

A Current Overview Of Oral Thin Films

Oral İnce Filmlere Güncel Bir Bakış

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ABSTRACT

The pharmaceutical industry is trying to discover thin films as a new drug delivery system. Thin films have been described as an alternative approach to conventional dosage forms. It is a versatile platform that provides fast, local or systemic effects. Also, these systems can be easily applied by themselves especially dysphagia patients, geriatric, pediatric or bedridden patients and as well as patients that are not easily accessible to water. These drug delivery systems can be administered in various ways such as oral, buccal, sublingual, ocular and transdermal. This review examines oral thin films in all aspects with today's point of overview and gives an idea about the growing market share in the world due to the increase in research fields and technological developments. At the same time provides an overview of the critical parameters associated with formulation design that affect the of thin films, including the design of thin films, anatomical and physiological limitations, the selection of appropriate manufacturing processes, characterization techniques, and the physicochemical properties of polymers and drugs. It also provides insight into the latest thin-film products developed by various pharmaceutical companies.

Key words: Drug delivery systems, oral thin film (OTF), pharmaceutical industry, polymers

ÖZ

İlaç endüstrisi, yeni bir ilaç taşıyıcı sistem olarak ince filmleri keşfetmeye çalışmaktadır. İnce filmler geleneksel dozaj formlarına alternatif bir yaklaşım olarak tarif edilmiştir. Hızlı, lokal veya sistemik etkiler sağlayan çok yönlü bir platformdur. Ayrıca, bu sistemler özellikle disfaji hastaları, geriyatrik, pediatrik veya yatalak hastalar ile suya kolayca erişilemeyen durumlardaki tüm hastalar tarafından kendi kendilerince kolayca uygulanabilmektedir. Bu ilaç taşıyıcı sistemler oral, bukkal, dil altı, oküler ve transdermal gibi çeşitli şekillerde uygulanabilir. Bu derleme, günümüzün genel bakış açısı ile oral ince filmleri her yönüyle incelemekte, araştırma alanlarındaki ve teknolojik gelişmelerdeki artış nedeniyle dünyada büyüyen pazar payı hakkında fikir vermektedir. Aynı zamanda, ince filmlerin tasarımına, ilaçların ve

polimerlerin fizikokimyasal özelliklerine, anatomik ve fizyolojik sınırlamalarına, uygun üretim süreçlerinin seçimine, karakterizasyon tekniklerine ve fizikokimyasal özellikleri de dahil olmak üzere ince filmleri etkileyen formülasyon tasarımı ile ilişkili kritik parametrelere genel bir bakış sağlar. Ayrıca, çeşitli ilaç şirketleri tarafından geliştirilen en son ince film ürünleri hakkında da fikir vermektedir.

Anahtar kelimeler: İlaç taşıyıcı sistemler, oral ince film (OTF), ilaç endüstrisi, polimerler

INTRODUCTION

The oral mucosa epithelium is a 40-50 cell layer called mucus that is made up of carbohydrates and proteins. Mucosa thickness, mouth base, tongue and gums range from 100-200 μm . The submucosa layer releases a small amount of gel-like fluid known as mucus, consisting of 90-99% water, 1-5% water-insoluble glycoprotein and components such as proteins, enzymes, electrolytes, nucleic acids. On the other hand, the salivary glands, consist of lobules that secrete saliva and parotid from the salivary duct near the sublingual canals and submandibular teeth. Small salivary glands are most often found on the lips and cheek mucosa. The total amount of saliva secreted in one minute is about 1-2 mL. Saliva content composes of mucus, water, amylase (enzyme), lysozyme, mineral salts, immunoglobulins, and blood clotting factors. Mucin and saliva also serve as a barrier for oral mucosa (1, 2). The mucosa epithelial structure contains two different areas, the membrane of the stratified epithelium which is a lipophilic area and space between cells, and a more hydrophilic area (3). The oral mucosa has a permeability between the intestinal mucosa and epidermis in terms of permeation. It is guessed that the buccal mucosa permeability is 4-4000 times better than of the skin (2). Mucous epithelium offers two main drug absorption pathways, the paracellular path (intercellular) and transcellular path (intercellular) (Figure 1). The lipophilic structure of the cell membranes facilitates the passage of molecules with a high partition coefficient throughout the cells, while the polar nature of the intercellular space facilitates the penetration of more hydrophilic molecules. The hydrophobic, hydrophilic or amphiphilic nature of the drug molecule determines its absorption (2, 3).

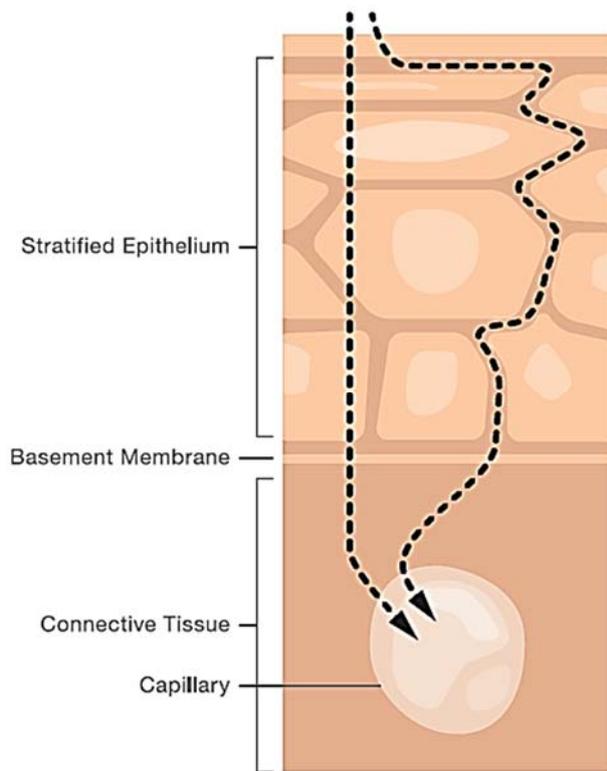


Figure 1. Mucosal pathways: Intracellular and Intercellular pathway (3)

