was observed that films had desired tensile strength and optimum *in vitro* dissolution time [23].

Pullulan

Pullulan is a biopolymer. It is water soluble, neutral linear polysaccharide consisting of α (1→6) linked maltotriose residues. It is a fungal exopolysaccharide produced from starch by black yeast *Aureobasidium pullulan* [24]. Bender and Wallenfels discovered the enzyme pullulanase, which specifically hydrolyzes α (1→6) linkage in pullulan and converts the polysaccharide to maltotriose. Catley and coworkers established the occurrence of a minor percentage of randomly distributed maltotetraose subunits in pullulan [25]. The regular occurrence of α (1→6) linkage in pullulan interrupts a linear amylase chain. This unique pattern of linkage is responsible for the structural flexibility of pullulan, resulting in distinct film forming characteristics [26]. Pullulan PI-20 grade is the deionised form of pullulan having an average molecular weight of 2,00,000 daltons and possess excellent film forming properties. Pullulan is used in range 0.3-15% w/w [27].

Advantages of Pullulan

a). It is non-hygroscopic

b). It is impermeable to oxygen Impermeability of pullulan films to oxygen is suitable for protection of readily oxidized fats and vitamins in food. Pullulan films have 300 times stronger oxygen barrier than HPMC films and 9 times stronger oxygen barrier than gelatin films of the same thickness [28].

c). No branching in structure in contrast to gum arabic, forming much stronger films [29].

d). It is easily soluble in cold and hot water to make clear and viscous solution

e). It also has high adhesion and film forming abilities

f). It is a nonionic polysaccharide and is bio-compatible, biodegradable

g). It is non-toxic, non-immunogenic, non-mutagenic and non-carcinogenic [30].

h). Pullulan films are thermally stable and possess antistatic and elastic properties

i). Pullulan films can be developed into compression molding

j). Pullulan films are highly water soluble, colorless, tasteless, odorless, transparent and flexible

- Mishra *et al.* formulated rapidly dissolving films of Cetirizine hydrochloride using pullulan (15% w/w) as a film forming agent. They found that the amount of plasticizer was critical for film formation and separation properties. Acceptable mechanical properties and *in vitro* disintegration time were obtained [31].
- Orally disintegrating film formulation of Nicotine is shown in (Table **4**).

Starch

Starch is the major carbohydrate reserve in plant tubers and seed endosperm where it is found as granules. Each granule contains millions of amylopectin molecules accompanied by smaller amylase molecules. Amylose is responsible for the film forming capacity of starch [33].

Table 4. Nicotine Orally Disintegrating Film.

Ingredients	Amount per Film (mg)
Nicotine base	1.00
Alginic acid	0.50
Pullulan	29.48
Purified water	0.0038
Sucralose	0.48
Solutol H15	1.00
Sucrose fatty acid esters D-1811	1.00
Alcohol	0.00
Glycerin	3.20
Triethyl citrate	2.00
Tween 80	0.60
Span 80	0.10
Peppermint oil	0.40
Menthol	0.20
FD & C Yellow #6	0.04
TOTAL	**40.00**

In above formulation, hydroalchoholic vehicle was used [32].

Advantages of Starch

a). Starch films are biodegradable

b). Starch films are transparent or translucent

c). Starch films are flavorless, tasteless and colorless [34].

Disadvantages of Starch

a). Starch films have poor mechanical strength

b). Film forming conditions have an effect on crystallinity of the starch films and their properties

Films of high-amylose corn starch or potato starch were more stable during aging, lost little of their elongation and had slight or no increase in tensile strength [35]. Films from cassava starch had good flexibility and low water permeability, indicating the potential application as edible film former [36].

Modified starch, due to its low cost, is being widely used in combination with pullulan.

Lycoat

Lycoat is a novel granular hydroxypropyl starch polymer obtained from pea starch that has been designed especially for fast dissolving OTFs. It is manufactured by Roquette Pharma.

Advantages of Lycoat

a). Lycoat disperses easily in cold water without formation of lumps

b). It can be used alone as film forming polymer to formulate fast dissolving OTFs with excellent functionality without the need of additional film forming agent [37].

c). It is neutral in taste

d). It forms films without the use of organic solvents

e). APIs can be loaded in crystalline form or they can be solubilized in an organic solvent

- Popescu *et al.* formulated oral disintegrating films of Benzocaine using Lycoat RS 720 as a film forming polymer. They concluded that Lycoat RS 720 alone was capable of producing orally disintegrating films. It also offered dose homogeneity and fast dissolution [38].
- Doaa *et al.* formulated Tianeptine sodium orodispersible films using Lycoat NG 73 as a film forming polymer. They concluded that the films made up of Lycoat NG 73 showed the highest dissolution rate, suitable *in vitro* disintegration time and satisfactory physico-mechanical properties as compared to those made up of other polymers [39].

Maltodextrin

Maltodextrin is a non- sweet nutritive saccharide polymer. It is produced by partial hydrolysis of starch. Maltodextrin consists of D-glucose units connected in chains of variable length. The glucose units are primarily linked with α (1→4) glycosidic bond. Maltodextrin is typically composed of a mixture of chains that vary from 3-19 glucose units [40]. Maltodextrins are classified by DE (dextrose equivalent) and have DE between 3-20. Higher the DE value, shorter the glucose chains, higher the sweetness and higher the solubility [18]. Maltodextrin is used in the range of 2-10% w/w [41].

- Cilurzo *et al.* formulated Nicotine fast dissolving films made of maltodextrin. They found that on decreasing the DE value of maltodextrin, the tenacity of the film improved [42].

SYNTHETIC POLYMERS

Hydroxypropylmethyl Cellulose (HPMC)

HPMC or hypromellose is partly O-methylated and O-(2-hydroxypropylated) cellulose [43]. Depending upon the viscosity grades, concentrations of 2-20% w/w are used for film forming solutions [44]. Lower grades of HPMC like HPMC E3, HPMC E5and HPMC E15 are particularly used for film formation because of their low viscosity [45]. Lower grades are used with aqueous solvent [38]. Additives are incorporated to improve specific properties of films. Several studies have been carried out to investigate the influence of additives on physico-chemical properties of HPMC films. Lipids such as waxes, triglycerides (tristearin), fatty acids (stearic acid, palmitic acid) result in decreased water affinity and moisture transfer due to their high hydrophobic properties [23].

Advantages of HPMC

a). It has good film forming properties and excellent acceptability

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