**Review Article**

**Oral Strip Technology: A review**

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**ABSTRACT**

Over the recent past, many of the research groups are focusing their research on this technology. Amongst Oral drug delivery system Oral Strip Technology (OST) is gaining much attention. The advantages of OST are the administration to pediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated. This technology has been used for local action, rapid release products and for buccoadhesive systems that are retained in the oral cavity to release drug in controlled fashion. OST offers an alternate platform for molecules that undergo first pass metabolism and for delivery of peptides. An ideal OST should have the following properties: high stability, transportability, ease of handling and administration, no special packaging material and/or processing requirements, no water necessary for application, and a pleasant taste. All these requirement are fulfilled by the oral films. The OST is a good tool for product life cycle management for increasing the patent life of existing molecules or products. Compared to some of the complicated and expensive process (like lyophilization) used to manufacture ODTs (Orally Disintegrating Tablets), the OST is relatively easy to fabricate, thus reducing the overall cost of the therapy. One of the reasons is that the buccal mucosa is less permeable and is thus not able to elicit a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more advantageous for retentive systems used for oral trans mucosal drug delivery. The primary disadvantage associated with buccal delivery route is the low flux that in turn results in low drug bioavailability. To overcome this hurdle, various buccal penetration enhancers have been studied which improve the absorption pattern of the molecules. The article shows OST encompassing materials used in OST, method of preparation, evaluation, applications, commercial technologies and future Business prospects of this technology.

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**Introduction**

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. These delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing.[1] They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of drugs.[1]

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The epithelia of oral cavity are also composed of an intercellular ground substance called as mucus which basically consists of proteins and carbohydrates. It maintains hydrated condition of the oral cavity, provides adequate lubrication, concentrate protective molecules such as secretory immunoglobulins, and reduces the attachment of microorganisms. The negatively charged mucin contains sulfhydryl groups and sialic acid residues that are responsible form muco-adhesion phenomena. The saliva and salivary mucin contribute to the barrier properties of oral mucosa. While the major salivary glands consist of lobules of cells that secrete saliva; parotids through salivary ducts near the upper teeth, submandibular (tongue regions), and the sublingual ducts, the minor salivary glands are located in the lips, buccal mucosa, and in linings of the mouth and throat. It is interesting to note that the permeability of buccal mucosa is greater than that of the skin, but less than that of the intestine.[2–4] Total turnover rate of the total whole saliva (output from the major and minor salivary glands) at normal physiological conditions has a flow rate of 1–2 ml/min [5]. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane. It is also reported that the permeability of the buccal mucosa is approximately 4–4000 times greater than that of the skin.[4] Hence the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration. However, the primary barrier to permeability in the oral mucosa is the result of intercellular material derived from the so-called ‘membrane coating granules’ present at the uppermost 200 micron layer.[6,7] Drug absorption through the buccal cavity can take place either by the transcellular route (or intracellular route, crossing across the cell membrane and entering the cell) or paracellular pathway (passing between the cells). The mucosa in sublingual region is relatively more permeable leading to rapid absorption with improved bioavailability.[8] In view of the systemic transmucosal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa. The constant salivary secretion within the oral cavity makes it quite difficult for dosage forms to be retained for long periods of time. Accidental swallowing of dosage forms and salivary scavenging is another limitation in buccal delivery systems. It is documented that the maximum duration of buccal delivery is 4–6 h.[9] An ideal buccoadhesive system is the one that adhere to the site of attachment for a few hours, releases the drug in a controlled fashion, facilitates the rate and extent of drug absorption, does not cause any irritation or inconvenience to the patient, does not interfere with the normal functions such as talking, drinking etc. and that provides unidirectional drug release toward the mucosa. In spite of these challenges the buccal route is still the preferred route for delivery of active pharmaceutical ingredients (API) that are prone to high level of degradation in the gastrointestinal tract. Different buccal delivery products have been marketed or are proposed for certain diseases like trigeminal neuralgia, Meniere's disease, diabetes, addiction etc. [10,11]. The buccal cavity can be a platform for mucoadhesive (buccoadhesive) systems, gingival dosage forms, local delivery into the oral cavity and buccal delivery systems. Developing formulations for children has been a challenging task. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens [12,13]. Although solid dosage forms are widely accepted by elders and adolescents, younger children tend to prefer liquid formulations that are easier to swallow[14]. Keeping the ease of administration and swallowing in mind, pharmaceutical research has led to the development of Oral Disintegrating Tablets (ODTs). ODTs have been defined as “A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. United States Food and Drug Administration further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative [15].

