MOUTH DISSOLVING STRIPS: A NOVEL APPROACH FOR DRUG DELIVERY SYSTEM

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ABSTRACT
Mouth dissolving strips are oral drug delivery system, which disintegrate or dissolve within a minute when placed in the mouth without drinking of water or chewing. Worldwide gaining interest as an alternative to fast dissolving tablets to definitely eliminate patient’s fear of choking and also for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid dosage forms. Mouth dissolving strips suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse effects and also make it cost effective.

KEYWORDS: Mouth dissolving strips, Polymers, Plasticizers, Solvent Casting Method, Improved Patients Compliance.

INTRODUCTION
Mouth Dissolving Drug Delivery System (MDDDs) has become increasingly important because of their unique properties. They quickly disintegrate and dissolve, and can be administered without water, making them particularly suitable for pediatrics and geriatric patients.[1,2] Mouth dissolving strips is a new drug delivery system for oral delivery of drug. Mouth strip is a type of strips which is used in acute condition such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, and asthma etc. Mouth dissolving strips has gained popularity due to its availability in various size and shape. Mouth dissolving strips...
are intended which disintegrate or dissolve within seconds. They offer several advantages such as administration without water, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients absorption is possible through the oral mucosa and may improve bioavailability of the drugs.\textsuperscript{[3,4]}

Viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Mouth Dissolving Drug Delivery System (MDDDs) has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric strips for mouth delivery, also known as mouth dissolving strips.\textsuperscript{[5,6]}

**The concept of oral dissolving strips**\textsuperscript{[7]}

- This delivery system consists a thin strips.
- After placing it on top of the tongue, the strips dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug.
- This dissolves in the mouth like a cotton candy.

Mouth dissolving strips use as dissolving strips to administer drugs via absorption in the mouth (buccally or sublingually) or via the small intestines (enterically). A strips is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, and delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Mouth dissolving strips drug delivery has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and over the counter medications. Similar in size, shape and thickness to a postage stamp, thin strips are typically designed for oral administration, with the user placing the on or under the tongue or along the inside of the cheek.\textsuperscript{[8]}

**Classification of Mouth Dissolves Technology**\textsuperscript{[9,10]}

For easiness of description, fast-dissolve technologies can be separated in to three broad groups.

1. **Lyophilized systems**
2. **Compressed tablet-based systems and**
3. **Thin film strips**
Ideal Characteristic of Mouth Dissolving Strips\textsuperscript{[11,12,13]}

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose
- It should have an acceptable taste.
- It should give a pleasing mouth feel.
- Fast Dissolution and Disintegration
- It should be less friable and have good mechanical strength to withstand the post manufacturing handling.
- It should be stable in environmental conditions.
- Subsequent to oral administration, it should leave least or no residue in mouth.
- It should quickly dissolve to release drug instantaneously in mouth.
- It should be compatible with the other ingredients.

Advantages of Mouth Dissolving Strips\textsuperscript{[14-19]}

- Accessibility of large surface area that leads to fast disintegrating and dissolution in the oral cavity.
- The drawback of most ODT is that they are delicate and brittle which warrant special package for protection during storage and transportation. Since the strips are elastic they are not as delicate as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.
- As compared to drops or syrup formulations, accuracy in the administered dose is ensured from each of the strips.
- Pharmaceutical company and customers alike have embraced OTFs as a practical and conventional alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and transportable, without the need for water or measuring device.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergo first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- Since the first pass effect can be avoid, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
- Patients suffering from dysphagia, motion sickness, repeated emesis and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a material of seconds for the rapid release of one or more APIs.

**Disadvantage of Mouth Dissolving Strip**[14-19]

- The disadvantage of oral strip is that high dose cannot be incorporated into the strip. However, research has confirmed that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-XÆ thin strip has a loading of 62.5 mg of simethicone per strip. There remain a number of technical limitations with the use of film strips.
- The volume of the dosage unit is obviously proportional to the size of the dose, which means these extremely thin dosage forms are best suitable to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly limits the range of compatible drug products.
- The other methodological challenge with these dosage forms is achieving dose uniformity.

**Special feature of Mouth dissolving strips**[20,21]

- Available in various size and shape.
- Thin elegant strip.
- Un-obstructive.
- Fast disintegration or dissolution.
- Rapid drug release.
- Cost effective.
- Ease of administration.
- Palatable.