Many pharmaceutical preparations are applied in tablet, granule, powder and liquid form. In general, a tablet design is in a form presented to patients to swallow or chew a precise dose of medication. However, especially geriatric and pediatric patients have complication in chewing or swallowing solid dosage forms (4). Therefore many children and elderly people are reluctant to get these solid dosage forms owing to fear of asphyxiation. Orally dissolving tablets (ODTs) have emerged to meet this need. However, the fear of swallowing the solid dosage form (tablet, capsule) and the risk of asphyxiation still occur though short dissolution/disintegration times for some patient populations. Oral Thin Film (oral thin film, OTF) drug delivery systems are a preferable alternative in these conditions. The oral bioavailability of many drugs is insufficient due to the enzymes, common first pass metabolism, and pH of the stomach. Such conventional drugs have been administered parenterally and have shown low patient compliance. Situations like these have paved the way for the pharmaceutical industry to develop alternative systems for the transportation of drugs by developing thin dispersible/dissolving films in the mouth (1, 5, 6). Fear of drowning that may be dangerous with ODTs has been associated with these patient groups. Rapid dissolution/disintegration of OTF drug delivery systems is a preferable alternative to ODTs in patients with fear of asphyxiation. When it placed on the tongue, OTFs are immediately wetted with saliva. As a result, it is dispersed and/or dissolved to release the drug for systemic and/or local absorption. ODTs are fragile and they can break during transport. Therefore, oral fast disintegrating/dissolving OTF drug delivery systems are developed as an alternative (7).

Table 1. Differences of OTFs from ODTs: (5, 8)

OTF	ODT
Film	Tablet
More dissolution owing to the larger surface area.	Less dissolution owing to the lesser surface area.
It is more durable compared to ODTs.	It is less durable than OTFs.
Patient compliance is high.	Patient compliance is low.

It may contain a low dose.	It may contain a high dose.
No risk of asphyxiation.	There is a fear of asphyxiation.

Oral disintegrating/dissolving films or strips can be defined as follows: "These are drug delivery systems that they are quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue". The sublingual mucosa has a high membrane permeability due to its thin membrane structure and high blood vessels. Due to this rapid blood supply, it offers a very good bioavailability (4, 9). Enhanced systemic bioavailability is owing to skipping the first-pass effect and better permeability is owing to high blood flow and lymphatic circulation too. In addition, oral mucosa is a very effective and selective way in systemic drug delivery because of large surface area and the ease of application for absorption (6). In general, OTFs are characterized as a thin and flexible polymer layer, with or without plasticizers in their content. They can be said to be less disturbing and more acceptable by patients, as they are thin and flexible its natural structure. Thin films are polymeric systems that provide many requirements expected from a drug delivery system. In the studies, thin films have shown their abilities such as improving the initial effect of the drug and the duration of this effect, decreasing the frequency of the dose and increasing the effectiveness of the drug. By thin-film technology, it can be beneficial to eliminate the side effects of drugs and reduce common metabolism procured by proteolytic enzymes. Ideal thin films should possess the desired properties in a drug delivery system, like a suitable drug loading capacity, rapid dispersion/dissolution or prolonged application and reasonable formulation stability. Also, they must be non-toxic, biodegradable and biocompatible (10).

The existence of a variety of biocompatible polymers and variability in production technologies has produced it possible to develop a different variety of OTFs. For this reason, OTFs are gaining acceptance and popularity as a new drug carrier dosage form in pharmaceutical technology. A great endeavor has been made to formulate polymeric OTFs that oral, buccal, sublingual, ocular and, applied to the skin. Among these applications, the use of OTFs for drug delivery from buccal or sublingual mucosa has gained great attention in recent times. Mechanical strength, related properties, mucoadhesive properties and, drug release rate can also be adjusted by using combinations of polymers, which are the basic structure of thin films, in different proportions. Pharmaceutical industry is affected by the attractive properties of OTFs, and as a result, their thin films technologies are developing and are currently getting patent for these formulations (10).

According to the European Medicines Agency (EMA), a thin film that easily solves in the oral mucosa is often referred to as an orodispers film. Rapidly dissolving oral films are usually postage scale-sized OTFs that dissolve/disperse in the oral cavity within one minute of contact with saliva, result in quick absorption and immediate bioavailability of drugs (1, 10). These innovative dosage forms are taken orally however do not require water for ingestion and absorption such as conventional drugs (11). OTFs should not be confused by buccal films that are designed to remain on the cheek mucosa longtime (12).

According to the FDA: OTF defines as "including one or more active pharmaceutical ingredients (APIs), flexible and non-brittle strip that is placed on the tongue before passing into the gastrointestinal tract, aiming for a quick dissolution or disintegration in the saliva".

The first prescribed OTF is Zuplenz (Ondansetron HCl, 4-8 mg) and was approved in 2010. Suboxon (Buprenorphine and Naloxan) quickly followed as a second approved. Statistics show that four out of five patients choose orally dissolving/disintegrating dosage forms compared to traditional oral solid dosage forms (7). At the current point, in many prescription and over-the-counter product groups, especially in cough, cold, sore throat, erectile dysfunction disorders, allergic reactions, asthma, gastrointestinal disorders, pain, snoring

complaints, sleep problems, multivitamin combinations etc. OTFs are available and continue to increase (13). Fast dissolving oral films have many advantages compared to another solid dosage forms, like a flexibility, increased efficacy of the API. Also oral films have dissolution and disintegration with very little saliva fluid in less than one minute compared to the ODTs (1).