Figure: 1 Different layers of oral mucosa
Special features of mouth dissolving films

- Thin elegant film
- Available in various size and shapes
- Unobstructive

Advantages of oral films

- The oral film administered sublingually and buccally deliver the drug with high potential to improve onset of action, lower the dose, and enhance the efficacy and safety profile of the medicament
- Fast dissolving film can avoid first pass metabolism and yield quicker onset of action at lower doses
- Oral film is more stable, durable and quicker dissolving than other conventional dosage forms.
- Oral film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain a precise amount of the drug.
- Oral film ensures more accurate administration of drugs.
- Oral film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations[25].

Disadvantages of oral film

- Oral disintegrating films have disadvantage in terms of amount of drug that is to be incorporated. for lyophilized dosage form the drug dose must be generally less than 400mg for insoluble drugs & for soluble drug it should be less than 60 mg.
- Due to fragile nature of the dosage form packaging cost is increased [26]

Composition of oral film

Strip forming polymers

A variety of polymers are available for preparation of OS(Oral Strip). The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation [27]. On the other hand, fast dissolving strip dosage form should have the property to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously. A list of polymers and their properties are given in Table 1 [28,66]. As the strip forming polymer (which forms the platform for the OS) is the most essential and major component of the OS, at least 45%w/w of polymer should generally be present based on the total weight of dry OS [67]. Of the various polymers available, pullulan, gelatin and hypromellose are most commonly used for preparation of OS. Pullulan is a natural polymer obtained from non-animal origin and does not require chemical modification. This polymer provides highly clear and homogenous films. It has

General composition of fast dissolving oral film:
The oral film comprises of general ingredients in the following amount:[21,22]

- Drug 1-30%w/w
- Water soluble polymer 40-50%w/w
- Plasticizers 0-20%w/w
- Saliva stimulating agent 2 to 6%w/w
- Sweetening agent 3 to 6 %w/w
- Surfactants qs.
- Fillers, colors, flavors etc. 0-40%w/w

Special features of mouth dissolving films[23,24]

- Excellent mucoadhesion
- Fast disintegration
- Rapid release

The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer. Some examples of permeation enhancer are as follows:

- Aprotinin[10]
- Azone[12-14]
- Benzalkonium chloride [15]
- Cyclodextrin[16]
- Dextran sulfate [17]
- Menthol [11]
- Sodium taurodeoxycholate[18]

Fast dissolving oral films are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

The introduction of ODT in market was accompanied by educating the mass about the proper way to administer the product like giving instructions “do not swallow” or “do not chew”. The process of manipulating the ODT in oral or buccal cavity was also important. However since the OST derived products were readily popular in the market in the form of breath-freshening strips, no further efforts were needed to re-instruct the populace about the technique of administration of this dosage form. OST was already popular amongst the people in the early 2000 year with the introduction and widespread use of Listerine pocket strips, a new launch in the mouthwash style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion by 2010 [26]. However only a few products consisting bitter molecules have been able to be commercialized because of the complexity associated with the OST.[20]
low oxygen permeability and low water content which makes it most suitable for production of OS [68]. Modified starches are also used for preparation of OS. Due to low cost of this excipient it is used in combination of pullulan to decrease the overall cost of the product. About 50 to 80% w/w of pullulan can be replaced by starch in the production of OS without loss of required properties of Pullulan. Typically 60 to 65% w/w of water soluble polymer is preferred for preparation of OS with desired properties [69,70]. Many times, mixtures of polymers are used to improve hydrophilicity, flexibility, mouth-feel and solubility characteristics of OS. Polyvinyl pyrrolidone films are brittle in nature and therefore copovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating strips [71]. Combination of microcrystalline cellulose and maltodextrin has been used to formulate OS of piroxicam made by hot melt extrusion technique. In this case, microcrystalline cellulose is used to render the film non-sticky and smooth. Microcrystalline cellulose was also used to decrease the disintegration time and improve the dissolution of drug from the OS.

