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Review Article

RECENT ADVANCES ON MOUTH DISSOLVING DRUG DELIVERY SYSTEM

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Abstract

A mouth dissolving drug delivery system is developed to facilitate ease of medication and the field has become a rapidly growing area in the pharmaceutical industry. They are designed to be dissolved on the tongue rather than swallowed whole. Such formulation provide an opportunity for product line extension in the many elderly person who have difficulties in taking conventional oral dosage form (viz., solution, suspension ,tablets, and capsules) because of hand tremor and dysphagia. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in these dosage forms which dissolve rapidly in saliva without chewing and additional water. Taste masking of active ingredients becomes essential in this system because the drug is entirely released in mouth.

Keywords: Dysphagia, Mouth Dissolving Drug Delivery System, Paediatrics, Geriatrics

Mouth dissolving tablets are solid dosage form that dissolves and disintegrates in the mouth saliva without water within 60 seconds or less than 60 seconds. Oral drug delivery forms are the largest portion/segment of all types of dosage forms and growing as much as ten percent per year. Orange book defined ODT as "A solid dosage form disintegrates rapidly within a matter of seconds when placed upon tongue". The European pharmacopoeia defines Orodispersible when placed in mouth disperses rapidly before swallowing. The Centre for Drug Evaluation and Research (CDER) defined that a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. ODT are called Orodispersible, disintegrating, mouth dissolving, fast-melt, and quick - dissolve, and rapid disintegrating tablets.

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 paediatric 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. Around 35 % of general population, additional 30-40% of elderly institutionalized patients and around 18-22 % of person has difficulty in swallowing.

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, 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.
- **Physiology of taste buds**

Taste buds have structures like onion-shaped containing 50-100 taste cells. In case of mouth dissolving dosage form, the active ingredients first come in contact with oral cavity where it get dissolved by saliva and enter via taste pore.

They interact with surface protein known as taste receptors. Taste transduction has interaction of molecule with a taste receptor cells known as taste buds. The taste buds have main function is information about taste of molecule to central nervous system. These interactions because electrical changes within taste cells that send chemical signals neurotransmission to brain.

The transduction of most bitter and sweet compound is mediated by G protein (gustducin & transduction) but salty and sour is done by ion channels. Dissociation of gustducin into alpha and beta subunit decreases cAMP level and activate phospholipase C that generates second messenger IP_3 and DAG. This complex results in taste cells sending signal to brain and we examined the unpleasant and bitter taste by negative and positive charged atoms. Many factors are considered taste masking like total dose of drug, particle shape and size distribution, disintegration and dissolution, bioavailability and release rate, extent of bitter taste etc.

Table 1: Taste sensation and related area of tongue

Taste	Threshold conc.	Area of tongue
Sweet (glycerol, sugar)	0.5%	Tip of tongue
Salt (sodium)	0.25%	Tip and sides of tongue
Sour (acidic substance)	0.007%	Sides of tongue
Bitter	0.000054%	Back of tongue

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 produce flavours, strawberry to produce pleasant taste and mouth feel. But some unpleasant drug cannot be masked by adding flavours and sweetners. Others methods are used for highly bitter drugs like complexation & coating on drug.

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.

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 functionality can be used to formulate chewable and dispersible tablets.

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 saccarin
Guaifenesin	solution	Mono Sodium glycyrrhizinate
Famotidine	solution	Sodium bicarbonate, Citric acid

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.

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.

Taste masking by microencapsulation

In microencapsulation process the tiny droplets of solid or liquid material are coated with polymeric material are used. 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.

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 takes place 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 anesthetic 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 was 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 5: Taste masking using inclusion complex

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

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

Table 7: Taste masking by microencapsulation

Techniques	Drug	Coating agent	Dosage form
Wurster fluid 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

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.

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 - alcoholic 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 ingredients 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.

Role of disintegration in MDT formulation

Disintegrants added to tablet to induce break up of tablet when it comes in contact with aqueous fluid and process of disaggregation of particles before drug dissolution occurs known as disintegration process and excipient used known as disintegrants. The main objective of adding disintegrants are to increase surface area of tablet and cohesive force keep particles together in tablet. Addition of superdisintegrants in fast dissolving tablets leads to quick disintegration and improves dissolution. Disintegration efficiency is based on combined measurement of swelling force development and amount of water absorption.

