Dosage form design for oral quick release formulations: A review

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Abstract
Pharmaceutical dosage forms containing drug(s) formulated in a way to dissolve in the oral cavity had gained tremendous popularity owing to their fast dissolution and quick absorption. In the ongoing pattern, the advancement of oral quick released dosage forms popularly known as mouth dissolving tablets acceptance is developing and picking up prevalence since it is easy to administer and prompts better patient convenience and compliance. These dosage forms are set in the mouth, permitted to scatter or break up in the saliva. The medication is discharged when on contact with the saliva, by disintegration followed by dissolution; in this manner minimize the requirement for water for oral administration. The point of this article is to survey the advancement of the developing technologies. In the present review, stress is given on the technologies available as well as design of orally dispersible formulations.

Keywords: Mouth dissolving tablets, dissolution, disintegration, quick released tablets, oral tablets

Introduction
Amongst the various routes of drug delivery, oral route is convenient and most widely used route of drug administration. Oral route is the most common route to give medications, in which the patient swallows. The oral route is most widely used because of various factors like convenience, economy, stability and patient acceptance. In this route of delivery, the medication must reach the intestine where it is broken down, absorbed across the intestinal wall, picked up in the blood stream and delivered to its intended target. These steps, however, take time up-to 30- 45 minutes between the administration of the medication and its therapeutic effect. On the other hand, peroral administration of drugs has disadvantages like lag period, hepatic first pass metabolism and enzymatic degradation within the GI tract. Thus, for drug administration other absorptive mucosae are considered as potential sites. First pass effect can be bypassed by oral transmucosal drug delivery and prevent pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.

Drug delivery inside the oral cavity is classified into three categories:

1) **Sublingual delivery**: intended for administration through the membrane of the ventral surface of the tongue and the floor of the mouth. The sublingual mucosa is most widely accepted route because it provides rapid absorption and acceptable bioavailability of many drugs and is very convenient for patients.

2) **Buccal delivery**: Buccal cavity is mainly composed of the inner lining of the cheeks where drug is administered through the buccal mucosa.

3) **Local delivery**: meant for administration through all areas other the former two regions. Local delivery includes the treatment of toothaches, periodontal diseases, bacterial and fungal infections, dental stomatitis and in facilitating tooth movement with prostaglandins. Tablets and capsules are the most widely accepted dosage forms except for persons having ‘Dysphagia’ or difficulty in swallowing, also persons having problem like: Parkinsonism, Motion sickness, Unconsciousness, Elderly patients, Children, Mentally, disabled persons and unavailability of water.

Recent advances in Novel Drug Delivery Systems (NDDS) are aim at designing a dosage form to achieve better patient compliance, minimum lag period using a conveniently administered dosage form. Mouth dissolving tablets are developed by Pharmaceutical technologists who have used their best efforts and latest technologies. Out of the various dosage forms developed mouth dissolving tablets facilitate ease of medication.
Need for an oral quick release dosage forms
The mouth dissolving tablets also designated as oral quick release dosage forms (OQ RDF) have been developed for pediatric, geriatric, bed-ridden patients and also for travelling patients who may not have access to water [12]. Because of hand tremors and dysphagia, the mouth dissolving tablets provide easiness to many elderly persons to take their medicine, who have problem in taking conventional oral dosage forms viz., solutions, suspensions, tablets and capsules [13]. Other groups include the mentally ill, the developmentally disabled and uncooperative patients on reduced liquid-intake plans or are nauseated [14].

OQRDF offers a new formulation, which combines the advantages of both liquid and conventional tablet formulations and provide added advantages over the traditional dosage forms. Mouth dissolving drug delivery systems offer the benefit of accurate dosing as compare to liquid and disperse systems. Mouth dissolving tablets (MDT) quickly dissolve in the saliva generally in less than 60 seconds [15, 16].

Mouth dissolving tablets (MDT’S)
United States of America food and drug administration (FDA) defines MDT as "A solid dosage form containing medicinal substances or active ingredients which disintegrate rapidly usually within a matter of seconds when placed upon the tongue" [17].

