Mouth Dissolving Tablets I: An Overview of Formulation Technology

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Abstract

Methods to improve patient’s compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Therefore, these dosage forms have lured the market for a certain section of the patient population which include dysphagic, bed ridden, psychic, geriatric and paediatric patients. Several techniques have been developed in the recent past, to improve the disintegration quality of these delicate dosage forms without affecting their integrity. This article focuses on the technologies available and the advances made so far in the field of fabrication of mouth dissolving tablets. Apart from the conventional methods of fabrication, this review also provides the detailed concept of some unique patented technologies like Zydis, Lyoc, Quicksolv, Orasolv, Durasolv, Flashtab, Oraquick, Wowtab and Ziplet alongwith their advantages and limitations.

Keywords

Mouth dissolving • Fast disintegrating • Dysphagia • Lyophilization • Direct compression
Introduction

The concept of MDDDS emerged with an objective to improve patient’s compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients [1]. This 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]. One study showed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste [4]. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain a healthy life [6, 7]. Children may also have difficulty in ingesting because of their underdeveloped muscular and nervous systems [8]. The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water [3]. Aforementioned problems can be resolved by means of Mouth Dissolving Tablets (MDTs).

MDTs are known by various names such as “fast-melting, fast-dissolving, oral disintegrating or orodisperse”. The European Pharmacopoeia defines the term “orodisperse” as a tablet that can be placed in the mouth where it disperses rapidly before swallowing [9]. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction [10].

MDTs disintegrate and/or dissolve rapidly in saliva; therefore, water is not required during administration. Some tablets are designed to dissolve in saliva within few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast-disintegrating tablets, as they may take about one minute to disintegrate completely.

MDTs offer several advantages over other dosage forms like effervescent tablets, dry syrups and chewing gums/tablets, which are commonly used to enhance patient’s compliance. Administering effervescent tablets/granules and dry syrups involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage form if the taste masking coat ruptures during mastication.

Advantages of MDDDS

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients [11, 12].

- Patient’s compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
• Good mouth feel property of MDDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients due to improved taste of bitter drugs.

• Convenience of administration and accurate dosing as compared to liquid formulations.

• Benefit of liquid medication in the form of solid preparation.

• More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action [12, 13].

• Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects [14].

• New business opportunities: product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent-life extension [12, 13].

**Ideal Properties of MDTs**

They should [15, 16] -

• not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.

• allow high drug loading.

• be compatible with taste masking and other excipients.

• have a pleasing mouth feel.

• leave minimal or no residue in the mouth after oral administration.

• have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.

• exhibit low sensitivity to environmental conditions such as humidity and temperature.

• be adaptable and amenable to existing processing and packaging machinery.

• allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

**Techniques of MDT Formulation**

The fast-dissolving property of the MDTs is attributed to quick ingress of water into tablet matrix resulting in rapid disintegration. Hence, the basic approaches to develop MDTs include:
• Maximizing the porous structure of the tablet matrix.
• Incorporating the appropriate disintegrating agent/agents.
• Using highly water-soluble excipients in the formulation [15].

So far, several techniques have been developed on the basis of different principles. The resulting dosage forms vary on grounds like mechanical strength of the final product, drug and dosage form stability, mouth feel, taste, rate of dissolution and absorption from saliva, swallowability and overall bioavailability. Table 1 shows the list of some patented technologies.

