

Mouth dissolving tablets: An overview on future compaction in oral formulation technologies

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ABSTRACT

The desire of improved palatability in orally administered products has prompted the development of numerous formulations with improved performance and acceptability. Orally Disintegrating tablets (ODTs) have received ever-increasing demand during the last few decades, and the field has become a rapidly growing area in the pharmaceutical industry. The unique property of mouth dissolving tablet is that they are rapidly disintegrating and/or dissolving and release the drug as soon as they come in contact with saliva, thus obviate the requirement of water during administration. This article reviews the earlier applications and methodologies of taste masking and also emphasize on the recent developments and approaches of bitterness reduction for orally used pharmaceuticals. Apart from the conventional methods of fabrication, this review also provides the detailed concept of some unique patents; technologies developed and marketed formulations of Mouth Dissolving Tablets (MDTs).

Keywords: orally disintegrating tablets (ODTs), orodispersible tablets, taste masking, mouth dissolving tablets (MDTs).

INTRODUCTION

Orally disintegrating tablets offer great advantages for patients having difficulty in swallowing. The condition in which patient suffers from difficulty in swallowing is known as 'Dysphagia'. It is common among all age groups, especially in elderly patients [1]. Disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy [2–5]. There is an important role of drinking water in the swallowing of oral dosage forms but some time people experiences an inconvenience in swallowing. The problems can be resolved by means of Mouth Dissolving Tablets (MDTs), when water is not available as during journey, also in case of the motion sickness (kinetosis) and sudden episodes of coughing

during the common cold, allergic condition and bronchitis. MDTs are also abbreviated as “fast-melting, fast-dissolving, oral disintegrating or orodisperse tablets”. The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations [6]. Recently European Pharmacopoeia defines the term “Orodispersible tablet” as a tablet that to be placed in the mouth where it disperses rapidly before swallowing in less than three minutes [7].

1. Desired characteristics and development challenges of ODT

- ✓ Rapid disintegration of tablet
- ✓ Sufficient mechanical strength
- ✓ Avoid tablet size enlargement
- ✓ Taste and mouth feel
- ✓ Stability
- ✓ Good packing
- ✓ Good compatibility with development technology
- ✓ Swellability
- ✓ Minimum or no residue in mouth
- ✓ No effect of drug properties on formulation
- ✓ Bioavailability

2. Salient features of fast dissolving drug delivery system: [8, 9]

- ✓ Should dissolve or disintegrate in the mouth within a few seconds.
- ✓ High drug loading should be allowed.
- ✓ They should be compatible with taste masking and other excipients.
- ✓ The mouth feel should be pleasant.
- ✓ After oral administration they should leave minimal or no residue in mouth.
- ✓ To withstand the rigors of the manufacturing process and post manufacturing handling, they must have sufficient strength.
- ✓ They should be less sensitive to environmental conditions such as humidity and temperature.
- ✓ The cost of manufacturing of tablets should be low.

3. Traditional taste masking techniques in oral pharmaceuticals

3.1 Taste masking using flavours and sweeteners: Artificial sweeteners and flavours are generally being used along with other taste-masking techniques to improve the efficiency of these techniques in dentifrices, mouthwashes and cough drops [10]. The examples are given in Table no. 1.

3.2 Taste masking using Lipophilic Vehicles: - It is the property of oils, surfactants, poly alcohols and lipids to increase the viscosity in the mouth and to coat the taste buds and therefore they are potential taste masking agents. Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Examples are given in Table no. 2.

