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A review on mouth dissolving drug delivery system

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Abstract
The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The desire of the improved palatability in orally administered products has prompted the development of numerous formulations with improved performance and acceptability. Mouth dissolving tablets (MDTs) and Solid dispersion technique have received ever increasing demand during the last few decades and the field has become a rapidly growing area in the pharmaceutical industry. The oral bioavailability of BCS class II drugs with poor solubility and reasonable permeability is limited by the drug dissolution step from drug products. A variety of dosage forms like tablets, films, wafers, chewing gums, microparticles, nanoparticles etc. have been developed for enhancing the performance attributes in the orally disintegrating systems. This review depicts the various aspects of MDT formulation and various preparation techniques for solid dispersion.

Keywords: mouth dissolving tablets; superdisintegrants; solid dispersion etc.

Introduction
The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration. Mouth dissolving drug delivery system with good flavor increases the acceptability of bitter drugs by various groups of population. It has been investigated for their potential in improving bioavailability of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs. United States food and drug administration (FDA) defined MDT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for MDTs generally ranges from several seconds to about a minute. In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor. The solubility of a drug is a key determined of its oral bioavailability and permeability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole come immediately to mind. A term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. Taste, odour, and appearance are important parameters that govern compliance. The undesirable taste is one of the formulation problems so that masking of drug is essential to improve patient compliance. MDT release drug in mouth for absorption through local oromucosal tissues and through pregastric that is oral cavity, gastric is stomach, esophagus, pharynax and postgastric that is small and large intestines of the gastrointestinal tract (GIT). Many patients who have difficulties in swallowing that are mentally retarded, Schizophrenic, uncooperative, cancer patients having nausea for long time, allergic and bronchitis people, dysphasia in geriatric patients, under developed central nervous system in padiatric patients. The traveling patients suffering from motion sickness (kinetosis) and sudden episodes of coughing during common cold and unavailability of water so that in case people use orodispersible tablets for quicker absorption and clinical effects Srivastava Saurabh *et al*.

Biopharmaceutical classification system
It is scientific framework for classifying drug substance based on its aqueous solubility and intestinal permeability. The biopharmaceutical classification system is guidance for predicting intestinal drug absorption provided by U.S food and drug administration.

Table 1: Biopharmaceutical classification of Drugs

Class 1 High solubility & high permeability	**Class 2** Low solubility & high permeability
Class 3 High solubility & low permeability	**Class 4** Low solubility & low permeability

Class 1: High Permeability and high solubility
Class 1 Compound bioavailability is determined by delivery of drug solution to intestine. examples - loratidine, loxoprofen.

Class 2: High Permeability and Low solubility
Bioavailability of class 2 compound by drug solubility/dissolution. examples- Nimusulide, Aceclofenac.

Class 3: Low Permeability and high solubility
Bioavailability of class 3 compound is limited by intestinal permeability. e.g Atropine.

Class 4: Low permeability and low solubility
Class 4 drug bioavailability is limited both by dissolution / solubility and intestinal permeability e.g. furosemide, hydroclorthiazide.

Mouth dissolving drug delivery system
- It requires no water for oral administration yet dissolves /disperse /disintegrate in mouth in a matter of seconds.
- It has a pleasing mouth feel
- It has an acceptable taste masking property.
- It is very harder and less friable.
- There is no residue in mouth after administration.
- It exhibit low sensitivity to environmental condition (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipments.

Advantages of mouth dissolving drug delivery system
1. There is no need of water to swallow the tablet
2. It can be easily administered to pediatric, elderly and mentally disabled patients.
3. It gives accurate dosing as compared to liquids
4. The dissolution and absorption of drug is fast offering rapid onset of action
5. Bioavailability of drugs is increased as some drugs are absorbed from mouth. Pharynx and esophagus through saliva passing down into the stomach
6. It is advantageous over liquid medication in terms of administration as well as transportation
7. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.

Challenges in formulation of MDT
Taste of active ingredients
A taste of mouth active ingredients is critical for patient acceptance. If the taste of product is bad, the consumer could not care about convenience of carrying MDT and prefer swallow tablet.

Fast disintegration
MDT needs to disintegrate in mouth and amount of saliva of patient. It can be designed to leave no residue or minimal in mouth after administration and also provide pleasant mouth feel.

Tablet strength and porosity
Strength of tablet is related to porosity and compression pressure.

API property
API should have unique properties such as solubility, hygroscopicity, particle size, crystal morphology, compressibility and bulk density of drug.

Moisture sensitivity
MDT should have low sensitivity to moisture. So, high water soluble excipients are used in formulation to enhance fast dissolving properties as well as good mouth feel.

API selection criteria
- Short half-life and frequent dosing drugs are unsuitable for MDT.
- API should have good stability in water and saliva.
- Ability to permeate the oral mucosa.
- API should remain non - ionized at oral cavity pH.
- Small to moderate molecular weight and ability to diffuse and partition into epithelium of upper GIT.