**Tab. 1.** List of Patented technologies based branded Products

<table>
<thead>
<tr>
<th>Patented Technology</th>
<th>Basis of Technology</th>
<th>Technology developed by Company</th>
<th>Active Ingredient (Brand Names)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zydis</td>
<td>Lyophilization</td>
<td>R.P.Scherer,Inc.</td>
<td>Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-Tab)</td>
</tr>
<tr>
<td>Quicksolv</td>
<td>Lyophilization</td>
<td>Janssen pharmaceutics</td>
<td>Phloroglucinol Hydrate (Spasfon Lyoc)</td>
</tr>
<tr>
<td>Lyoc</td>
<td>Lyophilization</td>
<td>Farmalyoc</td>
<td>Ibuprofen (Nurofen FlashTab)</td>
</tr>
<tr>
<td>Flashtab</td>
<td>Direct compression</td>
<td>Ethypharm</td>
<td>Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt), Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)</td>
</tr>
<tr>
<td>Orasolv</td>
<td>Direct compression</td>
<td>Cima Labs,Inc.</td>
<td></td>
</tr>
<tr>
<td>Durasolv</td>
<td>Direct compression</td>
<td>Cima Labs, Inc.</td>
<td></td>
</tr>
<tr>
<td>Wowtab</td>
<td>Direct compression</td>
<td>Yamanouchi Pharma Tech. Inc.</td>
<td>Famotidine (Gaster D)</td>
</tr>
<tr>
<td>Zipllets</td>
<td>Direct compression</td>
<td>Eurand International</td>
<td>Ibuprofen (Cibalginina DueFast)</td>
</tr>
<tr>
<td>Advatab</td>
<td>Direct compression</td>
<td>Eurand International</td>
<td>AdvaTab cetrizine, AdvaTab Paracetamol</td>
</tr>
<tr>
<td>Flashdose</td>
<td>Cotton Candy Process</td>
<td>Fuisz Technology, Ltd.</td>
<td>Tramadol HCl (Relivia Flash dose)</td>
</tr>
<tr>
<td>Oraquick</td>
<td>Micromask taste masking</td>
<td>KV Pharm.Co.,Inc.</td>
<td>Hyoscyamine SulfateODT</td>
</tr>
</tbody>
</table>
Various manufacturing techniques for MDDDS include:

1. Lyophilization
2. Moulding
3. Direct Compression
4. Cotton Candy Process
5. Spray Drying
6. Sublimation
7. Mass Extrusion
8. Nanonization
9. Fast Dissolving Films

**Freeze-Drying or Lyophilization**

In freeze-drying process, the water is sublimed from the product after it is frozen. This technique forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture MDTs. Jaccard and Leyder used lyophilization to develop an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability of several drugs such as spironolactone and trolendomycin [14]. Corveleyn and Remon studied various formulation and process parameters by using hydrochlorothiazide as a model drug [17, 18].

Zydis technology (ZT) is a patented technique [13, 19–21], which had been used for drugs like famotidine, loperamide, piroxicam, oxazepam, lorazepam, domeperidone, brompheniramine, olanzepine, ondansetron and rizatriptan. Thirteen products are currently available in the market, which had been manufactured using this technology [22]. In U.S., the MDT products available are: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. In the worldwide market, Zydis formulations are also available for oxazepam, lorazepam, loperamide, and enalapril [23].

ZT utilizes a unique freeze-drying process to manufacture finished dosage units which significantly differ from conventional oral systems [24]. The process involves the following steps:

Stage 1 - bulk preparation of an aqueous drug solution or suspension and its subsequent precise dosing into pre-formed blisters. It is the blister that actually forms the tablet shape and is, therefore, an integral component of the total product package.

Stage 2 - passing the filled blisters through a specially designed cryogenic freezing process to control the ultimate size of the ice crystals which ensures that the tablets possess a porous matrix to facilitate the rapid disintegration property. These frozen units are then transferred to large-scale freeze dryers for the sublimation process, where the majority of the remaining moisture is removed from the tablets.
Stage 3 - sealing the open blisters using a heat-seal process to ensure stability and protection of the product from varying environmental conditions.

Lyoc is a porous and solid galenic form obtained by lyophilization of an oil-in-water emulsion placed directly in the blister alveolus [14, 25]. Its unusual properties are the result of its unique method of preparation, which involves freezing a thickened (paste like) emulsion containing the active as bulk or as coated microparticles. This product is capable of accommodating high dose and disintegrates rapidly but possesses poor mechanical strength.

Quicksolv is a porous solid form obtained by freezing an aqueous dispersion/solution of the drug containing matrix and then drying it by removing the water using excess of alcohol (solvent extraction) [26]. The final form disintegrates very rapidly but is limited to low drug content and can be used only for those drugs that are insoluble in the extraction solvent. The ideal drug characteristics required for this technology are relative low aqueous solubility, fine particle size < 50 µm [27, 28] and good aqueous stability in the suspension.

The maximum drug loading capacity for water insoluble and soluble drugs are 400 mg and 60 mg, respectively [12, 27]. The primary problems associated with water soluble drugs are the formation of eutectic mixtures resulting in freezing-point depression and the formation of a glassy solid on freezing which might collapse on drying due to loss of supporting structure during sublimation process [12, 13, 27].