OTF should have that the ideal features: (14)

- It should be taste good,
- Drugs should be very moisture resistant and soluble in the saliva,
- It should have appropriate tension resistance,
- It should be ionized in the oral cavity pH,
- It should be able to penetrate the oral mucosa,
- It should be able to make a quick effect.

OTF's advantages over other dosage forms: (1, 7, 10)

- Practical,
- It does not require water use,
- Can be used safely even when access to water is not possible (such as travel),
- No risk of suffocation,
- Improved stability,
- Easy to apply,
- Easy application to mental and incompatible patients,
- There is little or no residue in the mouth after application,
- Bypassing the gastrointestinal tract and thus increasing bioavailability,
- Low dosage and low side effects,
- It provides more accurate dosage when compared to liquid dosage forms,
- No need to measure, which is an important disadvantage in liquid dosage forms,
- Leaving a good feeling in the mouth,
- Providing rapid onset of effects in conditions requiring urgent intervention, for example, allergic attacks such as asthma and intraoral diseases,
- Improving the absorption rate and amount of drugs,
- Provides enhanced bioavailability for less water-soluble drugs that especially via giving a large surface area while rapidly dissolving,
- It does not prevent normal functions such as speaking and drinking,
- It offers administration of drugs with a high risk of disruption in the gastrointestinal tract,
- Having an expanding market and product variety,
- It can be developed and placed on the market within 12-16 months.

Disadvantages of OTFs: (1, 7, 10)

- For packing requires special equipment,
- It is not suitable for drugs that cause irritation in the oral pH and are not durable,
- Only a small dose of medication can be administered, but research has shown that the API concentration can be increased by up to 50% by weight (For example, each film strip of Gas-X[®] of Novartis Consumer Health contains 62.5 mg of Simethicone).
- It is hygroscopic by nature. For this reason, it causes difficulties in long-term protection,
- Only drugs absorbed by passive diffusion can be applied in this way,
- Since OTFs are resolved rapidly, dose termination is not possible,
- OTFs are not registered to any pharmacopoeia,
- Preparation method is costly compared to oral dissolving tablets.

OTFs are classified in three ways: (8, 9, 15)

1. Flash Release (Quick Release)

2. Mucoadhesive Melt Away Wafers (Mucoadhesive Wafer)

3. Mucoadhesive Sustained Release Wafers (Mucoadhesive Extended Release Wafer)

In Table 2 below, the features that distinguish the above OTF types are shown: (8, 9, 15)

Table 2. Features distinguishing OTF types from each other

Features	Quick Release	Mucoadhesive Wafer	Mucoadhesive Extended Release Wafer
Area (cm ²)	2-8	2-7	2-4
Thickness (mm)	20-70	50-500	50-250
Structure	Single layer	Multilayer or single	Multilayer
Excipients	Water-soluble polymers	Water-soluble polymers	Low-solubility or insoluble polymers
Pharmaceutical Phase	Solid or dissolved / dispersed	Drug molecules in solid or suspended form	Suspension, solid or dissolved / dispersed
Application area	Language	Buccal or gingival region	Other suitable areas in the gums or oral cavity
Dissolution	60 seconds	Gel consists in minutes	8-10 hours maximum
Effect	Local or systemic	Local or systemic	Local or systemic

Because of its ease of application and high effectiveness, it is not surprising that drugs in the form of thin-film dosage take a high market share. This technology attracts the attention of both old and newly established pharmaceutical companies. Important sales figures have been reached in the USA and European countries. While the pharmaceutical products market in oral thin film formulations was 500 million dollars in 2007, it was seen that this rate reached 2 billion dollars until 2010. Also, according to a research report, the thin film pharmaceutical products market in the world pharmaceutical market is expected to increase from \$ 7 billion in 2015 to over \$ 15 billion by the end of 2024. Therefore, it is estimated that there will be an increase of 117% in 10 years (Figure 2) (15).

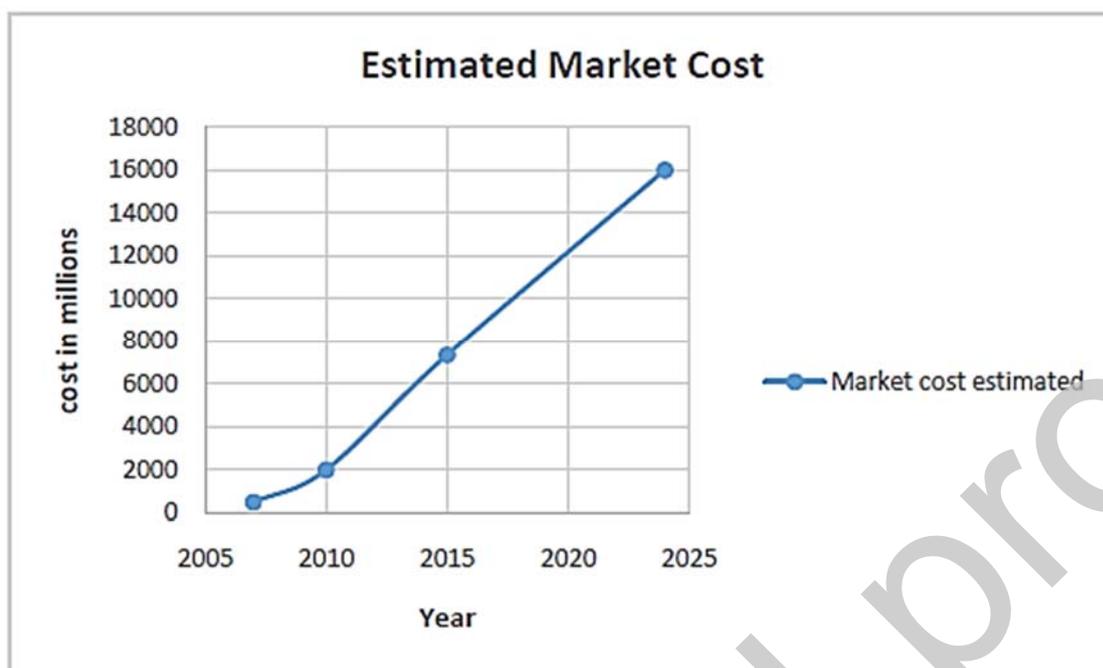


Figure 2. Estimated market shares of OTFs by years (15)

In Table 3 below, are a few examples of OTFs currently used in the world in and auxiliary substances used in OTF formulations in Table 4.