Taste masking of bitter API
Techniques used for taste masking
Taste masking by sweetners and flavours
Flavours and Sweetners are sugar based highly water soluble, pleasant taste and dissolve quickly in saliva. Aspartame, sucralose, peppermint flavour, strawberry, to produce pleasant taste and mouth feel. But some unpleasant drug cannot be masked by adding flavours and saweetners. Others methods are used for highly bitter drugs like complexation & coating on drug Vummaneni Vishnumurthy *et al.*

Flavour selection
In the salt taste sensation case apple, butterscotch is used. Chocolate, wild cherry is used in bitter taste. Vanilla and strawberry flavour is used in sweet taste and sour and mint taste sensation citrous flavour and peppermint are used. Menthol reduces the bitter taste and low calorie formulations. The flavour like wild cherry, raspberry, grape are recognized as good masking agent for saline drugs. Alkali metals like carbonate and bicarbonate in combination with mint flavour and sweeteners are used.

Table 2: Relative sweetness of commonly used sweetners

Sweetening agents	Relative Sweeteners	Comment
Sucralose	600	Synergestic sweetening effect
Glycerrhizin	50	Moderately expensive
Aspartame	200	Not very stable in solution
Acesulfame k	137-200	Bitter after taste if used higher conc.
Sucrose	1	Most commonly used
Saccharin	450	Unpleasant after taste
Cyclamate	40	Banned
Manitol	0.60	Negative heat of solution

Table 3: Reagent/Chemicals used in taste masking

Drug/Active agent	Types of formulation	Taste masking agent
Acetaminophen	Solution	Cheery flavour, Citric acid, Sodium bicarbonate
Chlorpheniramine, phenylpropanolamine	Solution	Sodium bicarbonate, Orange flavour, Citric acid
Ibuprofen	Syrup	Sodium saccharin
Guaifenesin	solution	Mono Sodium glycyrrhizinate
Famotidine	solution	Sodium bicarbonate, Citric acid

Taste masking by ion exchange resins

Ion exchange resins are solid and insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with surrounding medium stochiometrically and reversibly.

Advantages

Free from local and systemic toxicity and used as taste masking and rapid release. Weak acid cation-exchange resins carboxylic acid fuinctionality can be used to formulate chewable and dispersible tablets Lewis Shaila *et al.*

Table 4: Types of ion exchange resins

Type	Functional group	Polymer backbone	Commercial resins
Strong anion	- N - R_3	Polystyrene - DVB	Amberlite IR 400
Weak anion	- N - R_2	Polystyrene - DVB	Dowex 2
Strong cation	- So_3H	Polystyrene - DVB	Amberlite IR
Weak cation	-CooH	Methacrylic acid	Tulsion 335

Taste masking using inclusion complex

Complexation of drug with complexing agent improves biopharmaceutical parameters like improves drug dissolution rate and mask bitterness. Cyclodextrin (CD) is most widely used complexing agent e.g. Gama CD, Beta cyclodextrin. The complexing agent masks the bitter taste of drug taste by either decreasing its oral solubility on ingestion or decreasing amount of drug particle exposed to taste buds thereby reducing the perception of bitter taste.

Table 5: Taste masking using inclusion complex

Drug/Active agent	Complexing agent
Chlorampheniramine maleate	Indion CRP 244, 254
Ibuprofen	Hydroxy Propyl B – cyclodextrin
Diphenhydramine HCL	Indion CRP 244
Carbetapentane citrate	Cyclodextrin

Taste masking by granulation

Some saliva insoluble polymers can also act as binding agent. The granules with saliva insoluble polymer prepared from these polymers show less solubility in saliva and taste could be masked.

Taste masking by coating

The core material is coated with material which prevents rapid release of drug in saliva but allow release of drug in gastrointestinal tract where drug is expected to absorb. Coating with sugar solution and polymeric film coating like hydroxypropyl cellulose, povidone, hydroxypropyl methyl cellulose.

Table 6: Coating materials used in taste masking

Drug	Category	Coating material used
Acetaminophen	NSAIDS	Cellulose acetate butyrate, polyvinyl pyrrolidone
Dextromethorphan	Antitussive	Eudragit E 100
Ibuprofen	NSAIDS	Hydroxy ethyl cellulose

Taste masking by microencapsulation

In microencapsulation process the tiny droplets of solid or liquid material are coated with polymeric material are used. PCM formulation used different eudragits, ethyl cellulose, cellulose acetate with different emulsifying agents/emulsifier and plasticizer. The techniques used like air suspension coating, Multi orifice centrifugal process, Coacervation phase separation, spray drying, solvent evaporation.

Table 7: Taste masking by microencapsulation

Techniques	Drug	Coating agent	Dosage form
Wursterfluid bed coating	Acetaminophen, Caffeine	Eudragit E-100, Cross Carmellose	Dispersible and Chewable tablets
Tangential spray fluid bed coating	Acetaminophen	Cellulose acetate	Chewable tablet
Top spray fluid bed coating	Dextromethorphan hydrobromide, Chlorpheniramine maleate,	PVP K-30, Ethyl cellulose	Mouth melt tablet

Taste masking with lipophilic vehicles

Lipids

Oils, multiple emulsions O/W/O containing paraffin oil could mask bitter taste of chloroquine to some extent. Liposomes are carrier molecules of lipids which bitter drug is entrapped within lipid molecule. Inhibition of bitterness of drug by phospholipids such as soya lecithin, phosphatidic acid etc. Acetaminophen granules were improved by spraying with molten stearyl stearate mixing with suitable excipients.