Table. 1: Taste masking using flavours and sweeteners

S. No	Drug(s)	Taste masking agent(s)	Ref.
1	Aspirin	Sodium phenolate	11
2	Chlorpheniramine, Phenyl propanolamine	Sod. bicarbonate, citric acid, orange/cream flavour	12
3	Famotidine	Sod. bicarbonate, citric acid, lemon flavour	13
4	Ibuprofen	Sod. citrate dihydrate, sod. saccharin, refined sugar	14
5	Theophylline	D-sorbitol, sodium saccharin, sodium glutamate, and vanilla essence	15
6	Acetaminophen	Sod. bicarbonate, citric acid, cherry flavour	16
7	Caffeine	Starch, lactose, and mannitol	17

Table. 2: Taste masking using lipophilic vehicles

S. No	Drug(s)	Taste masking agent(s)	Ref.
1	Isoprothiolane	Hydrogenated oil and HPMC	18
2	Acetaminophen	Molten stearyl stearate	19
3	Talampicillin HCl	Magnesium aluminum silicate & soyabean lecithin	20
4	Clarithromycin	Glyceryl monostearate and AMCE	21
5	Indeloxazine HC	Hydrogenated oil and surfactants	22

Note: HPMC=Hydroxypropyl methyl cellulose; AMCE=aminoalkyl methacrylate copolymer E

3.3 Taste masking by Coating with Hydrophilic Vehicles: - Carbohydrates can be used as a coating material to mask the taste of orally administered drugs. Various forms of proteins have been used extensively for taste masking. Some examples are given in Table no. 3.

Table. 3: Taste masking using polymer coating

S. No	Drug(s)	Polymer(s) used	Ref.
1	Pinaverium bromide	Cellulose or shellac	20
2	Ibuprofen	Methacrylic acid copolymer (Eudragit)	23
3	Sparfloxacin	L-HPC, EC, HMC/EC, HPMC, Tio ₂ , sucrose, fatty acid ester mixture	24,25
4	Amoxicillin trihydrate	MCC, L-HPC	26
5	Clarithromycin	Carbopol, PVP	27
6	Roxithromycin	PEG, Eudragit L 100-55	28
7	Cefuroxime axetil	Eudragit L-55 and RL	29
8	Pirenzepine & Oxybutynin	Eudragit E-100, MCC, HPC	30
9	Levofloxacin	Eudragit E100, cellulose acetate	31

HPMC= Hydroxypropyl methyl cellulose; HEC= Hydroxyethyl cellulose; HPC=Hydroxypropyl cellulose; L-HPC= Low substituted hydroxypropyl cellulose; CMC= Carboxy methyl cellulose; PVP= Polyvinyl pyrrolidone; EC=Ethyl cellulose; MCC= Microcrystalline cellulose; PEG= Polyethylene glycol; Tio₂=Titanium di-oxide.

3.4 Taste masking by Ion-Exchange Resins (IERS):- To stabilize the sensitive components, to sustain the drug release, to disintegrate tablets, and to mask taste, ion-exchange resins are used in formulations. Some examples of drugs and taste masking agents and ion exchange resins are given in Table no.4.

Table. 4: List of drugs and taste masking ion exchange resins

S. No	Drug(s)	Resin/complexing agent	Ref.
1	Carbetapentane citrate	Cyclodextrin	32
2	Ibuprofen	Hydroxypropyl b-cyclodextrin	33
3	Diphenhydramine HCl	Indion CRP 244, indion CRP 254	34
4	Buflomedil	Amberlite IRP 69	35
5	Orbifloxacin	Amberlite IRP 69	36

4. Newer manufacturing technologies used now a days for MDT's

Some of the new advanced technologies which are commonly being used in last few decades are summarized as:-

- | | |
|----------------------------------|---------------------------|
| 4.1 Freeze drying/Lyophilization | 4.6 Sublimation |
| 4.2 Molding | 4.7 Mass Extrusion |
| 4.3 Direct Compression | 4.8 Nanonization |
| 4.4 Cotton Candy Process | 4.9 Fast Dissolving Films |
| 4.5 Spray Drying | |

4.1 Freeze drying or lyophilization: - It is one of the first generation techniques for preparing MDT, in which sublimation of water takes place from the product after freezing. The formulations show enhanced dissolution characteristics due to the appearance of glossy amorphous structure to bulking agents and sometimes to drug. The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspensions. Primary problems associated with water-soluble drugs are formation of eutectic mixture, because of freezing point depression and formation of glassy solid on freezing, which might collapse on sublimation. The addition of mannitol or crystal forming materials induces crystallinity and imparts rigidity to amorphous material. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects. High cost of equipment and processing limits the use of this process. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms [37-39].