Table 3. OTC and prescription OTF examples used in the world (16, 17)

Trade Name	Year	Drug	Polymer	Plasticizer
OTC Products				
Listerine, PocketPaks [®] Oral Care Strips (Johnson & Johnson)	2001	Menthol	Pullulan	Glyceryl Oleate Macrogol
Sudafed [®] PE (Johnson&Johnson)	2005	Phenylephrine	Maltodextrin Pullulan Carragen	Glycerine
Theraflu [®] Day Time Thin Strips (Novartis Consumer Healthcare)	2004	Dextromethorphan Diphenhydramine Phenylephrine	Hypromellose (HPMC) Maltodextrin	Propylene glycol Macrogol
Gas-X Thin Strips [®] (Novartis Consumer Healthcare)	2006	Simethicone	Maltodextrin HPMC	Polyethylene glycol Sorbitol
Chloraseptic [®] Sore Throat Relief Strips (InnoZen)	2004	Benzocaine	Corn starch	Erythritol Macrogol
Supress Cough Strips [®] (InnoZen)	2005	Menthol	Carrageen Pectin Sodium alginate	Glycerine
Pedia-Lax [™] Quick Dissolve Strip	2008	Sennoside	HPMC	Glycerine

(C. B. Fleet)				
SpotScent Oral Care Strips® (Spotscent)	2003	Parsley seed oil	Modified cellulose	Glycerine
Orajel™ Kids Sore Throat Relief Strips (Church & Dwight Co.)	2007	Benzocaine	Pectin	Glycerine
Day Time Triaminic Thin Strips® Cough & Cold (Novartis Consumer Healthcare)	2004	Phenylephrine Dextromethorphan	HPMC	Polyethylene glycol
IvyFilm®, IvyFilm Kiddies® extract (Lamar-Forrester Pharma)	2016	Hedera helix	Pullulan	Glycerine
Benadryl® Allergy quick dissolve strips (McNeill-PPC)	2006	Diphenhydramine	Carrageen Pullulan	Glycerine
Prescribed Products				
Sildenafil Sandoz Orodispersible film® (Sandoz)	2014	Sildenafil	HHPMC	Glycerine
Sildenafil Orodispersible film (IBSA Farmaceutici Italia Srl)	2016	Sildenafil	Maltodextrin	Glycerine Polisorbat Propylene glycol Monocaprylate
Zuplenz® (Vestiq Pharmaceuticals)	2012	Ondansetron	HHPMC	Polyethylene Oxide Colloidal Silicon Dioxide
Risperidon HEXAL® SF Schmelzfilm	2010	Risperidone	HHPMC Maltodextrin	Glycerine

Table 4. Formulation components of OTFs: (1, 7)

Component	Amount	Examples
Active substance	5-30 %	Montelukast sodium, Ropinirol hydrochloride, Triclosan, Sertraline, Metoclopramide hydrochloride, Telmisartan, Dicyclomine hydrochloride, Tianeptin sodium, Amlodipine besylate, Livocyrizine dihydrochloride...
Film-forming polymer	40-50 %	Carbohydrates, proteins, cellulose derivatives
Plasticizer	0-20 %	Glycerin, PEG-400,300, Propylene glycol, Malic acid, Sorbitol, Castor oil, Triethyl citrate, Tributyl citrate, Triacetin etc.
Saliva stimulants	2-6 %	Ascorbic acid, Citric acid, Lactic acid, Tartaric acid and Malic acid.

Sweeteners	3-6 %	Natural (Sucrose, Mannitol, Sorbitol, Dextrose, Glucose, Liquid glucose, Fructose, Isomaltose etc.), Synthetic (Aspartame, Saccharin, Sucralose, Acesulfame-K, Cyclamate, Alitam and Neotame etc.)
Superdisintegrant	% 0-8	Sodium starch glycollate, Crosspovidone, Polacrillin potassium
Flavoring agents	qs.	Peppermint, Cinnamon, Clove, Lemon, Orange, Vanilla, Chocolate etc.
Surfactants	qs.	Sodium lauryl sulfate, Benzalkonium chloride, Polysorbate, Poloxamer 407 etc.
Coloring agents	qs.	Titanium oxide, Silicon dioxide, Zinc dioxide etc.

Active Ingredients Used in OTFs

The API must be dissolved for absorption to occur. If the active substance is very lipophilic, it is insoluble in the aqueous medium and absorption may not be at the desired level. Therefore, there is a delicate balance between the lipophilicity and solubility of the drug. The primary mechanism of drug absorption is passive diffusion. As a result, the partition coefficient, degree of ionization and molecular weight have a major influence on the transport of drugs across the oral mucosal membranes. The API's pKa and the degree of ionization at ambient pH must be taken into account for bioavailability. The degree of absorption is generally proportional to the lipophilicity or partition coefficient of the API. However, the solubility of the drug also acts a significant role. The non-ionize of the drug shows more lipid-soluble properties and therefore penetrates through diffusion through biological membranes (3, 14, 17).

There is no uniformity problem in the distribution of water-soluble APIs. However, water-insoluble APIs must be distributed homogeneously to have an acceptable content uniformity (7).