The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spreadability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Various polymers can be employed to modulate the disintegration property of the oral strip. This is especially used in case of slowly disintegrating oral bioadhesive strips or patches that need to be retained in intact form for longer duration in the oral cavity. The bioadhesive polymer used in such formulations imparts the adhesive property to the strip such that it adheres to buccal mucosa to deliver the drug for prolonged period. Bioadhesive polymer should ideally adhere quickly to the buccal mucosa and should have sufficient mechanical strength. Polymers used for OS should have good shelf life and they should not aid in causing secondary infections in the oral mucosa or dental regions. It would be ideal to have a polymer that would have local enzyme inhibition action along with penetration enhancing property. The details of properties of bioadhesive or mucoadhesive polymers and their applications are discussed elsewhere [72,29].

Mucoadhesive polymers include polycarbophil, cellulose derivatives like hydroxypropylmethylcellulose, poly(acrylic acid) derivatives, sodium carboxymethylcellulose, hydroxyethyl cellulose, hyaluronic acid, xanthan gum, locust bean gum, guar gum, carrageenan, sodium alginate, chitosan, poly(ethylene oxide), poly (ortho esters), poly (hydroxyethyl butylate), poly(cyano acrylates), polyphosphazenes, poly (vinyl alcohol) etc. Second generation mucoadhesive polymers include thiolated polymers. They are multifunctional polymers consisting of hydrophilic macro molecule having free thiol groups on the polymer backbone. The polymer forms disulfide bonds with cysteine-rich subdomains of mucus glycoproteins. Corium International has developed a new class of adhesive hydrogels (Corplex™) [30]. The polymer has properties of both hydrophobic pressure sensitive adhesives and hydrophilic bioadhesives. This is prepared by non-covalent (Hydrogen bond) cross-linking of film forming hydrophilic polymer (like polyvinyl pyrrolidone) with a short-chain plasticizer (typically; polyethylene glycol) bearing complementary reactive hydroxyl groups at the chain ends.

There are a number of marketed products available that are based on mucoadhesion phenomena. Oramoist® is a Timed Release oral disk that adheres to the roof of the mouth and has a moisturizing effect for about 4 h [31,32]. It is recommended for dry mouth syndrome (xerostomia). Compeed® is another formulation that is intended to treat cold sore. This system is similar to transdermal formulation wherein the patch has to be applied onto the affected area. The disadvantage is that since it does not contain biosolubilizing ingredients, the patch has to be removed after use. Canker Cover® is a tablet-like patch that is used in the treatment of canker sore. It adheres to the canker sores and lasts for 8–12 h. It forms a clear gel patch after application. The patch once applied needs careful manipulation using water for its removal and at times may cause pain. Striant® is a bioadhesive delivery system for testosterone replacement therapy [33]. It is a small monoconvex tablet that rapidly adheres to the buccal mucosa, gets hydrated due to saliva to form gel like form that remains in the region of where the gum meets the upper lip above the incisor teeth for a period of 12 h. Dentipatch® is an oral anesthetic patch. This is similar to a transdermal system and the formulation has to be retrieved after its use. BioErodibleMucoAdhesive (BEMA™) technology, which is designed to deliver either local or systemic levels of drugs across mucosal tissues. It consists of a small, bioerodible polymer film for application to the mucosal membranes (inner lining of cheek). As compared to the OS, most of the above marketed disk formulations have higher thickness. Hence this might cause inconvenience to the individual when the system is residing in the buccal cavity. Additionally there is a risk of inadvertent detachment of the system leading to loss of clinical response.