MDTs manufactured using lyophilization process, usually contain excipients like polymers (e.g., gelatin, alginates and dextrin) to provide strength and rigidity to tablets; polysaccharides (e.g., mannitol and sorbitol) to impart crystallinity and hardness to the matrix and to improve palatability; collapse protectants (e.g., glycine) to prevent the product from shrinking in its packaging during manufacturing or storage; flocculating agents (e.g., xanthan gum and acacia) to provide uniform dispersion of drug particles; preservatives (e.g., parabens) to prevent microbial growth; permeation enhancers (e.g., sodium lauryl sulfate) to improve transmucosal permeability; pH adjusters (e.g. citric acid etc.) to optimize chemical stability; flavors and sweeteners to improve patient compliance and water to ensure formation of porous units.

Advantages
The major advantage of using this technique is that the tablets produced by this technology have very low disintegration time and have great mouthfeel due to fast melting effect.

Disadvantages
Although being a fairly routine process, lyophilization has some disadvantages like it is a relatively expensive and time consuming process. Furthermore, the product obtained is poorly stable and fragile, rendering conventional packaging unsuitable.

Tablet Moulding
Moulded tablets invariably contain water-soluble ingredients due to which the tablets dissolve completely and rapidly. Following are the different tablet moulding techniques:
**Compression Moulding Process**

This manufacturing process involves moistening the powder blend with a hydroalcoholic solvent followed by pressing into mould plates to form a wetted mass (compression moulding). The solvent is then removed by air drying, a process similar to the manufacture of tablet triturates. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution [15].

**Heat-Moulding Process**

Heat-moulding process involves setting the molten mass containing a dispersed drug [29]. This process uses agar solution as a binder and a blister packaging well as a mould to manufacture the tablet. A suspension containing drug, agar and sugar is prepared followed by pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly and finally drying at approximately 30 °C under vacuum.

**Moulding by Vacuum Evaporation without Lyophilization [30]**

This process involves pouring of the drug excipient mixture (in the form of a slurry or paste) into a mould of desired dimension, freezing the mixture to form a solidified matrix and finally subjecting it to vacuum drying at a temperature within the range of its collapse temperature and equilibrium freezing temperature. This results in the formation of a partially collapsed matrix. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process. Unlike lyophilization, vacuum drying helps to densify the matrix and thereby improves the mechanical strength of the product. Pebley et al. [30], evaporated the frozen mixture containing a gum (e.g., acacia, carrageenan, guar, tragacanth or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol or maltodextrin) and solvent in a tablet-shaped mould to design a MDT with a disintegration time of about 20–60 secs.

Tablets produced by moulding are solid dispersions. The drug, depending on its solubility in the carrier, exists either as discrete particles or microparticles dispersed in the matrix and is dissolved totally/partially to form a solid solution/ dispersion in the carrier matrix.

**Advantages**

As the dispersion matrix is made from water-soluble sugars, moulded tablets disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the moulding process are used. In comparison to lyophilization process, tablets produced by moulding technique are easier to adapt to the industrial scale.

**Disadvantage**

As the moulded tablets have poor mechanical strength, they may undergo erosion and breaking during handling. Though hardening can increase the strength of the tablets but it would be at the cost of their disintegration time.
**Direct Compression (DC)**

DC is the simplest and most cost effective tablet manufacturing technique for MDTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tabletting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugar-based excipients.

**Disintegrants**

In many MDT products based on DC process, the disintegrants mainly affect the rate of disintegration and hence dissolution which is further enhanced in the presence of water soluble excipients and effervescent agents.

The introduction of superdisintegrants has increased the popularity of this technology [31]. Tablet disintegration time can be optimized by focusing on the disintegrant concentration. Below a critical disintegrant concentration, tablet disintegration time becomes inversely proportional to disintegrant concentration. However, above the critical concentration level of disintegrant, disintegration time remains approximately constant or the decrease is insignificant [32].

Another DC based technology; Flashtab contains coated crystals of drug and microgranules alongwith disintegrants [33]. In this technology, two types of disintegrants are used: a disintegrating agent (e.g., modified cellulose), which has a high swelling force and a swelling agent (e.g., starch) which has a low swelling force [34].