APIs to be used in OTFs: (7)

- It should be used in low dosage,
- The feeling and taste left in the mouth should be appropriate,
- It must have low molecular weight,
- It must be stable and soluble in saliva.

Its potential and therapeutic effectiveness are also important in the selection of the API. The most suitable APIs for OTFs are anticancer drugs, antiasthmatic, antitussives, antihistamines, antiepileptics, antianginal drugs, antiemetics, cardiovascular drugs, neuroleptics, analgesics, anxiolytics, antiallergic drugs, hypnotics, sedatives, antibacterial drugs, anti-Alzheimer's drugs, diuretics and expectorants (1, 14).

Film Forming Polymers Used in OTFs

The selection of polymers is one of the most critical and important parameters in the succeeding preparation of oral films due to their tensile strengths that depend on the type and amount of films used. According to the total weight of the dry film, at least 45% polymer by weight must be present, but 60-65% by weight of the polymer is chosen to achieve the desired properties. The polymers could be utilized combined or alone to achieve the desired film properties. Because of OTFs are rapidly dispersed and dissolved in the oral cavity that the film-forming polymers utilized have to be water-soluble. At the same time, the films obtained must be durable, which will not cause any damage during transport and storage (Table 5) (1, 7, 14).

The properties of an ideal polymer for OTFs: (1, 7, 14)

- The polymer used must be non-toxic, non-irritating,

- Should not be impurities,
- It must have enough wetting and spreading properties,
- It must have sufficient stress and tensile strength,
- It should be accessible and not too expensive,
- Shelf life should be reasonable,
- It should not make secondary infections in dental areas or oral mucosa,
- It should have a good feeling in the oral cavity,
- It must not be an impediment to the disintegration time.

Table 5. Common polymers utilized in OTFs (1, 7, 14, 18)

Component	Class	Examples
Natural	Carbohydrate	Pectin, Pullulan, Maltodextrin, Sodium alginate, Sodium starch glycollate
	Protein	Gelatine
	Resin	Polymerized resin (new film-forming)
Synthetic	Cellulose Derivatives	Hydroxy propylmethylcellulose (K50, K3, K15, E5, E3, E15), Carboxy methylcellulose, Methylcellulose (A3, A15, A6), Sodium carboxymethyl cellulose, Croscarmellose sodium (CCS), Microcrystalline cellulose
	Vinyl polymer	Polyvinylpyrrolidone (K90, K30), Polyvinyl alcohol, Polyethylene oxide
	Acrylic polymer	Eudragit (RL-100, 9, 10, 11, 12 and RD-100)

The combined use of different polymers provides specific properties to OTFs. For example, gelatins are different molecular weight, so that high-molecular-weight glossy and highly attractive films can be obtained using gelatins. Pullulan is often used to prepare a thin film with high mechanical strength and dissolution, also is stable at a wide range of temperatures. The mixture of high methoxy pectin (HMP) and chitosan or low methoxy pectin (LMP) results in a thin film that showed perfect mechanical strength. Film-forming polymers like methylcellulose, hydroxypropyl cellulose (HPC) and carboxymethyl cellulose (CMC) form a thin film that disperses and/or swells due to its hydrophilic structures that help to absorb water. The using combined polymers and the properties of the obtained OTFs are given in Table 6 (10).

Table 6. Combined polymers and the properties of the obtained OTFs (9)

Combined Polymers	Dispersion Time (seconds)	Appearance	Film Forming Capacity
HPMC E-15 + PEG 400	120	Transparent	Well
HPMC E-15 + Glycerine	92	Transparent	Well
HPMC K4M	-	-	Very Low
HPMC E-15 + Pullulan	-	-	Low
HPMC E-15 + PVA	78	Transparent	Medium
HPMC E-15 + PVP	67	Transparent	Medium
HPMC E-15 + PVA + MCC	-	-	Low

HPMC E-15 + MCC	42	Semi-Transparent	Best
PVA	52	Transparent	Medium
PVA + PVP + Glycerine	64	Transparent	Medium
PVA + PVP + PEG 400	52	Transparent	Medium
PVP	-	-	Very Low
Pullulan + PVA	-	-	Very Low
Gelatine	-	-	Very Low
Eudragite RL-100	-	-	Very Low
Pullulan + Guar Gum + Xanthan Gum + Carrageenan	19	Transparent	Very Well

Plasticizers Used in OTFs

Plasticizers help increase flexibility and lower Tg of the polymer, reducing the friability of the film. Plasticizers also increase tensile strength. Plasticizers must be compatible with the drug, solvent and polymer used. Sorbitol, mannitol, glycerin, diethyl phthalate, triethyl citrate, tributyl citrate, macrogol, propylene glycol, and citric acid esters are most commonly used (1, 7, 14, 16).

Table 7. Plasticizers used in OTFs and their ratios (7)

Polymer	Plasticizers	Concentration (w/w %)
HPMC, PVA	Glycerine	15 14-15
Maltodextrin	Propylene glycol	7-8
Lycoat NG 73, PVA, HPMC	Polyethylene glycol 400	25 7-8
Pullulan	Polyethylene glycol 4000	20-25

Surfactants Used in OTFs

Surfactants as dispersing or wetting agents, helping the film dissolve in a short time and release the API quickly. It is mostly preferred to use Poloxamer 407, sodium lauryl sulfate, and polysorbate (14, 16).

Sweeteners Used in OTFs

Natural and artificial sweeteners are used to increase the flavor of OTFs. Polyhydric alcohols like mannitol, sorbitol, maltitol, and isomalt are the most frequently used. In addition, polyhydric alcohols can be used combined to provide a good feeling and coldness in the mouth. Also, polyhydric alcohols do not have a bitter taste in the mouth after tasting and are less carcinogenic. The sweetening feature of most polyols except xylitol and maltitol are less than half of the sucrose (both have a similar sweetness of sucrose). The usage of natural sugars in these preparations is restrained in diabetic patients. For that reason, artificial sweeteners are most popular in pharmaceutical preparations and foods. In OTFs, aspartame and saccharin are commonly used as artificial sweeteners (7, 14, 16).