The effective superdisintegrants improved compatibility, compressibility and have no negative impact on mechanical strength of formulation containing high dose drug.

The good superdisintegrants should have-

- Good hydration capacity
- Poor gel formation and poor solubility
- Good mouth feels and flow properties

By capillary action

If tablet comes in contact with suitable aqueous medium, the medium penetrates the tablet and replaces air absorbed on particles which break the intermolecular bond and break tablets into fine particles.

By swelling

Tablets with high porosity show poor disintegration due to lack of adequate swelling force.

Because of heat of wetting

The disintegrants with exothermic properties gets wetted; stress is generated due to capillary air expansion, which helps disintegration of tablet.

Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid.

By enzymatic reaction

The enzyme present in body act as disintegrants. So these enzymes destroy binding action of binder and helps disintegration.

Due to particle repulsive force/disintegrating particles

Guyot - Hermann discovered a particle repulsive theory that nonswelling particles cause disintegration of tablets.

Due to deformation

The disintegrated particles get deformed and deformed particles get into normal structure when come in contact with water or aqueous media.

Biopharmaceutical classification system

It is scientific framework for classifying drug substance based on its aqueous solubility and intestinal permeability. Acetaminophen is a BCS class 3 drugs. The biopharmaceutical classification system is guidance for predicting intestinal drug absorption provided by U.S food and drug administration.

Solubility

Drugs with poor aqueous solubility exhibit poor bioavailability. This leads to loss of therapeutic efficacy of drug molecule and increase dose of drug. Bioavailability is measurement of extent of therapeutically active drugs that reaches in systemic circulation and available at the site of action. Oral bioavailability of drug is affected by variety of factor which influences absorption from gastrointestinal tract. One determinant factor for absorption is drug dissolution which is influenced by solubility of drug in GI fluids.

Table 9: Biopharmaceutical classification of Drugs

Class 1 High solubility & high permeability e.g. loratidine, loxoprofen	Class 2 Low solubility & high permeability e.g. Nimusulide, Aceclofenac
Class 3 High solubility & low permeability e.g. Atropine	Class 4 Low solubility & low permeability e.g. furosemide, hydroclorthiazide

Table 10: Solubility determination

Descriptive term	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Insoluble or practically insoluble	More than 10000

Techniques of solubility and bioavailability enhancement

pH adjustment

By applying pH change, Poorly water soluble drugs with parts of molecule that can be protonated (base) or deprotonated (acid) may be dissolved in water. After pH adjustment, ionisable compounds may be acids or bases or zwitter ionic are stable and soluble.

Micro- emulsion

It is clear preconcentrate, thermodynamically stable translucent system containing mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves poorly water soluble drug.

Particle size reduction

By reducing particle size, increased surface area may improve dissolution properties of drug.

Complexation/Inclusion complexes

It can be formed simply by adding drug and excipients together, resulting in enhanced drug solubilization e.g. cyclodextrin.

Co- solvency

Co solvents are mixture of water and one or more water miscible solvents used to create solution with enhanced solubility of poorly soluble compounds.

Miceller solubilization

The use of surfactants like CMC to improve dissolution performance of poorly soluble compound has successfully employed.

Solid dispersion

A poorly soluble drug is dispersed in highly soluble solid hydrophilic matrix which enhanced dissolution of drug. e.g Carbamazepine in polyethylene glycol 4000 increased the rate and extent of dissolution of carbamazepine.

Nano – suspension

This technology is applied to poorly soluble drugs that are insoluble in both water and oils.

Milling

Nanoscale particles can be produced by wet milling process. In ball mills, particle size reduction is achieved by using attrition forces.

High pressure homogenization

It can be performed in water or non - aqueous media or water reduced media. The particles are disintegrated by shear force.

Wet granulation method

This process is using liquid binder mixing with powder mixture. In tablet process, all ingredients should be well mixed. The over wetting will cause them to be too soft and friable.

Any other suitable ingredients NaCl, Menthol (cooling sensation), Sodium bicarbonate, Citric acid, Strawberry, Peppermint flavor are used.

