



REVIEW ARTICLE

Oral thin films: an overview

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Abstract:

Oral thin films (OTFs) are the most advanced and promising new approaches for drug delivery as it offers more flexibility and comfort. These enable an ease of administration, as there is no need to drink high amounts of liquids or swallow large solid dosage forms. Also it improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. OTF offers an alternative to tablets, syrups or suppositories for the treatment of vomiting and nausea, especially for the pediatric population.

The oral thin-film technology is still in the beginning stages and but most popular because it fulfils all the need of patients. In due course, these formulations having APIs will be commercially launched using the oral film technology. These can be prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Water-soluble polymers are used as film formers for fast dissolving films. It seems that the value on the whole oral thin film market will grow significantly.

Keywords: Oral thin films, vomiting, nausea, hydrophilic polymers

Introduction:

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations of the intraoral dosage forms, quick dissolving dosage forms have gained much attention due to improved patient compliance and ease of administration.¹ Quick dissolving dosage forms include orally disintegrating tablets (ODTs), the only dosage form of this nature recognized by the FDA listed in the Orange book. The European Pharmacopoeia defines them as “orodisperse” tablets, which are to be placed in the mouth where they disperse rapidly before swallowing. The Centre for Drug Evaluation and Research defines ODT as “a solid form containing medicinal substances, which disintegrates rapidly, usually within seconds, when placed on the tongue”. Problems associated with conventional dosage forms like dissolution and bioavailability of drug molecules can be overcome with formulations intended for pregastric delivery².

Most of the introral dosage forms are intended to disintegrate, dissolve or release the drug in the oral cavity, where it has opportunity to be locally absorbed, in part or whole and alternatively may be swallowed and subsequently absorbed along the gastro-intestinal tract (GIT). Various types of intraoral dosage forms used to deliver drug systemically or locally include-

Liquids (solution sprays, syrups) Semi-solids (ointments, pastes)

Solid dosage forms (quick dissolve and slow dissolve tablets, sublingual tablets, lozenges, films, filaments, gums, patches, lollipops).

New dosage forms such as sprays, mucoadhesive patches or quick dissolving solid matrices using advanced manufacturing processes (i.e. lyophilized wafers, solvent cast films) have been introduced recently.

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A brief description of different types of intraoral dosage forms have been provided as described in table below ²-

Table 1: Different types of intraoral dosage forms

Dosage form	Description of the dosage form
Freeze dried wafers	A quick dissolving thin matrix consists of an active pharmaceutical agent (API) which does not require water for swallowing. This freeze dried dosage form when placed in the mouth disintegrates instantaneously, releasing the drug which dissolves or disperses in saliva. The saliva is
Orally disintegrating tablets(ODT)	A solid dosage form containing API that disintegrates rapidly, usually in minutes to seconds. It is placed on the tongue, where it releases the drug which dissolves or disperses in the saliva. The saliva is then swallowed and
Quick dissolving tablet	An oral tablet that requires no intake of liquid. The dosage form dissolves in less than a few minutes when placed in the mouth
Fast dissolving tablet	
Rapidly dissolving tablet	
Mouth dissolving tablet	
Fast melting tablet	
Orodispersing tablet	A tablet placed in the mouth where it disperses rapidly
Rapidly disintegrating	The tablet is placed in the patient's mouth and the saliva rapidly dissolves the tablet, releasing the API.
Or	

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Buccal gum	A non dissolving polymer matrix modified release dosage form containing the drug and other excipients that must be
Chewing gum	chewed but not swallowed to promote release of the drug from the dosage form in the oral cavity.
Buccal patch	A non dissolving thin matrix dosage form composed of one
Gingival patch	or more polymer films or layers containing drug and/or
Odontal patch	other excipients for specific delivery.
Buccal tablet	A modified release dosage form to be applied to the buccal cavity and that dissolves in the mouth, releasing the drug which is intended to be absorbed through the mucosal lining of the mouth without the need of water and should not be swallowed as a whole.
Sublingual tablet	A fast dissolving tablet intended to be kept below the tongue. The tablet dissolves slowly and the API is absorbed directly through the mucosa.
Spray	A unit actuation pump or aerosol spray for rapid drug absorption through buccal mucosa.
Quick dissolving film	A fast dissolving polymer film embedded with drug that
Quick dissolving wafer	melts and dissolves in the saliva of the oral cavity quickly and completely, releasing the drug for absorption through the oral mucosa. A fraction of the drug will be swallowed with the saliva and absorbed along the length of GIT.

Table 2: A list of Patented Technologies using manufacturing techniques is mentioned below³ -

Technology	Basis for technology	Company
Zydis	Lyophilization	R. P. Scherer Inc.
Quicksolv	Lyophilization	Janseen Pharmaceutica
Lyoc	Lyophilization	Farmlyoc
Flashtab	Multiparticulate Compressed Tablets	Ethypharm
Orasolv,Durasolv,	Compressed Tablets	Cima Labs Inc.
RapiTab	Compressed Tablets	Schwarz Pharma
WOWTAB	Compressed Molded Tablets	Yamanouchi Pharma Technologies, Inc.
Fast melt	Molding	Élan Corp.
Ziplets	Molding	Eurand
FlashDose	Cotton-candy process	Fuisz Technology Ltd.