Saliva Stimulants Used in OTFs

Saliva stimulating agents increase saliva production rate and help break down formulations faster. Also, acids generally used in food production could be utilized as saliva stimulating

agents. Ascorbic acid, malic acid, citric acid, tartaric acid, and, lactic acid are some of the saliva stimulating agents (7, 16).

Superdisintegrants Used in OTFs

Superdisintegrants, when added to OTF formulations, provide rapid disintegration as a result of the combined effect of both water absorption and swelling. Superdisintegrants accelerate disintegration and dissolution by providing absorption and swelling owing to their excessive water absorption. Powerful interaction with saliva is very important for disintegration. Some of the commonly used superdisintegrants and their concentrations are shown in Table 8 (7, 14).

Table 8. Superdisintegrants used in OTFs and their concentrations

Superdisintegrants	Commercial name	Concentration (w/w %)	Disintegration Mechanism
Sodium starch glycollate	Explotab, Primogel	2 - 8	Fast water absorption and subsequent fast swelling
Crosspovidone	PolyplasdoneXL10	2 - 5	Absorption and swelling go together
Polacrillin potassium	Amberlite IRP 88 Indion 294	0,5 - 5	Fast water absorption and subsequent fast swelling

Coloring Agents Used in OTFs

FD&C approved colorants, EU approved colorants, natural coloring agents or pigments can be included in formulations up to 1% by weight (7).

Flavouring agents Used in OTFs

The choice of pleasant flavour depends on the type of API to be used. The admission of the dosage form by the patient as a result of oral disintegration or dissolution depends on the taste perceived within the first few seconds after the consumption of the OTF and subsequently at least 10 minutes in the mouth. Therefore, the choice of flavoring agent is extremely important. Flavouring agents which are frequently used in formulations are given in Table 9 (7, 17).

Table 9. Flavouring agents used to mask the dominant tastes in OTFs (7)

Dominant taste	Flavouring agents
Salty	Peach, Butterscotch, Maple, Vanilla, Apricot
Sour	Citrus, Raspberry, Licorice Root
Sweet	Fruit or Vanilla
Bitter	Chocolate, Anise, Mint, Walnut, Wild Cherry

Preparation Methods of OTFs (1, 7, 10, 17)

One of the following methods or combinations could be utilized in the preparation of oral dissolving/disintegrating thin films:

Solvent and Semisolid Casting Method

Solvent Casting Method is the most generally utilized method to prepare oral thin film because of its simple preparation, low processing cost, fast and easy to apply (10, 19). In brief, water-soluble components are prepared by mixing in a heated magnetic stirrer. Then, drug and other excipients are added to this mixture to obtain a viscous solution. The solution

prepared in this method is poured into a petri dish and allowed the solvents to evaporate. Depending on the solvent system used, these are kept for 20-25 or 24-48 hours at room temperature or 40-50 °C in the oven for a shorter period of time. The films obtained after evaporation of the solvents are 15-20 mm in diameter, 0,2–0,3 mm thick and carefully separated from petri dishes. Depending on the amount of active substance it contains, they are cut into pieces of the wanted size (1, 7). In the semi-solid technique, the semi-solid gel mass is poured into suitable molds and dried using gel-forming polymers. Then they are prepared by cutting in desired sizes (9, 19).

Solvent Casting Method Advantages and Disadvantages (1, 7, 10)

- The thicknesses uniformity of the films are good,
- Films are clear and bright,
- Creates a quite flexible film,
- Prepared film thickness is quite thin (12 - 100 µm),
- Offers better physical properties,
- The method cost is suitable,
- Compared to the 'Hot melt extrusion' method, APIs are not exposed to high temperatures and do not stability problems.
- The polymer selected should be soluble in water or in a volatile solvent,
- It should have a suitable viscosity.

Hot Melt Extrusion Method

Hot Melt Extrusion Method is a widely utilized method to formulate sustained-release tablets, granules, transmucosal and transdermal drug delivery systems. The mixture forming the formulation components is mixed and melted by means of an extruder with heaters. Finally, the melt is filmed by the molds (9, 19).

Solid Dispersion Extrusion

In this method, the solid dispersion is prepared by extruding the formulation components with the drug and then is made into the thin film with molds (19).

Rolling Method

The solvents commonly used in this method are water and/or water/alcohol mixture. Through the high shear processor, the active compound and other components are solved in a small amount of aqueous solvent. The viscous mixture is transferred onto the carrier roller and rolled. The resulting films are prepared by cutting in desired sizes, then dried in a controlled way (9, 19).

Characterization of OTFs

Within the scope of the characterization studies of the prepared OTFs various analyzes and measurements are carried out. Among these, organoleptic and morphological control, moisture absorption, swelling ability, flexibility (elongation), folding ability, pH determination, weight variability, thickness, flavor, content uniformity, dispersion, dissolution rate, release kinetics, degree of transparency, SEM, XRD, FT-IR, and DSC analyzes and measurements are located (20-22).