Thus, Oral mucosal patches can be categorized into three types namely; patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix are designed to release drug into the oral cavity. The muco-adhesive layer (either in drug matrix or attached to drug matrix) would prolong the duration of drug matrix in the oral cavity. Hence, in comparison to other dosage forms, these systems are longer acting and can potentially deliver more drug quantities. Patches with non-dissolvable backing are usually designed for systemic delivery. Being closed systems the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for few hours. However, the disadvantages with these patches are that they use only a small mucosal area and the backings have to be removed by the patient after drug administration. Patches with dissolvable backing have the advantage of the entire patch being dissolved in the oral cavity. Patches with dissolvable backings are shorter acting as compared to those with non-dissolvable backing membranes. [34]
### Profile list of various oral film forming polymers

#### Table 1: Profile List of Various Oral Film Forming Polymers

<table>
<thead>
<tr>
<th>Property</th>
<th>Hydroxypropyl methyl cellulose (Hypromellose)</th>
<th>Hydroxypropyl cellulose</th>
<th>Pullulan</th>
<th>Gelatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonym</td>
<td>HPMC, Methocel, Metolose, Benecel</td>
<td>Hydroxypropyl ether, hyprolose, Klucel, Nisso HPC.</td>
<td>Citrus pectin, Methopectin, pectin, pectinic acid.</td>
<td>Byco, cryogel, Instagel, Solugel</td>
</tr>
<tr>
<td>Structure</td>
<td><img src="image1" alt="Structure diagram" /></td>
<td><img src="image2" alt="Structure diagram" /></td>
<td><img src="image3" alt="Structure diagram" /></td>
<td><img src="image4" alt="Structure diagram" /></td>
</tr>
<tr>
<td>Description</td>
<td>It is a odorless, tasteless and white or creamy white fibrous or granular powder</td>
<td>It is a white to slightly yellow colored, odorless and tasteless powder. It is stable material</td>
<td>It is available as white, odorless tasteless, stable powder</td>
<td>It occurs as light amber to faintly yellow colored, vitreous, brittle solid. It is odorless, tasteless.</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>10,000–1,500,000</td>
<td>50,000–1,250,000</td>
<td>8000–2,000,000</td>
<td>15,000–250,000</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in cold water, forming a viscous colloidal solution, insoluble in chloroform, ethanol.</td>
<td>It is freely soluble in water below 38 °C forming a smooth, clear, colloidal solution. Hydroxypropyl cellulose is soluble in many cold and hot polar organic solvents such as absolute ethanol, methanol, isopropyl alcohol and propylene glycol.</td>
<td>It is soluble in hot as well as cold water.</td>
<td>Soluble in glycerin, acid and alkali. Swells in water and softens. It is soluble in hot water.</td>
</tr>
<tr>
<td>Film forming Capacity</td>
<td>It has a film forming ability in 2–20%w/w concentrations.</td>
<td>It has a good film forming property and 5%w/w solution is generally used for film coating.</td>
<td>5–25%w/w solution forms flexible films. Films are low permeable to oxygen, stable.</td>
<td>It has a very good film forming ability.</td>
</tr>
<tr>
<td>Viscosity</td>
<td>A wide range of viscosity grades are commercially available. Viscosity of various grades ranges from 3 mPa s–100,000 mPa s</td>
<td>A wide range of viscosity types are commercially available. The viscosity of solutions ranges from 75 mPa s–6500 mPa s depending upon the</td>
<td>The viscosity (10%w/w, 30 °C) of pullulan was 100–180 mm2/s.</td>
<td>4.3–4.7 mPa s for a 6.67%w/v aqueous solution at 60 °C.</td>
</tr>
<tr>
<td>polymer grade</td>
<td>Moisture content</td>
<td>Melting point</td>
<td>Application/s</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>---------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>It absorbs moisture from the air. The amount of moisture absorption depends on initial moisture content, temperature and humidity of surrounding air.</td>
<td>Browns at 190–200 °C. glass transition temperature is 170–180 °C</td>
<td>Hypromellose is widely used in oral, ophthalmic and topical formulations. Hypromellose is primarily used as a tablet binder, film coating agent, film forming agent and as a matrix for use in extended release formulations. Hypromellose is also used as a suspending and thickening agent. Hypromellose is also used as an emulsifier, suspending agent and stabilizing agent in gels and ointments. Hypromellose is also used to manufacture capsules, as an adhesive in plastic bandage and as a wetting agent in contact lenses. Hydroxypropyl cellulose acts as a tablet binder in the range of 2–8% of tablet weight. The polymer is also used for preparation of modified release dosage form. Hydroxypropyl cellulose is most suitable for water soluble drugs. It is also used for the preparation of microcapsules. It is used as a thickening agent in the oral and topical formulations. Due to its non-ionic nature, it is used as an emulsifier in the cosmetic formulations. It imparts low surface and interfacial tension to its solution and thus can be used for the preparation of flexible films alone or in combination with Hypromellose.</td>
<td>Hydroxypropyl cellulose acts as a tablet binder in the range of 2–8% of tablet weight. The polymer is also used for preparation of modified release dosage form. Hydroxypropyl cellulose is most suitable for water soluble drugs. It is also used for the preparation of microcapsules. It is used as a thickening agent in the oral and topical formulations. Due to its non-ionic nature, it is used as an emulsifier in the cosmetic formulations. It imparts low surface and interfacial tension to its solution and thus can be used for the preparation of flexible films alone or in combination with Hypromellose.</td>
</tr>
<tr>
<td></td>
<td>It absorbs moisture from the air. Typical equilibrium moisture content values at 25 °C/50% RH are 4%w/w and 12%w/w at 84%RH.</td>
<td>It softens at 130°C; chars at 260–275°C</td>
<td>It is used extensively in food industry to provide bulk and texture. The hydrophobic grades of pullulan are used for preparation of nanoparticles for targeted delivery. Pullulan can be used as a replacement to dextran as a plasma expander. Pullulan films are strong therefore used for decoration of food products, in confectionaries. It acts as an ideal carrier system for flavors, colors and drugs. Pullulan is used in coating for immediate release tablets and it is also used for preparation of capsule shells.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>It contains less than 6%w/w of moisture.</td>
<td>107 °C</td>
<td>It is used extensively in an implantable delivery system. It is used for the preparation of hard and soft gelatin capsule. It is used for microencapsulation of drugs. It is used topically in wound dressing. Absorbable gelatin is available as sterile film, ophthalmic film, sterile sponge etc.</td>
<td></td>
</tr>
</tbody>
</table>