Ideal properties of mouth dissolving tablets (MDT’S):
A mouth dissolving tablet should have the following properties:

1. It must not require water or other liquid to swallow.
2. It should easily disintegrate within a few seconds in saliva.
3. It must have a pleasing taste.
4. It must not leave slight or no residue in the mouth.
5. It should be physically stable and resistant to breaking.
6. The drug incorporated as well as dosage form must be inert to environmental conditions like temperature, humidity etc.

Characteristics of mouth dissolving tablets
Ease of Administration
Mouth dissolving drug delivery systems are easy to administer and handle hence, leads to better patient compliance. As a result of tremors and dysphagia, elderly people feel difficulty in swallowing the other dosage forms like tablets, capsules, solutions and suspensions. Mouth dissolving tablets can be administered easily by elderly patients without need of water [18, 19].

Taste of the Medicament
Mouth dissolving tablets usually contain the medicament in taste masked form. Taste-masking is very important step in the formulation of an acceptable MDT. Taste of medicament can be masked by using sweeteners and flavors in mouth dissolving tablets; however, there are other means for taste-masking of many bitter drugs [20].

Hygroscopicity
Several mouth dissolving dosage forms are hygroscopic in nature and they cannot maintain physical integrity, hence they need specialized packing system [21].

Friability
Mouth dissolving tablets are compressed using low compression force, to make it more porous so that tablets can disintegrate quickly in the mouth. As, these tablets are very friable, hence they need specialized peel-off packing [22, 23].

Mouth Feel
Mouth feel plays a critical role, as a patient want to receive a product that feels pleasant. Large particles which are insoluble or slowly soluble in saliva can lead to an unpleasant gritty feeling. This problem can be resolved by decreasing the particle size. Certain flavors and sweeteners can provide an improved mouth feel so as to make product less gritty. Sometimes, effervescence can be added to increase disintegration and improve mouth feel of the product [24].

Advantages of mouth dissolving tablets (MDT’S) [25, 26, 27]
1. Mouth dissolving tablets can be easily administered by elderly patients (who cannot swallow), bedridden patients, paediatrics, geriatric and psychiatric patients.
2. Mouth dissolving tablets provide patient’s compliance to travelling people, where access to water is not possible.
3. Good mouth feel property of mouth dissolving tablets helps to increase acceptance of dosage form, particularly for paediatric patients because of taste masking of bitter drugs.
4. Mouth dissolving tablets provide accurate dosing as compared to liquid dosage forms.
5. Liquid medication can be given in the form of solid preparation.
6. Mouth dissolving tablets quickly disintegrate in pre-gastric area, as a result drug absorption occurs from mouth, pharynx and esophagus which may produce rapid onset of action.
7. Pre-gastric absorption can lead to increase in bioavailability of drug and reducing dose as well as reducing side effects.

Important criteria for excipients used in the formulation of mouth dissolving tablets
1. Excipient used must disintegrate quickly.
2. Properties of excipients should not affect disintegration of the MDTs.
3. It should not have any interactions with drug and other excipients.
4. Excipients should be inert so as to minimize interaction of excipients with drug.
5. Selection of binder (single or combination of binders) should be done so that it should not affect final integrity and stability of the product.
6. The binder used may be in liquid, semi liquid, solid or polymeric mixtures.

Ingredients used in the preparation of mouth dissolving tablets

- The Drug Property
To make an ideal mouth dissolving tablet technology, the tablet properties should not be affected by the properties of a drug. There are many drug properties, which could affect the parameters of mouth dissolving tablets. For example; Tablet strength and disintegration can be affected by the solubility,
crystal morphology, particle size and bulk density of a drug [28].