It is difficult to distinguish in OTFs due to the short periods of disintegration and dissolution processes. The American Association of Pharmaceutical Scientists / International Pharmacy Federation (AAPS / FIP) for OTFs has stated that the disintegration test can be utilized in place of the dissolution test utilized for ODTs. If the API is molecularly dissolved in OTF, the rate of API released is dependent just on the film's disintegration time. At the same time, if the API is dispersed at a particulate form in the film matrix, both the dissolution rate and disintegration time tests are recommended. While the European Pharmacopoeia has given disintegration time up to 3 minutes for ODTs, this time is recommended for 30 seconds or less according to the FDA (American Food and Drug Administration) and USP (American Pharmacopoeia) guidelines. Since the saliva volume in the mouth is less than 2 mL, these tests

are generally recommended in a small environment for disintegration testing in 2-7 mL of fluid under similar conditions prevailing in the oral cavity. OTF can be placed on the surface of the liquid in a petri dish, and the disintegration time can be determined utilizing a chronometer. In the meanwhile, petri dish can be continuously shaken to mimic the tongue's mouth movement. This method is simple and offers ease of application. Otherwise, it creates some difficulties and the process is very difficult to apply to automation (16).

Drug release from OTFs is usually carried out in an environment set at 37 °C (artificial saliva fluid or a pH 6.8 phosphate buffer) according to the pharmacopoeia requirements for solid oral dosage forms utilizing a pallet or basket apparatus. However, the dissolution apparatus has some disadvantages for OTFs. While using the basket apparatus, it may result in sticking to the edges and clogging of the basket pores, whereas in the use of the pallet apparatus, OTFs are probably stuck to the bottom or remain on the surface of the container in dissolution medium. Platinums and double-sided tapes are used to simulate adhesion *in vivo* and prevent swimming. To the bottom of the dissolution medium, each film is placed on a rectangular glass plate and fixed. As a consequence of fast disintegration, the drug is released very rapidly and specimens of the analyzed medium are taken in a short time (16).

In evaluating the taste-masking properties of OTFs, it can be determined *in vitro* using a dissolution test apparatus. *In vivo* testing with volunteers is the most safest, however ethically problematical. Before the experiment, four standard materials are used for volunteers and sensory sensitivity thresholds are assessed against flavors. These flavors are quinine (bitter), sodium chloride (salty), tartaric acid (sour), sucrose (sweet). Volunteers start by washing their mouths with distilled water firstly. Then they put an amount of pure drug and then a film specimen containing the same amount of drug into their tongue for 30 seconds. Then volunteers spit and rinse their mouth with water. For subsequent taste assessment, they are subjected to a numbered assessment: 0-tasteless, 1-some bitter taste, 2-moderate bitter taste, 3-very bitter taste (16).

There are many OTF studies in the literature used as an alternative to conventional drugs available on the market in the treatment of a wide range of diseases. Among the APIs used in these studies; Tramadol HCl, Chlorpromazine, Metoclopramide HCl, Lovastatin, Diclofenac Sodium, Palonosetron HCl, Zolpidem Tartarat, Bufotenin, Etoricoxib, Levocetizine Dihydrochloride, Leukotrin Receptor Antagonist, Cinitapride Hydrogen Tartarate, Meloxicam, Escitalopram, Phenylephrine HCl Ondansetron HCl, Fluticasone Propionate, Ergotamine, and Caffeine (4, 11-13, 23-36).

Evaluation of OTFs

- **Morphological and Organoleptic Control:** The color, homogeneity, transparency, smell, and texture of the OTFs are examined visually and sensually (23, 32). They should be evaluated especially in terms of taste and flavor characteristics (28, 31).

- **Moisture Absorption Capacity:** This test is carried out in high humidity conditions to control the physical stability and integrity of the films. After weighing the sample weights individually, they are placed in desiccators containing aluminum chloride solution and exposed to moisture for 3 days. Then the films are weighed and their % moisture absorption capacities are calculated with the formula below (1).

$$\% \text{ Moisture Absorption Capacities} = (\text{Initial Weight} - \text{Final Weight}) / (\text{Initial Weight}) \times 100$$

- **Tensile Strength:** Tensile strength is the maximum tensile force applied until the thin film specimen breaks. It is obtained by the divide of the applied force by the cross-section area of the film and multiplying by a hundred: (2)

$$\text{Tensile Strength} = (\text{Load at Failure} \times 100) / (\text{Film Thickness} \times \text{Film Width})$$

- **Percentage Elongation:** When a pulling force is applied, the tensile increases. This tensile continues until the integrity of the film form deteriorates. The percentage of elongation

can be determined by measuring the final size of the film before its integrity deteriorates. This rate increases as the amount of plasticizer enhances. Elongation percentages of OTF formulations are calculated by the formula below: (1, 2)

$$\% \text{ Percentage Elongation} = 100 \times (\text{Last Film Length} / \text{Initial Film Length})$$