**Plasticizers**

Plasticizer is a vital ingredient of the OS formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl
The glass transition temperature of the polymers. Cellulosic concentration of plasticizers play an important role in alleviating formation was observed due to the hydrogen bonding between various plasticizers for their plasticization effect on the gelatin strips. In these studies It was observed that malic acid was found to be better plasticizer as compared to citric acid, oleic acid and tartaric acid as it did not crystallize out when the strips were dried. Amongst the different grades of polyethylene glycol (PEG); PEG 300 was found to be better plasticizer for gelatin as compared to higher molecular weight PEG. This is because lower molecular weight PEG formed visually superior films and had low water vapor permeation rate. When sugars like mannitol and sorbitol were tested as plasticizers for gelatin strips, sorbitol was found to be better as compared to mannitol since mannitol crystallizes out from the gelatin strip [38]. Maltodextrin can also be plasticized and converted into OS with incorporation of glycercin and propylene glycol as plasticizer in the concentration range of 16–20%w/w. In this case, glycerine was found to be better than propylene glycol when the strips were manufactured by solvent casting as well as hot meltextrusion methods. However, PEG has miscibility problems with maltodextrins and do not act as good plasticizers.

Certain drug molecules themselves can act as plasticizer. For example, Ibuprofen interacted with Eudragit RS 30 D and played the role of a plasticizer. In this case, the glass transition temperature of Eudragit RS 30 D decreased and smooth film formation was observed due to the hydrogen bonding between the drug and the polymer. Also, the dissolution rate of ibuprofen decreased when its concentration in the formulation was increased [39].