Table 3: List of some patented products available in the market are indicated below in tabular form ³.

Patented technology	Products	Name of the company	Composition
Zydis	Claritin Reditab	R.P.Scherer/Schering Plough, Kenilworth, USA.	Micronized loratidine(10mg), citric acid, mannitol, gelatin, mint flavor
	Feldene melt	Pfizer Inc, NY, USA.	Piroxicam (10 or 20 mg), mannitol, gelatin, aspartame, citric anhydrous
	Maxalt- MLT	R.P.Scherer/Merck & Co.,NY, USA	Rizatriptan (5 or 10 mg), mannitol, gelatin,aspartame, peppermint flavor
	Zyprexa	R.P.Scherer/Eli Lilly, Indianapolis, USA.	Olanzapine(5,10,15or20mg), mannitol,gelatin, aspartame, methyl paraben sodium, propyl paraben sodium
	Zydis		
	Pepcid RPD	Merck & CO., NY, USA	Famotidine (20 or 40 mg), mannitol, gelatin, aspartame
	Zyprexa Zydis	R.P.Scherer/Eli Lilly, Indianapolis, USA.	Olanzapine(5,10,15or20mg), mannitol,gelatin, aspartame, methyl paraben
	Zofran ODT	R.P.Scherer/ Glaxo Wellcome, Middlesex, UK.	Ondansetron (4 or 8 mg), mannitol, gelatin, aspartame, methyl paraben sodium, propyl paraben sodium, strawberry flavor
Orasolv	Remeron	CIMA/Organon, Glaxo Wellcome, Middlesex, UK	Mirtazepine (15,30, or 45 mg), mannitol, aspartame, citric acid, cross povidone, avicel, sodium bicarbonate, HPMC, magnesium
	Soltab		
	Tempra FirstTabs	CIMA/Mead Johnson, Bristol Myers Squibb, NY, USA.	Acetaminophen (80 or 160mg), inactive ingredients including mannitol (currently available in Canada)
Durasolv	Nulev	CIMA/Schwarz Pharma	Hyoscyamine sulphate (0.125mg), aspartame, colloidal silicon dioxide, cross povidone, mint flavor, magnesium stearate, mannitol, avicel
Durasolv			

Zoming ZMT	CIMA/ Astra Zeneca, Wilmington, USA.	Zolmitriptan (2.5mg), mannitol, aspartame, citric acid anhydrous, cross povidone, avicel, sodium bicarbonate, magnesium stearate, colloidal silicon dioxide, orange flavor
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1.1.1 Advantages of orally thin film/ tablets (OTF/ODT)

The administration of ODT may not compulsorily result in a faster therapeutic onset, but can overcome problems faced by pediatric and geriatric patients in swallowing conventional solid dosage forms. The following are the advantages of an ODT formulation:

- Improved patient compliance which allows patients to easily swallow the dosage form for systemic absorption through rapid dissolution or disintegration in the oral cavity
- Improved patient convenience to carry and administer dosage forms especially when traveling.
- Rapid absorption and onset of action of rapid disintegrating/dissolving dosage forms.
- Avoidance of first pass effect which improves bioavailability.
- Elimination of water
- Improved stability compared to liquid dosage forms
- Extends product life cycle by providing product differentiation.

1.1.2 Limitation of ODT-

The major limitation of ODT is the low amount of drug that can be incorporated in each dose. For lyophilized dosage forms, the drug dose must be generally less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs ².

Various technologies are used in the production of quick-dissolving tablets which includes DuraSolv and OraSolv technologies. The taste of the active ingredient is masked by the use of an appropriate coating over the drug particles and by the incorporation of effective flavoring agents and an artificial sweetener^{4,5}.

1.1.3 Technologies used in the production of quick dissolving tablets have been mentioned in brief below-

OraSolv:

OraSolv technology is characterized by relatively soft tablets which disintegrate rapidly and the constituents partially dissolve in the mouth by the action of saliva. The partially dissolved excipients and powder are swallowed with the saliva. Chewing is not desired to obtain rapid breakdown of the tablet. Effervescent excipients are added to promote rapid disintegration while also assists taste masking. On the other hand the DuraSolv tablets, dissolves rapidly without pronounced disintegration. The reason for it may be the presence of a large proportion of fast-dissolving excipients present in fine particle form. Incorporation of wicking agents promotes the process of rapid uptake of saliva into the tablet.