- **Weight Variability:** 1×1 cm² films are cut from each formulation and are calculated by weighing them individually on a sensitive scale (31).
- **Thickness:** The thickness measurement is required as it is directly related to the quantity of drug in the OTF. At the same time, a suitable thickness is necessary for the comfortable application of the films. For example, the ideal thickness of buccal thin films should be between 50 and 1000 μm (10). For this purpose, at least 5 films from each formulation are measured from 5 different points and the results are given as mean and standard deviation (\bar{x} and SS) (7).
- **Flexibility (Folding Endurance):** The flexibility of thin films is determined by over and over folding a film at the same place at an angle of 180° until it breaks. The number of last folds before breaking is noted. The film, which exhibits 300 times or more folding endurance, is considered to have excellent flexibility (7, 10, 34).
- **Determination of pH Value:** Determining the pH of OTFs is important in terms of their solubility/dispersion in the oral cavity, taste properties and rapid release of the drugs. For this purpose, 1.5 - 2% (w/v) agar is added to the isotonic solution and dissolved. Then this solution is poured into a petri dish and waited until it forms a gel at room temperature. Thin film samples are placed on it. After that, pH papers with a pH range of 1-11 are touched to OTFs, and their pH is determined according to the change in the color of the paper (7, 31).
- **Determination of Swelling Degrees:** The swelling of the polymeric film is important in terms of measuring the water absorption capacities of OTFs and obtaining information about their resistance to water. Randomly selected OTFs are weighted individually and kept in simulated physiological fluid in a petri dish within the specified period. Then each film is weighed and measured at different time intervals until the increase in weight reaches a constant level. The degree of swelling is calculated using the below equation: (10)
$$\% \text{ Swelling Degree} = 100 \times (\text{Final Weight} - \text{Initial Weight}) / \text{Initial Weight}$$
- **Content Uniformity:** For content uniformity, each film is filtered after being dissolved in a suitable solvent and the drug content in each film is measured by the appropriate quantification method. It is expected that the % RSD is not more than 6% (7, 12).
- **Disintegration Test:** The disintegration time is described as the time (seconds) that a film disperses when it comes into touch with saliva or water. Disintegration time is when the thin film begins to disintegration or disperse. The weight and thickness of film act a significant role in determining the physical properties of water-soluble films (5).
 - The disintegration test apparatus specified in pharmacopoeias can also be used to determine the disintegration times of OTFs. Normally, the disintegration time of the film composition is usually 5 to 30 seconds and this is a phenomenon that varies according to the formulation content. There is no official guide to detect the disintegration times of films that break down fast (22).
- **Dissolution Rate Test:** In literature, many studies used Franz diffusion cells to test drug release from polymeric films while some improvisations were made on the apparatus to be used for dissolution rate testing (37). The biggest obstacle in dissolution rate assay is the placement of film specimens. In addition, various methods have been applied in the literature in which the dissolution rate of the film is adhered to the bottom of the glass container or the mixing apparatus using a double-sided adhesive band (Figure 3) (7).

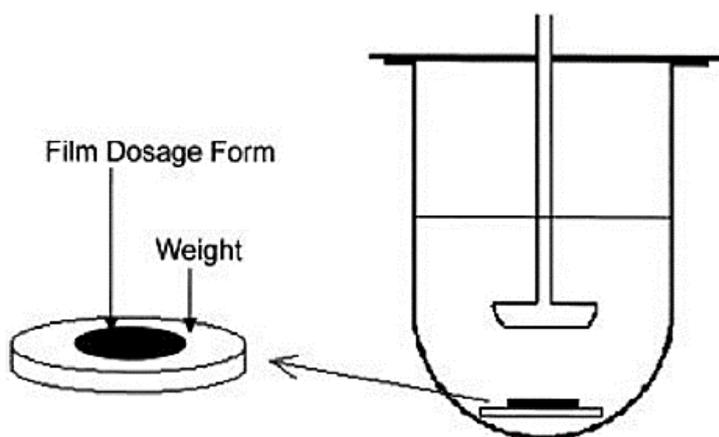


Figure 3. Modification of the disintegration test apparatus used in the evaluation of OTFs

- **Determination of Release Kinetics:** The dissolution results of all film formulations containing API in the pH 6.8 artificial saliva or pure water are applied to the computer program in order to determine the appropriate kinetic model. It is determined by mathematical programs and formulas that the formulations are compatible with 0. Degree, 1. Degree, Korsmeyer-Peppas or Higuchi models or not (26, 38).

- **Transparency:** The transparency of OTFs could be measured utilizing a UV spectrophotometer. OTF formulation specimens are cut rectangularly and placed inside the UV spectrophotometer cuvette. The permeability of the film is made at a wavelength of 600 nm. The following equation is used for the results obtained:(22)

$$\text{Transparency} = \log T_{600}/b$$

(T_{600} = Transmittance at 600 nm, b = Film thickness (mm))

- **Packaging:** Fast-dissolving film systems can be packaged in single packages, multiple blister packages and using a variety of options, such as multi-unit rolls. There are some patented packaging systems for OTFs in the pharmaceutical market at present (2).

- **Fourier Transform Infrared Spectroscopy (FT-IR):** Using FT-IR (ATR) spectrophotometer is measured and examined infrared spectra that all components entering the formulations to detect unwanted interactions between formulation components and the pure API (32).

- **Surface and Structural Morphology:** Surface and structural morphology are examined using a Scanning Electron Microscope (SEM). In this way, the presence of smoothness, surface roughness or pores and particle distribution can be determined (7, 28).

- **X-Ray Diffraction (XRD):** The X-ray diffraction analysis helps determine the crystal or amorphous nature of the drugs included in the films. In this way, it can be checked whether the drugs in the OTFs have undergone any changes in the preparation process of their conformational sequences and whether they have turned into its polymorphs if any (7, 28).

- **Differential Scanning Calorimetry (DSC):** DSC analysis is performed to demonstrate the compatibility of the drug with other auxiliary substances. The reference and sample are brought to the same temperature and the interactions in the sample are examined depending on the heat exchange (7). For this purpose, a certain amount of OTF sample is cut, placed in the alumina pan and analyzed under a certain mL of nitrogen atmosphere flow per minute (28, 34).

OTF's Stability

According to the ICH guidelines, the stability of OTFs is maintained under controlled conditions (25 °C temperature / 60% relative humidity and 40 °C temperature / 75% relative humidity) for 12 months. During storage, OTFs must be controlled for weight uniformity,

morphological properties, film thickness, tensile properties, water content and dissolution tests at certain time intervals (9, 23, 27).

CONCLUSION

Oral thin films emerged as a revolutionary trend, and most pharmaceutical companies in this field continue their research and development activities to adapt their drugs in various categories to this technology. This technology is an innovative drug delivery system for all patient groups who have swallowing problems, especially pediatric and geriatric patients. It also offers many advantages over the other dosage forms, such as improved bioavailability and faster effect. It is one of the most important dosage forms that can be used orally in cases of emergency and when the effect is desired to be started immediately. Therefore, it can be concluded that the OTFs with excellent patients compliance and many advantages have innovative futuristic opportunities.

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