**Mechanism of Action of Mouth dissolving strips**[22]

- Delivery system is simply place a Strip on Tongue or in Buccal cavity.
- Instantly wet by saliva (Due to hydrophilic agent present in the strip).
- Hydrated strip dissolves and release medication and would be available for oro-mucosal absorption.
ORAL CAVITY$^{[23,24]}$

Anatomy of oral cavity

Oral cavity offers a unique environment for delivering the drugs. The oral mucosa allows direct access of drug to systemic circulation and avoids 1st pass metabolism. The epithelium of oral cavity is quite similar to that of the skin, with slight differences with regard to keratinization, protective and lubricant mucous which is spread across its surface. The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral cavity is divided into two regions.

- Outer being the oral vestibule bounded by the lips and cheeks; (Hard and soft palates)
- Floor of the mouth and Tonsils.

Figure 1: Mouth Dissolving Strip (M/A)

Figure 2: Anatomy of Oral Cavity.
COMPOSITION OF MOUTH DISSOLVING STRIP[11, 25-28]

Active Pharmaceutical Agents

Active pharmaceutical compound may be from the any class/or category, that can be administered either through orally or by oral mucosa membrane. It includes anti-emetic, anti-ulcer, anti-migraine, anti-asthmatics, anti-histaminic, anti-epileptic, expectorants, anti-anginal etc. For an effective formulation, drugs dose should be in mgs (less than 20 mg/day). Various categories of the drugs such as an cardiovascular agent, analgesics, anti-allergic, anti-epileptic, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs are used for erectile dysfunction, expectorants.

The ideal characteristics of a drug to be selected are as follows

- Drug should be stable.
- Should be soluble in the water as well as in the saliva.
- Must have ability to permeate through oral mucosal tissue.
- Drug should have pleasant taste and odour.
- Drug should have low dose generally less than about 20mg.
- Must be partially ionized at pH of oral cavity.

Table 1: List of drugs use in fast dissolving oral strip.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>02 mg</td>
<td>Anti-diarroheal</td>
</tr>
<tr>
<td>Nicotine</td>
<td>02 mg</td>
<td>Smoking cessationn</td>
</tr>
<tr>
<td>Triplolidine HCL</td>
<td>2.5 mg</td>
<td>Anti-histaminic</td>
</tr>
<tr>
<td>Larcanidipine HCL</td>
<td>10 mg</td>
<td>Anti-hypertension</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>12.5 mg</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Verapamil HCL</td>
<td>20 mg</td>
<td>Anti-hypertension</td>
</tr>
</tbody>
</table>

Water Soluble Polymers

Water-soluble polymers used as strip formers. The use of strips forming polymers in dissolvable strips has attracted the considerable attention in medical and the nutraceutical application. The water-soluble polymers achieve rapid disintegration and provide a good mouth feel and mechanical properties to the strips. The disintegration rate of the polymers is decreased by increasing a molecular weight of the polymer strip bases. Some of the water soluble polymers used as a strips former are HPMC E-5, E10 and K-4, K15, Methyl celluloseA-3, A-6andA-15, Pullulan, Carbox-methyl-cellulose, PVP K-90, Pectin, gelatine, sodium alginate, HPMC, PVP, PVA, maltodextrin, Eudragit etc.
Ideal properties of the polymers used in a mouth Strips are

- Polymers should be non toxic and non-irritant
- Polymers have good wetting and spreadibility property
- Polymers should be tasteless.
- It should have exhibit sufficient peel, shear and tensile strength.
- It should be non-bitter in taste.
- It should be inexpensive and should be readily available.
- It should not be an obstacle in disintegration time
- It should be devoid of the leachable impurities
- It should have a sufficient shelf life.
- It should not cause the secondary infection in oral cavity.

Table 2: Type of polymers.

<table>
<thead>
<tr>
<th>Natural Polymers</th>
<th>Synthetic Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pullulan</td>
<td>Hydroxyl propyl methyl cellulose (Hypermellose)</td>
</tr>
<tr>
<td>Gelatine</td>
<td>Polyvinyl pyrrolidone (PVP)</td>
</tr>
<tr>
<td>Modified starches</td>
<td>Polyvinyl alcohol</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>Polyethylene oxide</td>
</tr>
<tr>
<td>Locust bean gum</td>
<td>Low viscosity grade HPC</td>
</tr>
<tr>
<td>Guar gum</td>
<td>Sodium carboxymethyl cellulose</td>
</tr>
<tr>
<td>Carrageenan</td>
<td>Hydroxyl ethyl cellulose</td>
</tr>
</tbody>
</table>

PLASTICIZERS

Formulation considerations have been reported as plasticizer is important factors that affecting on mechanical properties of strips. The mechanical properties such as:

- Tensile strength and
- Elongation

The strips have also been improved by the addition of plasticizers. It is used in 1-20 % w/w of the dry polymer weigh and Their concentration may affect these properties. Low molecular weight of polyethylene glycol was found to better plasticizer than high m.w. polyethylene glycol.
Table 3: Examples of plasticizers.