There are two mechanisms propagated of how the plasticization takes place namely internal plasticization (involving chemical interaction) and external plasticizing effect. Formulators prefer to adopt the latter mechanism as it does not involve chemical interactive alterations in the product. An example of internal plasticization is where PEG 4000 was used as plasticizer for phenobarbital where the drug release was reduced to considerable extent [40]. The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellullosic polymers were plasticized with esters of citric acid and phthalic acid. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both Hypromellose as well as polyvinyl alcohol films [41].

Active pharmaceutical ingredient

The OS technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in OS. Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in the OS. Multivitamins up to 10%w/w of dry film weight was incorporated in the OS with dissolution time of less than 60 s. While water soluble APIs are present in the dissolved state in the OS or in the solid solution form, the water insoluble drugs are dispersed uniformly in the strip. The distribution of water insoluble molecules in water miscible polymer becomes important from the large scale manufacture point of view. APIs can also be added as milled, micronized or in the form of nanocrystals or particles depending upon the ultimate release profile desired. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OS. Many APIs, which are potential candidates for OS technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations.[42]

Thus before incorporating the API in the OS, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste. This is often termed as obscuration technique. Barrier technologies that can be used to mask the bitter taste include complexation, polymeric coating, conversion into microparticles/microcapsules, coated particles or coated granules. However, in the cases where the drug is encapsulated, the instantaneous release of medicament will not be achieved. Depending on the material employed in encapsulation and the manufacturing technique, the rate of drug release varies. Hence, the issue of palatability and drug response needs to be balanced to achieve maximum advantage of the developed OS formulation. Complexation technology involves use of cyclodextrins, resins which surround the bitter API and prevents the direct contact with saliva [43,44].

Matrixing of the bitter drug or coating of drug with water insoluble polymer has been used widely for taste masking of drugs. The bitter taste of paracetamol was masked with the use of lipidic excipients like hard fat and lecithin. Particulate technology has studied widely for the taste masking of APIs. Microparticulates of Famotidine and Eudragit EPO were prepared by spray drying technique. The results rendered a good taste mask dproduct which did not affect the bioavailability of the drug confirming the potential of the developed technology [45,46].

Monosol Rx technology utilizes particulate technology approach for preparation of taste masked product to be incorporated in the
OS. The limitation of barrier technologies is the dose of the API since the dose of the drug will ultimately decide the amount of microparticles or complex powder to be accommodated in the OS [47].

Chemical modification of API was used successfully by GlaxoSmithKline Beecham for the taste masking. Due to low solubility of ondansetron base than its salt form, base was used to prepare orally disintegrating tablets. The conversion of the salt of the base can be done in situ by addition of buffering agent in the OS. These agents alter the pH of the saliva and thus convert the salt form of the drug into the low soluble base form leading to taste masking of drug [48-49].

Recently a novel salting out technology was developed for the taste masking of API. The technology involved coating of drug substance with salting out layer consisting of salt and water soluble polymer. The salt reduced the dissolution of water soluble polymer and drug from the system resulting into taste masking of the drug. As the concentration of salt decreases in the system, the polymer and drug was released and resulted into immediate release of the drug. This salting-out taste-masking system generates lag time with subsequent immediate release. The technology was successfully utilized for the taste masking of paracetamol used as model drug. Other methods involve the obstructing of taste receptors. Nucleotide containing purine or pyrimidine group derivatives which are bound to ribose or deoxyribose sugar moiety inhibits the bitter or unpleasant taste. These compounds can be included in the OS to mask the bitter taste of drug substances. Adenosine 5’ mono phosphate, inosine 5’ monophosphate, adenosine 3, 5’ cyclic monophosphate are few examples which can be utilized in the concentration of 10.0–20.0%w/w in the formulation [50,51].

The OS technology offers advantages in certain critical clinical situations. For drugs that are projected as local anesthetic or pain killer, the OS has demonstrated improved clinical benefits. Certain pathologies require instantaneous release of the medicament for prompt relief. For instance, in the case of migraine a rapid clinical effect is desired by the individual. Region specific delivery of the medicament would be required in the cases of sore throat, cough, allergy and other local oral manifestations. Breath strips also offer superior consumer compliance. Similarly, cases of motion sickness need immediate attention. Also since OS technology does not require water during administration as compared to the regular tablet dosage forms; it is very handy during travel. This dosage form can also be used for natural extracts and nutraceuticals including vitamin B12, chromium picolinate, melatonin and possibly CoQ10 [52].