Bi et al. [35] and Watanbe. [36] used microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture MDTs wherein the ratio of MCC to HPC varied from 8:2 to 9:1. Ito and Sugihara [37] investigated the application of agar powder as a disintegrant due to its property of absorbing water and considerable swelling without forming a gel at physiological temperature.

**Effervescent Agents**

The evolution of CO₂ as a disintegrating mechanism forms the basis of the patented Orasolv technology (OT) and is frequently used to develop over-the-counter formulations [38–40]. The product contains microparticles and is slightly effervescent in nature. Saliva activates the effervescent agent which causes the tablet to disintegrate. The OT had been utilized in fabrication of six marketed products: four Triaminic Softchew formulations, Tempra FirsTabs and Remeron SolTab.

The present technology uses the concept of effervescence to achieve fast-disintegration [41, 42]. In this technology, the microparticles are prepared by dispersing the drug into a suitable polymer (ethyl cellulose, methyl cellulose, acrylate or methacrylic acid resins) along with other excipients (mannitol and magnesium oxide). The drug and mannitol are added to the polymeric dispersion under stirring, followed by addition of magnesium oxide. Here, mannitol and magnesium oxide are known as release promoters as they aid in drug release from the polymeric coating. This mixture is then dried for one hour at 50 °C, delumped and dried for another hour at the same temperature. The material is then screened (8-mesh) and dried for one hour at 60 °C. The formed microparticles, effervescent agents and other excipients are blended and compressed into tablets at 1.0–
2.0 kp hardness. The tablets obtained are fragile with in-vivo disintegration time of less than one minute [38, 42]. As the tablets are very soft, they are packed into aluminium blisters using a specially designed packaging system. To reduce their friability, a novel method, known as particulate effervescent couple, had been developed. In this method the organic acid crystals are coated using a stoichiometrically low quantity of base material as compared to acid. The particle size of the organic acid crystals is carefully chosen to be greater than the base material so that base gets uniformly coated onto the acid crystals. The coating process is initiated by the addition of a reaction initiator, which in this case, is purified water. The reaction is allowed to proceed only to an extent of completion of base coating on organic acid crystals. The required end-point for the reaction termination is determined by measuring CO₂ evolution. The resulting effervescent couple can be used in tablet preparation by mixing with polymer-coated drug particles and other required excipients [39].

Though, the Orasolv tablet has the appearance of a traditional compressed tablet, they are lightly compressed and are weaker and more brittle than the conventional tablets. Therefore, a special handling and packaging system for Orasolv was developed [40]. An advantage of low degree of compaction is that the particle coating used for taste masking is not compromised by fracture during compression.

Durasolv, a second-generation technology was developed to produce robust MDTs. Durasolv has much higher mechanical strength than its predecessor due to use of higher compaction pressure during compression. It is thus produced in a much faster and cost-effective manner and can be packed in either traditional blister packs or vials.

The limitations of Durasolv is its low drug loading capacity and high compaction pressure which are not suitable for incorporation of taste masked coated pellets. Therefore, the Durasolv technology is best suited for relatively small doses of drug [43]. This technology has been applied in the fabrication of two products: NuLev and Zomig ZMT. However, the major drawback of effervescent excipients is their hygroscopicity which require control of humidity during processing and protection of the final product resulting in increase in the cost of the product.

Sugar-Based Excipients

Another approach to manufacture MDTs by DC is the use of sugar-based excipients (e.g., dextrose, fructose, isomalt, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness and hence, imparts taste masking and a pleasing mouth feel.

Mizumoto et al., [44] have classified sugar-based excipients into two types based on their mouldability and dissolution rate.

Type I saccharides (e.g., lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type II saccharides (e.g., maltose and maltitol) exhibit high mouldability but low dissolution rate.
Mouldability is defined as the capacity of the compound to be compressed/ moulded and to dissolve. It does not refer to the formation of a true mould by melting or solvent wetting process. The mouldability of Type I saccharide can be improved by granulating it with a Type II saccharide solution.

The above technology forms the basis of WOWTAB [45] which involves the use of fluidized bed granulation for the surface treatment of Type I saccharide with Type II saccharide. This technique has been used in the production of Benadryl Fast melt tablets. Here, two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate [10]. Due to its significant hardness, the WOWTAB formulation is more stable to the environmental conditions than the Zydis or Orasolv and is suitable for both conventional bottle and blister packaging. The taste masking technology utilized in the WOWTAB is proprietary and claims to offer superior mouthfeel due to the patented smooth-melt action [46].