Quick disintegration is achieved by compressing water-soluble excipients using a lower range of compression forces than is normally used in conventional tableting. The time for the disintegration of OraSolv tablets within the oral cavity varies from 6 to 40 sec, depending largely on tablet size and the compression force used to form the tablet. The low compression force leads to high tablet porosity that, in turn, accelerates the rate of disintegration of the tablet and dissolution of the water-soluble excipients.

The active ingredients can be taste masked using a variety of techniques such as fluid bed coating, microencapsulation, or spray congealing. The type of taste-masking technique to be used is decided by the properties of the active pharmaceutical ingredient such as physicochemical properties and physical form. The unpleasant taste of active pharmaceutical ingredient can be reduced by minimizing drug dissolution within the oral cavity. However, the product should be totally dissolved in the gastrointestinal tract. Therefore, the taste-masking process must meet the two opposing requirements: insignificant dissolution in the oral cavity and maximum dissolution in the gastrointestinal tract. The manufacture of tablets

is done by a direct compression technique using conventional blending equipment and high-speed tablet presses. As the OraSolv tablets are produced at low compression forces, they are soft and friable. To reduce friability of the tablets, a specially designed packaging system is used. This specially designed package and processing system protects the OraSolv tablets from breaking and attrition during the rigors of shipping.

DuraSolv:

DuraSolv is CIMA's second-generation fast-dissolving tablet technology. This technology provides quick-dissolving tablets along with robust nature. The DuraSolv tablets consist of water-soluble excipients and are manufactured similar to Orasolv tablets using direct compression techniques. However, DuraSolv utilizes nondirectly compressible diluents in fine particle form. Diluents used have a high surface area, which increases dissolution rate. The incorporation of a high proportion of such diluents causes the tablet to "melt" or dissolve rather than disintegrate. Wicking agents assist the entry of water into the body of the tablet whereas swelling disintegrants are avoided.

WOWTAB tablets

It refers to "Without Water Tablet" (WOWTAB) technology developed by Yamanouchi Pharmaceutical Co. Ltd., Japan. WOWTAB tablet possesses sufficient hardness to maintain physical and mechanical integrity of the dosage form prior to contact with saliva. When placed in the oral cavity it rapidly becomes soft by absorption of saliva and disintegrates or dissolves within 15 to 20 seconds. The disintegration or dissolution is more quick when pressure is applied between the upper jaw and tongue or a licking movement is provided to the tablets. Conventional granulators, standard tablet compression machines are used for manufacturing.

The combination of poorly compressible saccharides such as lactose, mannitol, glucose, sucrose, and xylitol having a high dissolution rate with good compressible saccharides such as maltose, maltitol, sorbitol and lactosucrose having a slow dissolution rate is employed to achieve quick dissolution and adequate hardness of WOWTAB. The poor compressible saccharides have a hardness of less than 2 kg and good compressible saccharides have hardness above 2 kg when compressed under pressures of 10 to 50 kg/cm² per punch. Both water-soluble and water-insoluble drugs can be included in WOWTAB products.

ZYDIS tablets:

R.P. Scherer Corp. has developed and commercialized various quick dissolving products based on Zydis technology. The Zydis dosage form is a freeze-dried tablet made from excipients, which does not require water to aid swallowing. When placed on the tongue, the tablet disintegrates, instantaneously releasing the drug in the mouth. The drug in Zydis dosage form is physically entrapped or dissolved within the matrix of the fast-dissolving carrier material. The matrix of this fast-dissolving tablet is composed of glassy amorphous excipients that impart strength and hardness during handling of the tablet. Polymers such as gelatin, dextran, alginates, and saccharides such as mannitol or sorbitol are the examples of excipients used in Zydis fast dissolving tablets. The porous structure, poor crystallinity, and freeze-dried matrix are necessary attributes to achieve fast-dissolving tablets.

The dose of water-insoluble drugs in Zydis products is generally less than 400 mg to maintain the fast dissolving characteristics of the product. This limitation of drug loading also minimizes the taste of the drug in the mouth as the tablet dissolves in the saliva. To prevent sedimentation of drug and excipients during the manufacturing process, the particle size of insoluble drug and excipients should be less than 50 microns. Small particle size reduces the sensation of a gritty texture in the mouth and pharynx during swallowing. The dose of water-soluble drugs is limited to about 60 mg due to incompatibility with the freezing and drying process.

1.1.4 Classification of intra oral dosage forms ¹

Dosage forms targeted for delivery to the intraoral cavity can be classified in terms of their dissolution or disintegration kinetics as either-

1. Quick dissolving(QD)
2. Slow dissolving (SD)
3. Non dissolving (ND)

These dosage forms release the drug over a period of seconds up to 1 minute, 1 to 10 minutes and >10 minutes to hours respectively.

These IODs may be designed for local release in the mouth or to the GIT for subsequent absorption.

1. Quick dissolving delivery systems (QD): They undergo disintegration or dissolution in the saliva generally within a few seconds to a minute releasing the drug and inactive ingredients into the oral cavity. The major amount of the drug will eventually be swallowed with the saliva and transported along the GIT where the drug is subsequently absorbed.