Some of the examples of suitable drug molecule that can be incorporated in the OS are listed below

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Therapeutic category</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Smoking</td>
<td>Cessation</td>
<td>1.0–15.0 mg</td>
</tr>
<tr>
<td>Nitroglycerin derivatives</td>
<td>Vasodilator</td>
<td>0.3–0.6 mg</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Anti migraine</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Loratidine</td>
<td>Antihistaminic</td>
<td>5–10 mg</td>
</tr>
<tr>
<td>Desloratidine</td>
<td>Antihistaminic</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Diphenhydramine hydrochloride</td>
<td>Antidiarroheal</td>
<td>25.0 mg</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Antacid</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Antacid</td>
<td>10.0mg</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Antihistaminic</td>
<td>15.0–30.0 mg</td>
</tr>
<tr>
<td>Chlorpheniramine maleate</td>
<td>Antihistaminic</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>Opioid Analgesic</td>
<td>8.0 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Proton pump inhibitor</td>
<td>2.5–10.0 mg</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>Antihistaminic</td>
<td>25.0 mg</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Anti–inflammatory</td>
<td>10.0–20.0 mg</td>
</tr>
<tr>
<td>Citrizine</td>
<td>Antihistaminic</td>
<td>5.0–10.0 mg</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Antimigraine</td>
<td>12.5–25.0 mg</td>
</tr>
<tr>
<td>Azatidine maleate</td>
<td>Antimicrobial</td>
<td>35.0–70.0 mg</td>
</tr>
<tr>
<td>Sumatriptan succinate</td>
<td>Antihistaminic</td>
<td>0.12%</td>
</tr>
<tr>
<td>Chlorhexidine gluconate</td>
<td>Antimicrobial</td>
<td>2.50 mg</td>
</tr>
<tr>
<td>Tiprolidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydrochloride</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Examples of suitable drug molecule that can be incorporated in the OS
Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. The classical source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are also less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The sweetness property of most of the polyols is less than half of that of sucrose except xylitol and maltitol which have similar sweetness as that of sucrose (scale of 0.8–1.0). However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sacralose have more than 200 and 600 time sweetness as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200–300 time sweetness. The disadvantage of these artificial sweeteners is the after taste effect. This disadvantage of artificial sweeteners can be reduced by mixing or blending the natural and artificial sweetener. The flavor quality of these artificial sweeteners is different than the natural sweeteners and may not be acceptable to the patients who are accustomed to the natural sugars. The amalgamation of sweeteners may lead to synergism and improvement in the taste of the formulations. Aspartame was used for the preparation of oral strips of valdecoxib. For the oral strip of piroxicam, maltodextrin was employed as sweetening agent. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip. Other OS ingredients such as sweeteners also act as salivary stimulants. Food grade sugars as well as synthetic sugars are useful salivary stimulants along with acidulents. Glucose, fructose, xylitol, maltose, lactose are few examples of such sweeteners. The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow at equal time under same conditions. The comparison between the salivary stimulation using citric acid and other sugars is given in Table 3. The stimulant action of sweeteners is dependent on the sweetness value. Fructose has the sweetness value of 1.1 as compared to 0.7 of glucose and 1.0 of sucrose. The artificial sweetener is preferred over natural sugars because lower concentration is required and multiple uses don't result in dental caries in individuals.

<table>
<thead>
<tr>
<th>Stilumant</th>
<th>Molarity</th>
<th>Flow rate (ml/min)</th>
<th>Time required for returning to initial flow rate (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>0.26</td>
<td>1.68</td>
<td>7.3</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.17</td>
<td>0.52</td>
<td>6.7</td>
</tr>
<tr>
<td>Fructose</td>
<td>1.17</td>
<td>0.97</td>
<td>8.7</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.17</td>
<td>0.74</td>
<td>6.3</td>
</tr>
<tr>
<td>Aspartame</td>
<td>0.034</td>
<td>0.82</td>
<td>6.8</td>
</tr>
<tr>
<td>Sodium saccharin</td>
<td>0.42</td>
<td>1.04</td>
<td>10.5</td>
</tr>
</tbody>
</table>

The resting salivary flow rate was 0.34 ml/min.