Table 11: Marketed MDT products

Brand name	Active ingredient	Category	Name of company
Claritin ® RediTabs ®	Loratadine	Antihistamine	Scherig corporation
Feldene Melt ®	Piroxicam	NSAIDs	Pfizer
Maxalt® - MLT ®	Rizatritpan benzoate	Migrane	Merck
Pepeid ® ODT	Femotidene	Anti - ulcer	Merck
Zyperxa ®	Olazepine	Psychotropic	Eli Lilly
Zofran ® ODT	Olandansetron	Antiemetic	Galaxo Smith kline
Resperdal ® M - TabTM	Resperidone	Schizophrenia	Janssen
ZubrinTM (Pet drug)	Tepoxelin	Canine NSAIDs	Scherig corporation
ZelaparTM	Selegiline	Parkinsons disease	ElanlAmarin corporation
Klonopin ® wafer	Clonazepam	Sedation	Roche
Childrens Dimetapp ® ND	Loratadine	Allergy	Wyeth consumer Healthcare
Imodium Istant Melts	Loperamide HCL	Antidiarrheal	Jannsen
Propulsid ® Quicksolv ®	Cisapride Monohydrate	Gastrointestinal prokinetic Agent	Jannsen

Tempra Quicksolv ®	Acetaminophen	Analgesic	Bristol - Mters squibb
Remeron ® Soltab ®	Mirtazapine	Anti-dipression	Organon Inc.
Triaminic ® Softchews ®	Various combination	Pediatric cold cough, Allergy	Novartis consumer Health
Zomig-ZMT ® and Rapimelt ®	Zolmitriptan	Anti-migraine Astra Zeneca	AstraZeneca Alavert ® Loratadine Allergy
DuraSolv ® Alavert ®	Loratadine	Allergy	Wyeth Consumer Healthcare
NuLev ®	Hyoscyamine sulfate	Anti - ulcer	Schwarz Pharma
Kemstro™	Baclofen	Anti - spastic analgesic	Schwarz Pharma
Benadryl ® Fastmelt ®	Diphenhydramine citrate	sinus pressure relief	Pfizer
Nasea OD	Ramosetoron HCl	Anti - emetic	Yamanouchi
Gaster D	Famotidine	Anti - ulcer	Yamanouchi
Excedrin ® QuickTabs	Acetaminophen	Pain reliever	Bristol - Myers Squibb

Table 12: Excipients used in mouth dissolving tablets

Disintegrants	Cross Carmellose Sodium, SSG, Crosspovidone
Diluents	Mannitol, MCC
Sweetners	Aspartame, Sucralose, Ammonium glycyrrhin
Binder	PVP K 30, Ethyl cellulose, Eudragit
Solvent	Dichloromethane, Iso Propropyl Alcohol, Ethanol, Water
Glidents	Talc, Mg. stearate

Conclusion

Mouth dissolving tablet transform into easy-to-swallow suspension on contact with the saliva, after being ingested in mouth. These are particularly useful for paediatric or geriatric patients, can be taken without liquids and facilitate treatment of emergent pain, irrespective of the place and situation where it may arise. The concept of ODT evolved to overcome some of the problems that existed in the conventional solid dosage form i.e. difficulty in swallowing of tablet in paediatric and geriatric patients who constitute a large proportion of world's population. It may lead to improve efficacy, bioavailability, rapid onset of action, better patient compliance due to its quick absorption from mouth to GIT as the saliva passes. Orally disintegrating tablet acts like solid dosage form when outside the body and solution when administered. The formulations of MDTs obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth without water. In future MDT may be most acceptable and prescribed dosage form due to its quick action. Their characteristic advantages such as administration without water, anytime, anywhere lead to their increased patient compliance in today's scenario of hectic life. Because of increased patient demand, popularity of these dosage forms will surely expand in future.

Future prospects

The innovation in the arena of formulating MDTs are aimed at both increasing the performance of the dosage form by decreasing the disintegration time and increasing the patient compliance by masking the objectionable taste of the active ingredients. To fulfill these medical needs, formulators have devoted considerable efforts to develop a novel type of dosage form for oral administration. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under treated patient population. However, substantial amount of research remains to be conducted for the development of protein and peptide based systems that have limited bioavailability when administered by conventional tablets. Therefore in coming era, there is going to be continued interest for the development of natural polymers based orally disintegrating tablets. The future trends in the innovation of drug delivery systems will continue to bring together different technological disciplines and formulation aspects to create novel technologies.

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