▪ **Taste Masking**

For commercial success of mouth dissolving tablets, taste masking is the basic requirement for mouth dissolving tablets. Taste masking of the active pharmaceutical ingredients can be obtained by using various techniques [29, 30].

a) **Taste Masking Using Flavours and Sweeteners**

Natural and artificial flavours and sweeteners are used along with other taste masking technique to mask bitter taste of drug product and to improve efficiency of these techniques.

b) **Taste Masking Using Lipophilic Vehicles**

Oils, surfactants, polyalcohols and lipids has a property to increase the viscosity in the mouth and to coat the taste buds, hence they act as taste masking agents. Lecithin or lecithin like substances, are used in various pharmaceutical formulations to control bitter taste of drug.

c) **Taste Masking by Ion-Exchange Resins (IERs)**

To stabilize the sensitive components, to disintegrate tablets and to mask taste; ion-exchange resins are used in formulations.

▪ **Superdisintegrants**

Superdisintegrant is an ingredient which can increase the rate of disintegration of tablet and hence rate of dissolution of mouth dissolving tablets. Superdisintegrants are used in direct compression technique. Other ingredients such as water-soluble and effervescent excipients are used in the formulation may also increase the process of disintegration [31].

**Mechanism of Action of Superdisintegrants**

All the mechanisms involved in the action of superdisintegrants are listed below:-

a) By capillary action  
b) By swelling  
c) Because of heat of wetting  
d) Due to release of gases  
e) By enzymatic action  
f) Due to disintegrating particle/particle repulsive forces  
g) Due to deformation

![Fig 1: Mechanism of Action of Superdisintegrants](image)

▪ **Binders**

Binders are used to bind various ingredients of the mouth dissolving formulations. Various types of binder used are liquid, semi solid, solid or mixtures of varying molecular weight molecules such as polyethylene glycol.

Example: cellulose polymers, povidones, polyvinyl alcohols and acrylic polymers.

▪ **Flavours and Sweeteners**

Flavours and taste-masking agents are responsible for making the product more palatable and pleasing, so as to increase acceptance for patients. The addition of flavours and sweeteners may lead to overcome bitter and undesirable taste of some active ingredients. Organoleptic characteristics of mouth dissolving tablets can be improved by using natural and synthetic flavours. Amongst the wide range of sweeteners such as sugar, dextrose, fructose, aspartame, sodium saccharin, sugar alcohols and sucralose, can be used as a sweetener.

▪ **Bulking Materials**

The bulking material contributes functions of a diluent, filler and cost reducer. Bulking agents are used to make bulk of the tablet, to increase size of the tablet and in some cases bulking agents can enhance disintegration of mouth dissolving tablets. Sometimes bulking agents can also reduce the concentration of the active pharmaceutical ingredient in the composition [32].

▪ **Sugar Based Excipients**

Sugar based excipients can be used in another approach to manufacture mouth dissolving tablet by direct compression. Various bulking agents having high aqueous solubility & sweetness can be used to impart taste masking property and a pleasant mouth feel are dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol [33].

▪ **Lubricants**

Lubricants are the agents which are used in very small quantity in tablet and capsule dosage forms to decrease friction at the interface between a tablet/capsule surface and the die wall. Lubrication can enhance ejection of tablet/capsule from the dies and also reduce wear on dies & punches. Moreover, lubricant enhances flow of powder raw material from hopper to dies & punches by reducing
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interparticulate friction. This can result in accurate filling of tablet and capsules.
Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

Developmental challenges of mouth dissolving tablets [34, 35, 36]

• Taste of the Active Ingredients
Mouth dissolving dosage forms dissolve or disintegrate in the patient’s mouth in close proximity to the taste buds. Unless the drug is tasteless or does not have an undesirable taste, the use of taste masking techniques becomes critical to patient compliance. Taste masking can be done simply with flavouring agents and sweeteners. If the active ingredient is extremely bitter, taste masking can be done through the use of ion exchange resins to render the drug insoluble in the saliva.

• Dose
Dose is an important parameter for the development of mouth dissolving tablets. Three major challenges for developing mouth dissolving tablets, where high doses of molecules are required, are; a) taste masking of the active ingredient, b) mouth feel or grittiness, c) tablet size. All these challenges are related to each other because most drugs are bitter and will require taste masking.