Advantages of these dosage forms are-

- Ease of swallowing
- Administration without water anywhere and anytime
- Quick onset of action

Therapeutic categories of drugs for QD include non opioid analgesics, opioid analgesics, anti-migraine, cough and cold, GI, cardiovascular and CNS related drugs.

2. Slow dissolving delivery systems (SD): They dissolve in the oral cavity within 1 to 10 minutes and include the following products: chewable tablets, sublingual tablets, lollipops, mucoadhesive tablets and buccal tablets.

3. Non dissolving delivery systems (ND): They do not dissolve entirely when placed in the mouth and can provide for controlled drug delivery from 10 min to several hours and up to a day or longer. Examples of ND include the following dosage forms: chewing gums, buccal and gingival patches, periodontal fibers and drug delivery devices.

1.1.5 The quick dissolve or fast dissolve market comprises of the following technologies-

1. Lyophilized wafers

Cardinal Health (Zydis® Technology) and Biotron (Kryotab™ technology) technologies were developed on the principle of lyophilization or freeze drying that result in fragile porous wafer like tablets. Lyophilization is an expensive and time consuming process that requires specialized processing equipment to mold the unit dose in a blister pouch and requires more processing time. Resultant product is very fragile that can not be packaged in a bottle.

2. Orally disintegrating tablets (ODTs)

These technologies were developed by number of companies which include Biovail (FlashDose® technology), Cima labs (Orasolv®, Durasolv®), Elan (fast melt formulation technology), Ethypharm (Flashtab® technology) and Eurand (Ziplets® technology). These technologies are based on either in situ moulding of the dosage form in a unit dose blister pouch or conventional high speed tableting operations. These dosage forms are less fragile than lyophilized dosage forms and can be packed in multidose bottles.

3. Oral thin films and strips

These films and strips have been developed as a means to quickly release an active agent upon placing the strip on the tongue. Thin film and strip have been developed by several companies including LTS Lohmann Therapie Systeme AG, Zengen Inc., and Lavipharm Laboratories and are based on a unique solution coating process where the formulation is dispensed and metered to a controlled thickness on a moving web and dried in precision temperature controlled multi-zone ovens, die cut and packaged. The films are generally thin flexible strips (2 x 3 cm²) and can be packaged in multidose containers or individually packed.

4. Quick dissolve products

Many quick dissolve products have been developed and those that are categorized as ODT products in the US markets. These are based on various technologies and include products based on the Durasolv, Orasolv, Flashtab and Zydis technologies. Most of these drugs are product line extensions of already approved conventional tablet dosage forms and primarily offer patient convenience. QD products provide advantage where patient compliance is a problem such as conditions of depression and schizophrenia.

5. Intra oral liquid delivery technology

A number of liquid unit dose and metered spray IODs have been developed. Lingual aerosol and pump spray formulations developed by Flemington Pharmaceutical Corp. release nitroglycerin in the form of a fine mist into the mouth for immediate absorption into the blood stream via mucosal membranes.

Oral thin films (OTF) have recently acquired great importance due to their properties such as quick disintegration and dissolution, obviating need of water for disintegration and especially suitable for pediatric and geriatric patients. Orally disintegrating tablets (also called quick disintegrating tablets, mouth dissolve tablets) are the most common and widely used rapidly dissolving dosage form^{1-2,6-8}.

Fast-dissolving drug delivery was pioneered by scientists at Wyeth Laboratories in the UK during the late 1970s, which resulted in patenting of the “Zydis” drug delivery system (4). Fast-dissolving drug delivery systems can be manufactured by a variety of technologies, including direct compression, wet granulation, freeze drying, spray drying, vacuum drying and use of superdisintegrants^{1-2,6-8}.

An ideal rapidly dissolving drug delivery system should have following properties:

- High stability
- Transportability
- Ease of handling and administration
- No special packaging material and/or processing requirements
- No water necessary for application and pleasant taste.

1.2 Rapidly dissolving films (RDF)

Oral film strips have hit the mainstream in the last few years as a new way of freshening the breath. The wafers are slipped into the mouth and dissolve quickly to release the mint flavour^{1,2}.

The product attributes that a patient today seeks in a dosage form are-

- Better portability
- Ease and accuracy of dosing
- Overall convenience

These films generally dissolve within seconds to release the active agents but can be modified to release the drug more slowly depending upon film thickness and selection of the polymer matrix. A film or strip can be defined as a dosage form that employs a water dissolving polymer which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or in

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the oral cavity to provide rapid local or systemic drug delivery. Drug release may be either quick or slow by varying the rate of dissolution of the films. The breath freshening strip was created by Pfizer's Warner-Lambert's consumer healthcare division, which launched Listerine PocketPaks™ in 2001. Chloraseptic relief strips were the first oral thin film product to incorporate a drug and were introduced in the United States in September, 2003 by Prestige Brands international for relief of sore throat. Zengen Inc developed this new delivery technology, which is a medicated oral strip structured as a proprietary bilayer system. These films typically contain water soluble hydrocolloids such as HPMC, pullulan, pectin, carboxymethyl cellulose, an effective dose of active agent, other additives such as flavoring agents, plasticizers and preservatives. The disintegration and dissolution characteristic of thin film is dependent on thickness and combination of hydrocolloids.