<table>
<thead>
<tr>
<th>Plasticizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol, Polyethylene glycol</td>
</tr>
<tr>
<td>Dimethylphthalate, Castor oil</td>
</tr>
<tr>
<td>Diethylphthalate, Glycerine</td>
</tr>
<tr>
<td>Dibutylphthalate, Propylene glycol</td>
</tr>
</tbody>
</table>

**Saliva Stimulating Agents**

The saliva stimulating agents are improve, production of saliva that would aid in the quicker disintegration of the rapid dissolving film formulations and utilized as salivary stimulants. These agents are used in combination between 2 to 6% w/w of weight of the strip. Sweeteners are also act as salivary stimulants.

Table 4: Examples of Saliva Stimulating Agents.

<table>
<thead>
<tr>
<th>Saliva Stimulating Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid, Malic acid</td>
</tr>
<tr>
<td>Ascorbic acid, Tartaric acid</td>
</tr>
</tbody>
</table>

**Surfactant**

Surfactants are used as solubilising or wetting or dispersing agent so that the strip is getting dissolved within seconds and release active agent immediately. Some of the commonly used are: Sodium lauryl sulphate, benzalkonium chloride, bezthonium chloride, tweens etc.

Most important surfactant is polaxamer-407 that is used as solubilizing, wetting and dispersing agent.

**Flavour**

Any flavour can be added, such as intense mints, sour fruit flavours or sweet confectionery flavours.

Table 5: Examples of Natural Flavours.

<table>
<thead>
<tr>
<th>Natural Flavours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Juices</td>
<td>Raspberry</td>
</tr>
<tr>
<td>Extracts</td>
<td>Liquorices</td>
</tr>
<tr>
<td>Spirits</td>
<td>Lemon &amp; Orange</td>
</tr>
</tbody>
</table>

**Synthetic Flavours**

- Alcoholic solutions
- Aqueous solutions
- Powders
Table 6: List of taste masking agent.

<table>
<thead>
<tr>
<th>Basic Taste</th>
<th>Masking Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>Butterscotch, maple, apricot, peach, vanilla, wintergreen mint</td>
</tr>
<tr>
<td>Bitter</td>
<td>Wild cherry, walnut, chocolate, mint, anise</td>
</tr>
<tr>
<td>Sweet</td>
<td>Vanilla, fruit and berry</td>
</tr>
<tr>
<td>Sour</td>
<td>Citrus flavor, licorice, root beer, raspberry</td>
</tr>
</tbody>
</table>

Sweeteners

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 (3 to 6% w/w).

Natural Sweetener

E.g.: Sucrose, glucose, fructose, sorbitol, mannitol, glycerol, honey, liquorice.

Artificial Sweetener

E.g.: Saccharin, saccharin sodium, aspartame

- Nutritive: Sucrose, fructose and glucose
- Polyols: Mannitol, Sorbitol, xylitol, erythritol, maltitol.
- Non-Nutritive: Aspartame, sucralose, neotame and saccharine.
- Novel sweeteners: Trehalose, tagatose

METHOD OF PREPARATION[29-35]

One or combination of the following methods can be used for the preparation of mouth dissolving strips.
1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling Method.
Solvent Casting Method

In solvent casting method excipients are dissolved in the water, then water soluble polymers are added and in the last drug is added and stirred to form the homogeneous solution. Finally the solution is casted onto the Petri plate and dried.

![Flowchart showing the steps of solvent casting method]

Solvent/Water (or) suitable mixture of solvent

Add exipients

Heating upto 60°C  Stirring at 1000 rpm

Solution

Add Polymer

Cooling at room temperature  Stirring at 1000 rpm

Add APIs

Final strip solution

Casting/Defoaming  Drying at 60°C

Oral thin strips

Advantages

- Great uniformity of the thickness and great clarity than the extrusion.
- Films have fine gloss and freedom from the defect such as die lines.
- Films have more flexibility and better physical properties.

Disadvantages

- The polymer must be soluble in the volatile solvent or water.
- The stable solution with reasonable minimum solid content and a viscosity should be formed.
**Semisolid Casting Method**

Solution of the water soluble strips forming polymer is prepared

Resulting solution is then added to the solution of acid insoluble polymer

Appropriate amount of plasticizer is added to obtained a gel mass

Gel mass is then casted onto the strips or on ribbons using heat controlled drums

The thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to the film forming polymer should be 1:4.