In the process of granulation, low mouldable sugar was coated with high mouldable sugar followed by a specific humidity treatment, to achieve fast disintegration. The resulting tablet had a hardness of 1.0–2.0 kg (tablet-size dependent) and presented a preferable disintegration time of 1–40 secs. Various classes of drugs can be incorporated into the above sugar combination to achieve a MDT with optimum performance characteristics. A preferable ratio of 5–10% w/w of high mouldable sugar was found to be sufficient to achieve the desired hardness and disintegration property [45].

A series of experiments had been conducted to develop a MDT using a combination of starch/cellulose and one or more water-soluble saccharides [47]. Erythritol was found to be the best saccharide because it displayed rapid disintegration, good tolerability, sweetening and a refreshing mouth feel due to its negative heat of solution.

Recently, the Ziplet technology was developed, which can be used for water insoluble drugs or drugs as coated microparticles. It was found that the addition of a suitable amount of a water-insoluble inorganic excipient combined with one or more effective disintegrants imparted an excellent physical resistance to the MDT and simultaneously maintained optimal disintegration even at low compression force and tablet hardness [48]. In fact, breakage of the tablet edges or formation of powder during manufacturing and opening of the blister pack is avoided because of its superior mechanical resistance. The use of water-insoluble inorganic excipients also offers better enhancement of disintegration characteristics in comparison to the most commonly used water-soluble sugars or salts. In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in much longer disintegration time. As the soluble components dissolve on the tablet’s outer layer, a concentrated viscous solution is formed, which reduces the rate of water diffusion into the tablet core [31].

**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 [49, 50]. The Shearform technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as
sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F [51]. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation [52]. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

I. Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture [53].

II. 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 [54–56].

III. Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer-granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss [51].

IV. Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form [57].

Spray-Drying

Allen et al., [58] have used spray-drying for the production of MDTs. The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.
Sublimation
Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose [59]. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Makino et al., [60] reported a method using water as a pore-forming material.

Mass-Extrusion
This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste [61].

Nanonization
A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique [62]. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

Fast Dissolving Films
It is a new frontier in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film [63]. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste [64].

MDTs with Patented Taste Masking Technology
There are number of patented taste masking technologies which had been utilized to manufacture MDTs with acceptable taste. CIMA Labs’ taste masking technique involving coating of drug with dissolution retarding excipient [65], Microcaps process involving microencapsulation by coacervation-phase separation technique [66, 67], Solutab technology involving coating of drug with sustained release agent followed by coating with
enteric polymer and finally with mannitol [68] and blending of drug with cyclodextrins [69] are some of the taste masking approaches applied in fabrication of MDTs. One more formulation in this category is OraQuick formulation which produces microspheres, known as MicroMask, which has superior mouthfeel over other taste-masking alternatives. This process does not involve the use of solvents and therefore, leads to faster and more efficient production. Moreover, relatively lower heat of production makes OraQuick appropriate for heat-sensitive drugs. The matrix that protects the drug in microencapsulated particles is more pliable which enables the tablets to be compressed with significant mechanical strength without disrupting the taste-masking property. Along with good taste-masking ability, OraQuick also claims quick dissolution (in secs) of the MDT [70]. This technology had also been utilized in the development of MDTs containing Hyoscyamine sulfate, which is a bitter tasting anticholinergic/antispasmodic drug [71]. AdvaTab technology utilizes a combination of Microcaps technology for taste masking and Diffuscap controlled release technology for the development of a highly differentiated controlled release MDT product [72].

**Future Perspective**

With continued innovations in pharmaceutical excipients, one can expect the emergence of more novel technologies for MDTs in the days to come. These innovations may involve modifying formulation composition and processing to achieve new performance end-points or the merger of new technological advances with traditional pharmaceutical processing techniques for the production of novel mouth dissolving dosage forms. It is reasonable to expect that future trends in innovations of drug delivery systems will continue to bring together different technological disciplines to create novel technologies.

**Authors’ Statement**

**Competing Interests**
The authors declare no conflict of interest.

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