RDF are already being used in breath freshening product introductions from Warner Lambert and Wrigley's in the USA and Europe, and Boots in the UK, as well as vitamin products. Consumers have now been exposed to this concept through the introduction of multiple breath-freshening products introduced over the past 2 years, and the trend is now towards developing over the counter (OTC) and prescription products in this delivery form. The delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oramucosal absorption or, with formula modifications, will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed⁹⁻¹⁸.

The benefits of film over conventional delivery systems are numerous:

- Faster absorption into the bloodstream;
- More portable than syrups and tablets;
- Easy to administer;
- More cost-effective than conventional tablet solutions.

The key advantage for rapidly dissolving film is patient compliance and convenience. The main drawback is with drug loading. Drug loading is generally limited to roughly 20 mg. This problem can be addressed by increasing the thickness of the strip, but that in turn may change the dosage

form to slowly dissolving film. But drug companies have been interested in this technology as it provides fast, accurate dosing that is expected to increase compliance, particularly among children. There is no need for water or measuring, and upon melting, the dose of medicine is swallowed. The likely candidates for rapidly dissolving films or oral thin films are nicotine replacing its transdermal delivery, antiulcer drug and antihistamine products. Prescription products, antipsychotic and sleeping disorder drugs are the potential candidates⁹⁻¹⁸.

1.2.1 Manufacture:

One or a combination of the following processes may be used to manufacture the RDF (4)-

- Hot-Melt Extrusion
- Solid Dispersion Extrusion
- Rolling
- Semi-Solid Casting
- Solvent Coating

1.2.1.1 Solvent casting method

The current most preferred manufacturing process for fabricating RDF is the solvent casting. In this method, water-soluble hydrocolloids are completely dissolved in water in a mixing tank to form a homogenous viscous solution. Other ingredients, including active agents, are dissolved in small portions of the aqueous solvent using a high-shear processor. The active mixture is then added to the viscous hydrocolloid solution to form a homogenous viscous solution. This viscous solution is degassed under vacuum. The resulting bubble-free solution is coated on a non-treated casting film with a typical coating thickness of 5 to 20 mil. (1 mil= 25.4 μ m) The coated film is subsequently sent into an aeration-drying oven. The dry film is then cut into the desired shape and size for the intended application.

Polymers used to prepare quick dissolving films include Hydroxypropylmethyl cellulose (HPMC), Hydroxypropyl cellulose (HPC), pullulan, sodium alginate, pectin, Carboxy methyl cellulose (CMC), Polyvinyl alcohol (PVA). By carefully balancing the mechanical

properties, solubility rate, taste and mouth feel for the film strip, these polymers can be employed to design quick dissolve strips. By controlling the molecular weight distribution (MWD) of the film matrix, the properties can be optimized. Usually when designing quick dissolve strips, a polymer with low MWD or viscosity such as HPMC E5 or pullulan PI-20 is employed. When the desired physical properties are not obtained using a single low viscosity polymer, mixing various grades of polymers may overcome this problem. When mixing a high viscosity polymer with low viscosity polymer, the quick-dissolve strip will generally have mechanical properties similar to high molecular weight polymer and the solubility rate will be similar to the low molecular weight polymer¹⁸.

1.2.1.2 Hot melt extrusion (HME)^{19,20}

This method is commonly used to prepare granules, sustained release tablets; transdermal and transmucosal drug delivery system. Processing films by this technique, involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting technique.

Advantages of hot melt extrusion for film formation include-

- Neither solvent nor water is used in the process
- Fewer processing steps are needed; time consuming drying steps are eliminated.
- No requirement on the compressibility of the active ingredients.
- More uniform dispersion of the fine particles due to intense mixing and agitation causing suspended drug particles to deaggregate in the molten polymer
- The bioavailability of the drug substance could be improved when it is dispersed at the molecular level in hot melt extruded dosage forms.

The equipment used for hot melt extrusion consists of extruder, downstream auxiliary equipment and monitoring tools. Extruder is composed of a feeding hopper, barrel, screw, die, screw-driving unit and heating/cooling device. Producing thin films for transdermal/transmucosal drug delivery and wound care is via film casting from aqueous or organic solvents. Repka et al studied the influence of Chlorpheniramine maleate on topical HPC films by hot melt extrusion

technique. Chlorpheniramine has been reported to function as an effective plasticizer, increasing percent elongation and decreasing tensile strength in concentration dependent manner. Chlorpheniramine also acted as a processing aid in the extrusion of hot melt films and allowing film processing at lower temperature ¹⁸.