Flavoring agents

Perception for the flavors changes from individual to individual depending upon the ethnicity and liking. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. The selection of flavor is also dependant on the type of drug to be incorporated in the formulation. For example, mint flavor is generally added in products used for gastric related ailments like indigestion. The acceptance of the oral disintegrating or dissolving formulation by an individual by and large depends on the initial flavor quality which is observed in first few seconds after the product has been
consumed and the after taste of the formulation which lasts for at least about 10 min [72].

Flavoring agents can be selected from synthetic flavor oils, oleoresins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferably up to 10% w/w flavors are added in the OS formulations. Cooling agents like monomethyl succinate can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents like WS3, WS23 and Ultra coll II can also be used in conjunction with flavors [59].

**Coloring agents**

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1% w/w) in OS when some of the formulation ingredients or drugs are present in insoluble or suspension form [60].

**Stabilizing and thickening agents**

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Natural gums like xanthan gum, locust bean gum, carragenan and cellulosic derivatives can be used in the concentration up to 5% w/w as thickening agents and stabilizing agents. Other ingredients such as surfactants and emulsifying agents are also added in small amount to improve the strip properties [61].

**Manufacturing methods [62,63]**

There are five methods for manufacturing purpose

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

**Solvent casting**

In solvent casting method the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

**Semisolid Casting**

In this method solution of water soluble film forming polymer are mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate, cellulose acetate butyrate). After sonication it is coated on non-treated casting film. On drying the thickness of the film is about 0.381-1.27 cm. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

**Solid Dispersion Extrusion**

Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped in to films by means of dies.

**Rolling Method**

In this method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and gives desired shape and size.

**Evaluation**

The final product is then critically examined by the quality control department before it is finally packed into the secondary pack. Medicated strips are generally characterized by the quality control tests stated below [64].

**Thickness**

The thickness of strip can be measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

**Dryness test/tack tests**

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print free. Although these tests are primarily used for paint films, most of the studies can be adapted intricately to evaluate pharmaceutical OS as well. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.
Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks [60]. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

\[
\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}}
\]

Percent elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases [37].

\[
\%\text{elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}
\]

Tear resistance

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm (2 in.)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton’s (or pounds-force)[38].

Young’s modulus

Young’s modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

\[
\text{Young’s modulus} = \frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{cross-head speed}}
\]

Hard and brittle strips demonstrate a high tensile strength and Young’s modulus with small elongation.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value[39].

Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s [40].

Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API [41]. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

Assay/drug content and content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115%.

Organoleptic evaluation

Since the OS are intended to disintegrate rapidly or reside for more duration of time in the oral cavity, the product needs to have acceptable organoleptic palatable characteristics. The product should possess the desired features of sweetness and flavor which is acceptable to a large mass of population. For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high throughput screening of oral pharmaceutical formulations [42]. Experiments using electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste-masking formulation [43].

Stability studies

- Accelerated stability testing with common high stresses like:
  - Temperature
  - Humidity
  - Light
- Shelf life under accelerated conditions

Conclusion

Being a consumer-friendly alternative, many of the pharmaceutical companies are switching their product franchise from ODTs to OSTs. This technology option can also provide a good platform for patent on-infringing product development. OST allows brand extension for products. The OST is a good tool for product life cycle management for increasing the patent life of existing molecules or products. Compared to some of the complicated and expensive process (like lyophilization) used to manufacture ODTs, the OST is relatively easy to fabricate; thus reducing the overall cost of the therapy. The application of OTF has not only been limited to buccal fast dissolving system, but
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also expands its horizon to other applications like gastroretentive, topical, implantable, sublingual delivery options. This delivery platform shows business potential promise for future in pharmaceuticals, nutraceuticals as well as cosmeceuticals.

Conflict of interest statement

The author declares no conflict of interest.

References