• Moisture Sensitivity
Most of the mouth dissolving drug delivery technologies is moisture sensitive, hygroscopic and often physically unstable under ambient temperature and humidity conditions. Thus many of these mouth dissolving drug delivery systems require specialized packaging to protect the product from moisture.

• Friability
Most of the mouth dissolving dosage form is either very porous, soft moulded matrices or tablets compressed at very low compression forces. This is to maximize the tablet porosity and minimize oral dissolution or disintegration time. This causes tablets to be soft, friable and/or brittle, often requiring specialized peelable blister packaging.

Approaches for preparation of mouth dissolving tablets
Various technologies used in the manufacture of Mouth Dissolving Tablets include [37, 38, 39]
1. Direct compression
2. Sublimation
3. Freeze-drying or lyophilization
4. Spray drying
5. Moulding
6. Mass extrusion

• Direct Compression
Direct compression technique is most widely used to manufacture mouth dissolving tablets, which include mixing of all the ingredients and compressing using dies & punches. Direct compression technique has following advantages:-
  a. High doses compositions can be directly compressed.
  b. Most successful way to manufacture the tablets.
  c. No special equipment is needed to prepare the tablets.
  d. A few processing steps are involved.
  e. Cost-effective process.
Tablet size and hardness are two important parameters which strongly affect the disintegration of mouth dissolving tablets. Hard and large tablets have more disintegration time as compared to soft and small tablets. Hence, an optimum concentration of disintegrant is needed to achieve quick disintegration and high dissolution rates.

• Sublimation
Sublimation is the process of conversion of solid state of a substance into gaseous state, without changing to liquid state. In this process some inert volatile substances like urea, urethane, naphthalene, camphor etc are added to other excipients and resulting mixture is then compressed into tablet. Volatile material is then removed by sublimation which creates pores in tablet structure, as a result tablet disintegrate quickly when comes in contact with saliva. Mouth dissolving tablets can be prepared by using sublimation technique, which create highly porous structure and good mechanical strength [40].

Fig 2: Diagram of Sublimation Technique for Preparation of MDT’s

• Freeze Drying
Freeze drying is also known as lyophilization. The tablets prepared by freeze-drying or lyophilization are very porous and disintegrate rapidly when comes in contact with saliva. In
this process, material is freeze by lowering pressure and ice removed by sublimation. Then moisture content is reduced to 4% (w/w) by carrying out primary drying. Finally, secondary drying is performed to reduce the bound moisture to the required volume. As a result of freeze drying, drug matrix acquires amorphous structure and hence dissolution is enhanced. The drug matrix is dried partially below the equilibrium freezing point of the matrix. Tablets are vacuum dried above its collapse temperature to enhance structural integrity and disintegration time in saliva. However, due to high cost of equipment and processing the use of freeze-drying is limited. Freeze drying has one disadvantage that product may lose physical stability in standard blister packs. Freeze drying technique was successfully explored for formulation of quick release tablets of highly lipophilic drug indomethacin utilizing phosphate buffer pH 6-8 along with hydrophilic excipients [41, 42].

- **Spray Drying**
  Spray Drying is used to prepare highly porous and fine powder of an aqueous composition containing support matrix and other components. This support matrix is then mixed with active pharmaceutical ingredient and then compressed into tablets. Allen and Wang used this technique to prepare mouth-dissolving tablets having disintegration time within 20s.