Lecithin and lecithin like substances

Lecithin was added to solution or dispersion of drug with stirring to give a blend. The blend was mixed with powder excipients like lactose and mannitol.

Coating with hydrophilic vehicle

Carbohydrates coating act as barrier to drug particles minimizing interaction between taste buds and drug. The taste of orally administered drug can be masked by coating the drug with carbohydrate. Taste masking with Eudragit

EPO showed good mouth feel. Proteins, gelatins are used for taste masking.

Taste masking by effervescent agent
Taste masking with sodium bicarbonate and citric acid are advantageous for oral administration of drug. Some salts like NaCl are also used because of their salty taste.

Taste masking using ansesthetic agents and potentiators
The taste buds can temporarily anasthetized using local anesthetic agents like phenol and phenolic derivatives. Potentiators include thaumatic, neohesperidone dihyrochalcone (NHDC) and glycyrrhizin increase perception of acesulfame and sodium or calcium saccharin.

Taste masking by solid dispersion system
The dispersion of one or more active ingredients in inert or matrix carrier at solid state prepared by melting solvent method. Solid dispersion of one or more drug is prepared by solvent evaporation method, grinding, physical mixing and sugar carriers like dextrose.

Taste masking by prodrug formulation of drug
It can be used to increase or decrease aqueous solubility, mask bitterness, increase lipophilicity, improve adsorption, decrease local side effects.

Table 8: Taste masking by prodrug formulation of drug

Parent molecule	Reversible modification
Erythromycin	Alkyl ester
Clindamycin	Alkyl ester
Chloramphenicol	Palmitate or phosphate ester

Taste masking by adsorption and gelation
Adsorption involves preparing solution of drug and mixing with insoluble powder that adsorb the drug. Water insoluble gelation like sodium alginate in presence of bivalent metal ions on surface containing bitter drug can be used for taste masking.

Methods for preparation/formulation of mouth dissolving tablets
Sublimation
Compressed tablets composed of highly water soluble excipients as tablet matrix material do not dissolve rapidly in water. To generate porous matrix, volatile ingredients are used for sublimation process. Porous tablets have good mechanical strength and dissolve quickly. Sublimation materials like urea, ammonium carbonate, camphor, naphthalene were added to other tablet excipients and blend was compressed into tablet Srivastava Sourabh *et al.*

Moulding
Physical form of drug in tablets dissolves in molten carrier that made from water soluble sugars. The manufacturing process of molding tablets involves moistening the blend with hydro - alcohalic solvent followed by pressing into mold plates to form a wetted mass. The solvent is removed by air drying. The drug can exist as microparticles dispersed in matrix. It can dissolve in molten carrier to form solid solution and remaining particles dispersed and undissolved in matrix. The drug mouth feel and dissolution rate will depend on type of dissolution/dispersion.

Spray drying
Highly porous and fine powders can be produced by spray drying and solvent is evaporated rapidly during spray drying. Gelatin used as supporting agent and matrix lactose and mannitol as bulking agent and sodium starch glycolate and cross carmellose sodium used as superdisintegrants. Acidic ingredients like citric acid and alkaline ingedients like sodium bicarbonate to enhance dissolution and disintegration.

Freeze drying
In this process, water is sublimated from the product after freezing is called freeze drying. Freeze dried products have more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to bulking agent and sometimes the drug enhances the dissolution characteristics of formulation.

Mass- extrusion
This technology involves softening of active blend using solvent mixture of water soluble polyethylene glycol using methanol and syringe to get cylinder of product into segments using heated blade to form tablets. The dried cylinder used to coat granules of bitter tasting drugs and masking their bitter taste.

Melt granulation
In melt granulation process, the pharmaceutical powders are agglomerated by meltable binder. No water or organic solvent is needed in these techniques. In this process, no drying step, less time consuming and uses less energy than wet granulation. It is useful to enhance dissolution rate of poorly water soluble drugs like griseofulvin.

Phase transition process
Combination of low and high melting point sugar alcohols is used to make MDT without special apparatus. MDT were produced by compressing powder containing erythritol (melting point 122 ˚C) and xylitol (melting point 95 ˚C) and then heating about 93 ˚C for 15 min.

Direct compression
It is easiest method of manufacturing tablets with conventional equipment, commonly available excipients and limited number of processing steps is involved in direct compression. Disintegrants have major role in disintegration and dissolution of direct compression mouth dissolving tablet. Indirectly compressed tablets disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agent that generates carbon dioxide.

Limitations of Mouth Dissolving Tablets
- The tablets usually have insufficient mechanical strength hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

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