The HME process has recently gained acceptance in the pharmaceutical industry. Building on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers, and plasticizers into various final forms to achieve desired drug- release profiles. The benefits of using HME over traditional processing techniques include:

- fewer unit operations;
- better content uniformity;
- an anhydrous process;
- dispersion mechanism for poorly soluble drugs;
- a low energy alternative to high-shear granulation;
- less processing time compared with conventional wet granulation.

A few challenges in the formulation of RDF are that in order to maintain its fast- dissolving characteristics, the thickness of the film should be carefully controlled. Therefore, its drug loading capability is limited. Overcoming the unwanted taste of certain active ingredients can be a challenge to the formulator. The extent of these challenges depends on the size of the dose; the desired release profile and desired absorption kinetics. Although these products offer increased convenience, as with every medication there are certain dangers. It has been reported that those patients taking diphenylhydramine containing products should be counseled regarding the drowsiness effects it is likely to produce and cautioned about driving. Since patients will now be able to carry the medication with them at all times and these products resemble similar dosage form i.e. breath fresheners, patient may be tempted to go above and beyond normal recommended dose. Patient should be counseled not only regarding possible side effects, but also cautioned about using the product incorrectly.

Table 4: List of marketed films containing Active Pharmaceutical Ingredient (API) ¹¹

Product	Company	API	Use
Chloraseptic relief strips	Zengen	Benzocaine	Local anaesthetic, pain relief
Quick-Dis	Lavipharm		
Triaminic	Novartis	Dextromethorphan	Cold/allergy
Theraflu	Novartis	Diphenhydramine HCl	Cough suppressant
Spiderman	Aquafilm	Vitamin	Vitamin supplement
Sudafed	Pfizer	Phenylephrine	Nasal decongestant
Listerine pocketpak	Pfizer	Menthol	Mouth freshener
Orafilm	Apothecus	Benzocaine	Pain relieving strips
Benadryl	Pfizer	Diphenylhydramine	Cough and allergy

1.3 Taste masking

Bitterness reduction and its inhibition are important requirements of an ideal oral dosage form. Various methods for bitterness reduction and inhibition have resulted in improved taste acceptability of these formulations. Development of oral pharmaceuticals as replacement for parenteral peptides may become more common if bitterness can be reduced to certain extent.

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Some amount of success has been achieved in the development of taste-masked formulations in recent years.

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness or saltiness^{21,22}.

Various techniques available for masking bitter taste of drugs include-

1. Taste masking with ingredients such as flavors, sweeteners and amino acids
2. Polymer coating and conventional granulation
3. Ion exchange resins
4. Spray congealing with lipids
5. Formation of inclusion complexes with cyclodextrins
6. Freeze drying process
7. Preparing multiple emulsions
8. Miscellaneous: Using gelatin, gelatinized starch, liposomes, lecithin, surfactants, salts or polymeric membranes.
 1. Taste masking with ingredients such as flavors, sweeteners and amino acids: This is the simplest and commonest approach used for taste masking.
 2. Polymer coating and granulation: Coating provides a physical barrier to the drug particles which minimizes interaction between drug and taste buds.
 3. Ion exchange resins: Ion exchange resins provide taste masking by complex formation.
 4. Spray congealing with lipids: Lipids and lipophilic vehicles are used to provide taste masking property.
 5. Formation of inclusion complexes with cyclodextrins: The drug molecule fits into the cavity of complexing agent forming a stable complex.

6. Freeze drying process: Zydis and Lyoc technologies provide fast dissolving and taste masking property to the dosage form.
7. Multiple emulsions: By providing entrapment of bitter component into the emulsion, taste masking can be achieved.
8. Miscellaneous: Using gelatin, gelatinized starch, liposomes, lecithin, surfactants, salts or polymeric membranes taste masking can be achieved.

1.3.1 Taste making with flavors, sweeteners and amino acids ^{21,22}

Use of sweeteners and flavors is the simplest and commonest approach for taste masking especially in chewable tablets, paediatric and liquid formulations. But it is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with taste masking techniques for improving characteristics of the dosage form. Cooling effect of taste masking agents such as menthol reduces the bitterness of the drug. Menthol also produces anti-caries effect. Combination of citric acid and sodium bicarbonate with certain flavors masks the bitter taste of certain drugs like chlorpheniramine maleate and phenylpropanolamine. Aspartame is used as prominent sweetener in providing bitterness reduction. 0.8% concentration of aspartame is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose and mannitol have also exhibited taste masking properties of caffeine.