- **Moulding**
  Solid dispersions tablets are prepared by this method. Physical state of drug in the tablets depends on the extent it dissolves in the wetted mass. The drug exists as micro particles in the matrix, which can dissolve completely to form a solid solution or dissolve partially in the molten carrier. Various parameters like disintegration time, drug dissolution rate and mouth feel depends upon the type of dispersion used. Different moulding techniques used to prepare mouth dissolving tablets are:

  a. **Compression Moulding**
  The powder mixture is prepared by mixing all the ingredients and then solvent like ethanol/water added. This mixture is then compressed between mould plates to form a wetted mass.

  b. **Heat Moulding**
  Mouth dissolving tablets can be prepared by heat moulding method in which drug dispersed in a molten matrix can be moulded directly into mouth dissolving tablets.

  c. **No Vacuum Lyophilization**
  In this process solvent evaporate from a drug solution or suspension at a standard pressure condition. This process leads to the formation of porous tablets which enhances disintegration and dissolution rate. Because of the presence of water soluble sugars these tablets have pleasant taste. But moulded tablets have less mechanical strength as a result breakage occur during handling and opening of blister packs. On the other hand, mechanical strength can be increased by adding sucrose, acacia or polyvinyl pyrrolidone.

- **Mass Extrusion**
  In this technique, active drug and other ingredients are softened by using solvent mixture of water soluble polyethylene glycol and methanol. Then this softened mass is extruded with the help of the extruder or syringe to get cylindrical or rod shaped fragments of product. Finally these fragments are converted to tablets by cutting them into even size segments with the help of heated blades.

**Patented technologies for preparation of mouth dissolving tablet**

Commercially available patented technologies for manufacturing MDT’s are [43, 44, 45]:

- **Zydis Technology**
  Zydis is the first mouth dissolving technology in the market. In this technology active drug is placed in a water-soluble matrix. This matrix is then freeze dried to remove excess water. Zydis matrix is made by using various ingredients, Polymers such as gelatin, dextran or alginates are added to impart mechanical strength; Mannitol and sorbitol are added to provide crystallinity, elegance and hardness. To increase viscosity various gums can be added, also gums can prevent sedimentation of suspended drug particles. Water is used as a medium to ensure the formation of a porous dosage form. Glycine is used to prevent shrinkage of dosage form during freeze drying and long term storage. If necessary, other ingredients like, suspending agents, pH modifiers, preservative can also be added. Products made with Zydis technology are moisture sensitive, hence they are packed in blister packs to protect them from environmental moisture. A secondary foil is used to cover blister pack is called as moisture proof foil. Zydis tablet quickly disintegrates and dissolves in saliva when put into the mouth.

- **Orasolv Technology**
  It is CIMA lab’s first mouth dissolving formulation. In this technology taste of active drug is masked and effervescent disintegrating agents are also used. Conventional blenders and tablet compression equipments are used to prepare tablets. Less force of compaction is required to manufacture these tablets so as to obtain rapid disintegrating tablets.

- **Durasolv Technology**
  This technology has been developed by CIMA labs. This technique is suitable to prepare products having low amounts of active drug. In this technology drug, fillers and lubricants are used to prepare the tablet. Due to higher force of compaction, tablets prepared with this technology are very rigid. The product made with this technology can be packed into blister packs and other conventional packaging systems.

- **Wowtab Technology**
  The patent right of this technology is with yamanauchi pharmaceutical company. ‘wow’ means ‘without water’. In this technology the active ingredients may constitute upto (50% w/w) of the tablet and granules are prepared by using saccharides of both low and high compressibility. Highly compressible substance shows slow dissolution and vice-versa. The adequate hardness can be achieved by using combination of low and high compressible ingredients. Active ingredients are mixed with low compressible saccharides. The mixture is then granulated with high compressible saccharides and finally compressed into tablets. The product made with Wowtab technology dissolves quickly within 15sec or less. Wowtab product has a special feature that it can be packed in both bottle and blister packs.

- **Flashdose Technology**
  This technology is patented by Fuisz. In this technology both
Shearform and Ceform technologies are used in order to mask the bitter taste of the drug. Matrix used in this technology is called as 'Floss' which is made up of a combination of excipients alone or in combination with drug.

- **FlashTab Technology**
  Progpharm labs have a patent over this technology. In this technology, taste of active drug is masked and then converted to microgranules. These microgranules can be prepared by using conventional techniques like coacervation, microencapsulation and extrusion spherisation. All these processes utilize conventional tablet manufacturing technology. In this technology, all the ingredients like taste-masked active drug, disintegrating agent, a swelling agent and soluble diluents etc are compressed to form a tablet which disintegrates quickly.