4.2 Tablet Molding: - There are two types of molding process i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro-alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). Air-drying is done to remove the solvent. The tablets manufactured so formed are less compact than compressed tablets and possess a porous structure that hastens dissolution. In the heat molding process a suspension is prepared that contains a drug, agar and sugar (e.g. mannitol or lactose). This suspension is poured in the blister packaging wells, and then agar is solidified at the room temperature to form a jelly and dried at 30°C under vacuum. The main concern about these molded tablets is their mechanical strength, which can be achieved by using binding agents [40-43]. The spray congealing of a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form was used to prepare the taste masked drug particles. As compared to the lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial scale manufacturing [44, 45].

4.3 Direct Compression [40-43]:- Direct compression represents the simplest and most cost effective tablet manufacturing technique. MDT can be prepared by using this technique because of the availability of improved excipients especially super-disintegrants and sugar based excipients.

(a) Super-disintegrants: - The rate of disintegration gets affected by the addition of super-disintegrants and hence the dissolution. Other ingredients like water-soluble excipients and effervescent agents also increase the disintegration.

(b) Sugar based excipients: - The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel. Mizumito et al classified sugar-based excipients into two types on the basis of molding and dissolution rate: Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate. Type 2 saccharides (maltose and maltitol) exhibit high mouldability but low dissolution rate.

4.4 Cotton Candy Process: - The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament [46, 47]. A matrix known as ‘floss’, with a combination of excipients, either alone or with drugs is prepared by using shear form technology. Like cotton-candy fibers floss is fibrous material made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F [48]. However, other polysaccharides such as poly-maltodextrins and poly-dextrose can be transformed into fibers at 30–40% lower temperature than sucrose. Due to this modification thermo labile drugs can be safely incorporated into the formulation [49]. This process results in a highly porous product and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below:

(a) Floss blend: - The floss mix is prepared by blending the 80% sucrose in combination with mannitol/dextrose and 1% surfactant. The surfactant maintains the structural integrity of the floss fibers by acting as crystallization enhancer. This process helps in retaining the dispersed drug in the matrix, thereby minimizes the migration out of the mixture [50].

(b) Floss processing: - The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in ‘cotton-candy’ formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature [51-53].

(c) Floss chopping and conditioning: - In this step fibers are converted into smaller particles in a high shear mixer granulator. The partial crystallization is done by spraying ethanol (1%) onto the floss and subsequently evaporated it to impart improved flow and cohesive properties to the floss. This is called Conditioning. [48].

(d) Blending and compression: - Finally, the chopped and conditioned floss fibers are blended with the drug and other excipients and compressed into tablets. Exposure of the dosage forms to elevated temperature and humidity conditions (40 °C and 85% RH for 15min) improves the mechanical strength of tablets due to expected crystallization of floss material that result in binding and bridging, to improve the structural strength of the dosage form [53].

4.5 Sprays-Drying: - Allen et al., [54] have used spray-drying for the production of MDTs. The formulations contained hydrolyzed and non hydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. By adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate) disintegration and dissolution were further enhanced [55]. The porous powder was obtained by spray drying the above suspension which was compressed into tablets. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium.

4.6 Sublimation: - To produce MDTs with high porosity, sublimation is the technique which has been used successfully. When volatile ingredients are compressed along with other excipients into tablets, a porous matrix is formed which are finally subjected to a process of sublimation. For this purpose inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, urea and urethane) have been used [56]. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Makino et al., [55] reported a method using water as a pore-forming material.