1.3.2 Taste masking by inclusion complexation ^{21,22}

The drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs as high dose drug requires significantly higher amount of complexing agents. Cyclodextrins (CDs) possess lipophilic inner cavities and hydrophilic outer surfaces and are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes (Figure 1.1). They are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α -(1, 4) glucosidic bonds. The CDs are available in 3 different natural forms as α -, β -, and γ -CDs containing 6, 7, or 8 glucose units respectively. Each CD

differs in its ring size and solubility. Of the 3 naturally occurring CD, the cavity size of α -CD is insufficient for many drugs and γ -CD is expensive. β -CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs. β -cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch. But it has limited application due to low aqueous solubility and nephrotoxicity. Chemically modified CD derivatives have been prepared with a view to extend the physicochemical properties and inclusion capacity of parent CDs. Several amorphous, noncrystallizable CD derivatives with enhanced aqueous solubility, physical and microbiological stability, and reduced parenteral toxicity have been developed by chemical modification of parenteral CDs.

The strong bitter taste of carbetapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin. Palatable ibuprofen solutions are prepared by forming a 1:11 to 1:15 inclusion complex with ibuprofen and hydroxypropyl β -cyclodextrin (HP- β -CD) respectively. The complex masked the bitter component but created a sore taste that was masked by sweeteners. The disadvantage of the technique is only low dose drug are suitable for this method.

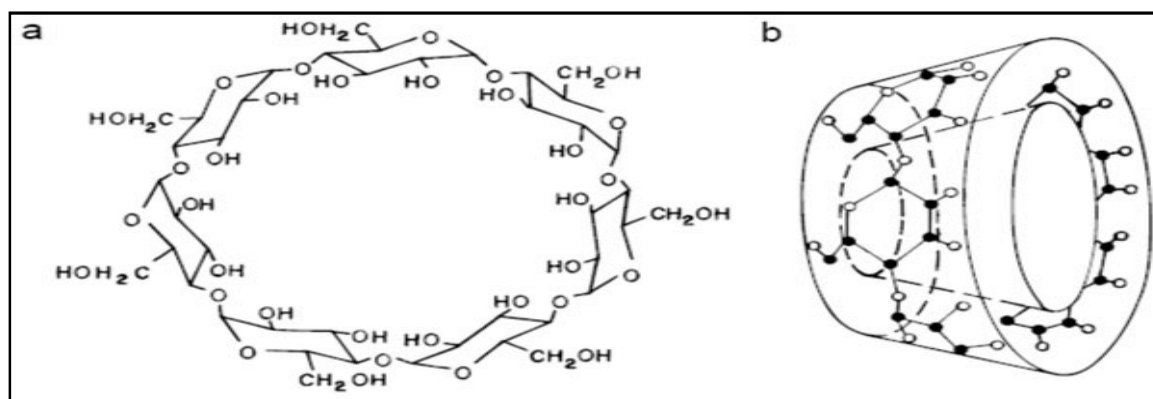


Figure 1.1 The chemical structure (a) and the toroidal shape (b) of the cyclodextrin molecule

1.3.3 Taste masking by ion exchange resins²³⁻²⁵

Ion-exchange resins (IERS) are high molecular weight polymers with cationic and anionic functional groups. They can exchange their mobile ions of equal charge with the surrounding

medium. Synthetic IER have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950s. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets, and mask bitter taste of the drug. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution.

Ion exchange resins contain positively or negatively charged sites are accordingly classified as either cation or anion exchanger. They are further classified as inorganic and organic resins. Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. Due to high molecular weight, they are not absorbed by the body which makes them safe. The most frequently employed polymeric network is a copolymer of styrene and divinylbenzene (DVB).

1.3.3.1 Classification of ion exchange resins-

Ion exchange resins can be classified into four major groups:

1. Strong acid cation-exchange resin.
2. Weak acid cation-exchange resin.
3. Strong base anion-exchange resin.
4. Weak base anion-exchange resin.

Strong acid cation resins (sulfonated styrene-divinylbenzene copolymer product) function throughout the entire pH range and can be used for masking the taste of basic drugs. Weak acid cation exchange resins function at pH values above 6.0. Similarly, strong base anion-exchange resins function throughout the entire pH range and can be used for masking the taste of acidic drugs, while the weak base anion exchange resins function well below pH 7.0. Polystyrene

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matrix cation-exchange resins (Indion CRP-244, Indion CRP-254) have been reported to mask the bitter taste of chlorpheniramine maleate, diphenhydramine HCl, ephedrine HCl, noscapine HCl, and amphetamine sulphate. Amberlite IRP-69, a cation-anion exchange resin, is used to mask the bitter taste of buflomedil. Oral liquid products of quinolones (orbifloxacin) and/or their derivatives are formulated using ion exchange resins, such as methacrylic acid polymer crosslinked with divinylbenzene, as the carrier. The formation of a quinolone-resin complex (resinate) eliminates the extreme bitterness of the quinolones to make the liquid oral dosage form palatable.