**Hot Melt Extrusion**

The drug is mixed with carriers in the solid form

Extruder having heater melts the mixture

Finally the melted mixture is shaped in a film by the dies
Advantages

- Fewer operation units.
- It is an anhydrous process
- Better content uniformity

Solid Dispersion Extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in inert carrier in a solid state in presence of the amorphous hydrophilic polymers.

Drug is dissolved in the suitable liquid solvent

Incorporated solution into the melted polyethylene glycol, below 70ºC

Solid dispersions are shaped into the strips by the means of dies.

Rolling Method

In rolling method a solution or suspension of drug with strips forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The strip is dried on the rollers and cut in to desired shapes and sizes.
EVALUATION PARAMETER OF MOUTH DISSOLVING STRIPS [36-40]

Weight Variation
For evaluation of strips weight, three strips of every formulation is selected randomly and individual weight of each 2x2 cm strip was taken on digital balance. The average weight was calculated.

Thickness
As the thickness of strip is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the strip. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations.

Dryness Test/Tack Test
About eight stages of strip 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 Mouth Dissolving Strips. 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.

Surface pH of Strip
Surface pH of the strip was determined by placing the strip and allow to swell in closed petri-disc at room temperature for 30 min. in 10 ml phosphate buffers (pH 6.8). The solution was placed under digital pH meter electrodes. The change in the pH was observed and reported.
Tensile Strength
Tensile strength is the maximum stress applied to a point at which the strips specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

\[
\text{Tensile strength} = \frac{\text{Load at breakage}}{\text{Strip thickness} \times \text{Strip Width}}
\]

Percentage 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.

\[
\% \text{ Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}
\]

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 strip is folded without breaking is computed as the folding endurance value.

Disintegration Time
Disintegration of Mouth Dissolving strips requires USP disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for Mouth Dissolving strips.

Assay/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 percent (%).

Organoleptic Evaluation
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 taste screening of oral pharmaceutical formulations.

**Swelling Property**
Strips swelling studies is conducted using simulated saliva solution. Each strip sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing strip sample is submerged into 15ml medium in a plastic container. Increase in the weight of the strip was determined at preset time interval until a constant weight was observed. The degree of swelling was calculated using parameters

\[ \alpha = \frac{wt - wo}{wo} \]

wt is weight of strip at time t, and
wo is weight of strip at time zero

**Transparency**
The transparency of the strip can be determined using a simple UV spectrophotometer. Cut the strip samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of strips at 600 nm. The transparency of the strips was calculated as follows.

Transparency = \((\log T_{600})/b = - \epsilon c\)

Where \(T_{600}\) is the transmittance at 600 nm and \(b\) is strips thickness (mm) & \(c\) is concentration.

**In-Vitro Dissolution Study**
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. 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.

**Stability Study**
A Stability study of the prepared strip was carried out by storing strips in an aluminium package for 30 days at 4 C/ 75% RH, 30 C/75% RH and 40 C/ 75% RH. The strips were observed for physical change (form and colour), disintegration time and drug content. Mouth dissolving strips were found to be physically and chemically stable as they showed no
significant change in terms of physical characteristics (no discoloration & no change in shape), disintegration time and drug content under all the storage conditions.

**Patent on Mouth Dissolving Strips Related Formulations.**

**Table 7: Patent on Mouth Dissolving Strips Related Formulations.**

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Patent No.</th>
<th>Title</th>
<th>Inventor</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>US 20120010160 A1</td>
<td>Rapidly Dissolving Oral Strip of Sugar for Hypoglycemia</td>
<td>Tania Degian</td>
<td>2012</td>
</tr>
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<td>film-strips with modified release active ingredients</td>
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<td>2010</td>
</tr>
<tr>
<td>5</td>
<td>US 20100256197 A1</td>
<td>Nicotine Dissolving Film With Or Without Menthol</td>
<td>Hanford N. Lockwood</td>
<td>2010</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Mouth dissolving strips have gained popularity because of better patient compliance, rapid drug delivery system, First pass metabolism and degradation in gastrointestinal tract can be avoided, And an innovative drug delivery system for all the population groups, specifically geriatric, pediatric patients and patients with swallowing difficulties. Mouth dissolving Strips are also having great potential of delivering the medicinal agent systemically as well locally and have several advantages over many dosage forms even over the fast disintegrating tablets. This explains the extensive research actively going on this technology.

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