4.7 Mass-Extrusion:- This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. This softened mass is extruded through the extruder or syringe and a cylindrical shaped extrude is obtained which are finally cut into even segments using heated blade to form tablets. Granules of bitter drugs can be coated using this method to mask their taste [57].

4.8 Nanonization: - A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique [58]. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into MDTs. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (up to 200 mg of drug per unit).

4.9 Fast Dissolving Films: - It is a newer developing front in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, CMC, HPMC, HEC, HPC, PVP, PVA etc.), drug and other taste masking ingredients are dissolved in non-aqueous solvent to prepare non-aqueous solution, which on evaporation of solvent forms a film. Resin adsorbate or coated micro particles of the drug can be incorporated into the film if the drug is bitter [59]. This film when placed in mouth, melts or dissolves rapidly and release the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 sec with instant drug delivery and flavored taste [60].

Table no. 5 and 6 listed various patented technologies and marketed preparations respectively.

Table: 5. Patented technologies for fast dissolving tablets

Patented Technology	Basis of Technology	Developing Company	Brand Names	Ref.
Oraquick	Taste masking	KV Pharm.Co.,Inc.	Hyoscyamine Sulfate ODT	61
Advatab	CR Technology	Eurand International	AdvaTab	62,63
Wowtab	Direct compression	Yamanouchi Pharma Tech. Inc.	Gaster D	34,68
Flashdose	Cotton Candy Process	Fuisz Technology Ltd.	Relivia Flash dose	64,65
Ziplets	Direct compression	Eurand International	Cibalgina DueFast	66
Orasolv	Direct compression	Cima Labs,Inc.	Tempra Quicklets, Zolmig Repimelt	34,67
Durasolv	Direct compression	Cima Labs, Inc.	NuLev , Zolmig ZMT	68
Flashtab	Direct compression	Ethypharm	Nurofen FlashTab	43
Zydis	Lyophilization	R.P.Scherer,Inc.	Claritin Reditab, Dimetapp Quick Dissolve	34,69
Lyoc	Lyophilization	Farmalyoc	Spasfon Lyoc	66
Quicksolv	Lyophilization	Janssen pharmaceuticals	Propulsid Quicksolv, Risperdal M Tab	66

Table: 6. Commercially available fast dissolving tablets

Trade Name	Active Drug	Manufacturer
Cefadur DT	Cefadroxil	Cipla (protec)
Cefinar DT	Cefixime	Zydus Alidac
Zofran ODT; Vomokind MD	Ondansetron	Glaxo Wellcome; Mankind
Torrox MT; Dolib MD;	Rofecoxib	Torrent pharmaceuticals; Panacea;
Acivir DT	Acyclovir	Cipla
Dom DT; Domestil DT	Domperidone	Dr. Morepen; Torrent Pharma
Nexus MD; Nimex MD; Nimed MD; Nimulid MD	Nimesulide	Lexus; Mexon Health Care; Zota pharma; Panacea Biotech
Romilast	Montelukast	Ranbaxy
Mosid MT	Mosapride	Torrent Pharma

CONCLUSION

The technologies depicted in this article demonstrate how recent advances in formulation development and processing technologies meet the efforts to achieve more sophisticated drug delivery system (Oral Disintegrating/Mouth Dissolving Tablets). MDT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in traveling, has difficulty in swallowing and may not have access to water. MDT offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid. Due to the constraints of the current mouth dissolving drug delivery system (MDDDS) as highlighted above, there is an unmet need for improved manufacturing processes for fast dissolving tablets that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets. To fulfill these medical needs, formulators have devoted considerable efforts to develop a novel type of dosage form (tablet) for oral administration. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. 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 populations. However, substantial amount of research remains to be conducted for the development of natural

polymer based system which is highly site specific. Furthermore, development of such system correlating well with all desired characteristics for effective delivery would nevertheless be an appropriate futuristic endeavor. 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 innovations of drug delivery systems will continue to bring together different technological disciplines and formulation aspects to create novel technologies.

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