Table 5: List of commercial resins available

Type	Exchange species	Polymer backbone	Commercial resins
Strong cation	-SO ₃ H	Polystyrene DVB	Amberlite IR 120 Dowex 50 Indion 244
	-SO ₃ Na	Sodium polystyrene	Tulsion T344 Amberlite IRP 69 Indion 254
Weak cation	-COOH	Methacrylic acid DVB	Amberlite IRC 50 Indion 204 Tulsion 335 Tulsion 339
	-COOK		Amberlite IRP88
Strong anion	-NR ₃	Polystyrene DVB	Amberlite IR 400 Indion 454 Duolite AP 143
			Amberlite IR 4B Dowex 2
Weak anion	NR ₂	Polystyrene DVB	

Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins. Drug resin complex dissociation does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odor of the drug. Use of ion exchange resins to taste mask the bitter drugs is a relatively new concept. Many bitter drugs have amine functional groups which causes obnoxious taste. The functional groups are blocked by complex formation which reduces bitterness drastically.

Drug-resinate (complex between resin and drug) can be prepared by 2 methods-

1. Batch process
2. Column process

Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution.

1.3.4 Taste masking with lipophilic vehicles^{21,22}

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminium silicate and then melt-granulated. The taste of cimetidine can be improved by granulating it with glyceryl monostearate. Gabapentin (acyclic amino acid, a drug for seizures) has improved taste when coated with gelatin and then mixed with partially hydrogenated soybean oil and glyceryl monostearate.

1.3.5 Taste masking by coating with hydrophilic vehicles

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing

acceptable bioavailability. A specialized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

Carbohydrates (Cellulose)

The taste of orally administered drugs can be masked by coating the drug with carbohydrates. e.g. pinaverium bromide has no bitter taste when formulated by polymer coating with a mixture of cellulose or shellac and a second film forming polymer soluble at pH less than 5. Methacrylic acid copolymer (Eudragit) coating provides taste-masked characteristics to the drug and its tablet. Coating of ethyl cellulose, cellulose, shellac, Eudragit, HPMC and related polymers is done to provide taste masking property. Various drugs can be taste masked with celluloses and/or starches containing carboxymethyl(CM) groups such as carboxymethyl cellulose (CMC), sodium CMC, and sodium CM starch. Drugs coated with a water insoluble polymer e.g. ethyl cellulose offer taste masking and reduced dissolution profiles. Pharmaceutical granules with bitter taste are coated with water-soluble polymers of hydroxypropyl methylcellulose and sugars such as sucrose and lactose to decrease the bitter perception at the time of administration.

Various forms of proteins have been used extensively for taste masking. e.g. Prolamine. Number of antibiotics, vitamins, dietary fibers, analgesics, enzymes, and hormones have been effectively taste masked using prolamine coatings. Prolamine coating does not affect the immediate bioavailability of the active substance. Hydrolyzed gelatin has been found to provide an improvement in taste and mouth feel when incorporated into small amounts in chewable tablets containing ingredients for taste masking. The unpleasant taste of certain drugs can be masked by microencapsulation followed by tablet formulation. Microencapsulation can be performed by simple coacervation method using gelatin. Cross-linked gelatin via glutaraldehyde and Eudragit resin L100, S100 and E100- coated microcapsules are effective in masking the bitter taste of clarithromycin and preventing its release under simulated storage conditions.

1.3.6 Effervescent agents

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. The formulations containing the drugs in combination with effervescent agent(s) promote absorption in the oral cavity and mask their bitter taste.

1.3.7 Rheological modification

Viscosity enhancement with rheological modifiers such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Xanthan gum (0.1–0.2%) and microcrystalline cellulose (0.6–1%) are used to reduce bitter taste of acetaminophen suspension. Polyhydric alcohol such as polyethylene glycol or polypropylene glycol with polyvinyl pyrrolidone, gum arabic, or gelatin also provide rheological modification thus providing taste masking. An aqueous solution of tannic acid and sodium alginate reduces bitter taste. Maltitol, a thickening agent is stable in the acidic pH range of 2 to 3 masks the unpleasant taste of the drug.

1.3.8 Salt formation

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin. Penicillin prepared as N,N'-dibenzylethylene-diamine diacetate salts or N,N'-bis(dehydroabietyl) ethylenediamine salts is tasteless.

1.3.9 Solid dispersion

Solid dispersions can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking.

1.3.10 Freeze drying

Fast-dissolving oral dosage forms are prepared using freeze drying technologies such as Zydis and Lyoc. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the high porosity produced by the freeze drying process. The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze dried. Most commonly used structural excipients are gelatin and mannitol although starches, gums can also be used. This process is ideally suited to low solubility drugs as these are more readily freeze dried. Artificial sweeteners (e.g. aspartame)

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and conventional flavors can be added to produce taste masking. Lyoc differs from Zydis in that the product is frozen on freeze-dryer shelves. Various drugs have been taste-masked by Zydis technology are lorazepam (Wyeth), piroxicam (Pfizer), loperamide (Janssen), ondansetron (Glaxo Wellcome), rizatriptan (Merck), loratadine (Schering Plough), olanzapine (Eli Lilly), selegiline (Elan), scopolamine/chlorpheniramine (Taisho) etc.

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