- **Nanocrystal Technology**
  For MDT, Elan’s proprietary Nanocrystal technology can be used to formulation and improve final product characteristics. Nanocrystalline technology is used to decrease particle size of drug. Decrease in particle size leads to increases the surface area which in turn increases dissolution rate. Nanocrystal particles are small particles of diameter less than 1000 nanometers (nm), which are produced by milling technology. Nanocrystal Fast Dissolving Technology Provides the Following:

  a) **Pharmacokinetic benefits** which includes orally administered nanoparticles having particle size <2 microns, in the form of a rapidly disintegrating tablet matrix

  b) **Exceptional durability**, which enables product to be packed in conventional packaging (i.e., bottles and/or blisters).

  c) **Wide range of doses** (up to 200mg of API per unit).

  d) **Employment of non moisture sensitive substances**: Nanocrystal colloidal dispersions are prepared by combining drug substance with water-soluble GRAS (Generally Regarded as Safe) ingredients. Then mixture is filled into blisters and lyophilized. The resultant product formed is remarkably robust and dissolve in very small quantity of water within few seconds.

- **OraVescent Technology**
  The OraVescent tablet, an oral transmucosal drug delivery system developed by CIMA Labs USA, is proposed to be put in the oral cavity either sublingually or between the buccal and gingival tissues, where it is permitted to break down inactively in more than a few minutes through effervescence. In-addition to the overwhelming advantages of oral transmucosal conveyance, the OraVescent innovation has been appeared to give upgraded fundamental absorption of certain medications over the mucosal tissue because of its mechanism of drug release. The improved performance of the OraVescent tablet is due to the dynamic, limited, transient pH changes that happen through the span of tablet breaking down and dissolution. As the tablet disintegrates in the oral cavity, a compound response happens among acidic and basic components in the tablet after contact with water in the saliva. This results in the liberation of carbon dioxide and produces slight decrease in the pH of the tablet microenvironment. For basic medications, a lower pH, below the pKa of the drug favors the ionized type of the medication, quickening its dissolution. A pH modifier; sodium carbonate is added as excipient in the tablet which provide basic pH, results in conversion of ionized drug to unionized form which is more permeable through mucosal surfaces for rapid absorption. OraVescent tablets are made by an ordinary direct compression fabricating process. The FENTORA® item (fentanyl effervescent buccal tablet) is created with the OraVescent® technology for the fast relief from back pain [46, 47].

**Design optimization of oral quick release formulations**

The major factors to be considered in the formulation of oral quick released dosage forms are the lipophilicility, pH for optimum dissolution at the site of absorption, dose, amount of saliva and patient’s acceptability [48, 49]. Majority of drugs available are moderate to highly lipophilic having log p value more than 2; examples are Ibuprofen, diclofenac, indomethacin. These drugs solubilize in the emulsified alkaline environment and absorbed in the small intestine. The absorption of drugs like flexoxacin is pH dependent and their dissolution and absorption takes place in the small intestine at pH 6.8. The dose of the drug is another issue to be considered as majority of antibiotics, NSAIDs are administered in a dose range from 100 mg to 500mg which makes it difficult to design a pharmaceutically & patient acceptable an oral quick release dosage form which would be easily disintegrate, dissolve in the low amount of saliva with good agreeable taste. Some of the marketed oral quick release dosage forms are listed in the Table 1.

### Table 1: Marketed Oral Quick Released Dosage Forms

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<tr>
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<th>Product</th>
<th>Company</th>
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<td>Ranbaxy Labs Ltd, India</td>
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<tr>
<td>Famotidine</td>
<td>Pepcid RPD</td>
<td>Merck &amp; Co, USA</td>
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<tr>
<td>Olanzapine</td>
<td>Olanx insb</td>
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<td>Zofter OD</td>
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**References**