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Orally disintegrating dosage forms and taste-masking technologies; 2010

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Introduction: In the last decade the development of orally disintegrating tablets (ODTs) and thin-film platforms has grown enormously in the field of pharmaceutical industry. A wide variety of new masking technologies combined with the aforementioned platforms have been developed in order to mask the taste of bitter active substances and achieve patient compliance. The commercial success and viability of such products requires the development of robust formulations with excellent palatability, disintegration times, physicochemical stability and pharmacokinetic profiles.

Areas covered: In this review, emerging taste-masking technologies applied to solid dosage form manufacturing are summarized. The unique features and principles of taste-masking approaches used with ODT platforms are discussed, including the advantages and limitations of each technology. A brief discussion is also included on the taste masking of thin-film technologies, owing to their similar applications and requirements.

Expert opinion: This review elucidates the unique features of current commercially available or highly promising ODT and thin-film technologies, along with taste-masking approaches used in the manufacturing of oral solid dosage forms. A better understanding of these drug delivery approaches will help researchers to select the appropriate platform, or to develop innovative products with improved safety, compliance and clinical value.

Keywords: complexation, drug delivery, microencapsulation, orally disintegrating tablets, taste masking

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1. Introduction

In the last decade orally disintegrating tablets (ODTs) have prospered enormously as a convenient, safe and acceptable alternative to conventional tablets and capsules. ODTs are designed to disintegrate rapidly on contact with saliva and thus are swallowed without water or chewing. These formulations offer ease of administration and improved compliance, particularly in certain populations such as children and elderly patients. Patients with swallowing difficulties, mental illnesses or disabilities experience difficulty in swallowing pills and consequently the prescribed medications are not properly administered. Recently the European Medicines Agency's Committee for Medicinal Product for Human Use (CHMP) described ODTs as presenting 'great promise for children' [1].

The FDA provides further recommendations [2] to point out the primary characteristics of ODTs, which are the tablet weight (< 500 mg) and disintegration times (< 30 s). These two features have a great influence on the ODTs' patient acceptance and compliance, followed by the product robustness and pharmacokinetic profiles, which should be applicable and bioequivalent to conventional oral dosage forms, respectively. However, the increased industrial interest in new taste-masking technologies indicates that palatability plays a key role in the commercial

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Article highlights.

- Lyophilized ODTs have a highly porous structure with rapid disintegration times (> 10 s) and effective taste masking.
- Compressed ODTs are compressed using conventional tooling while taste masking is achieved by microencapsulation, inclusion complexation or coacervation techniques.
- Heat-processed ODTs are designed to present taste-masking and rapid disintegration properties by using cotton candy, molding or hot melt extrusion approaches.
- Thin-film technologies can effectively deliver APIs with rapid or controlled release profiles and excellent taste masking.

This box summarizes the key points contained in the article.

success of the finished dosage form. Thus, the combined taste-masking and ODT technologies aim to address patient palatability by minimizing the bitter taste intention and duration, leaving a pleasant taste and mouth feel. ODT palatability refers to the elimination of bitter taste intensity and the gritty texture, and it can be assessed by both *in vitro* and *in vivo* methodologies [3-7].

Quick-dissolving thin films use the lingual or sublingual route of administration as they are applied to the tongue and dissolve rapidly within seconds to deliver the active substance. The advantages of thin films include quick dissolution in the absence of water, mucosal adsorption, taste masking for improved patient compliance and size/shape flexibility. Thin films have gained interest for the delivery of highly potent drugs that require a rapid onset action. Consequently, thin films are expected to deliver faster the active substances compared with conventional tablets.

The taste masking of bitter active substances is a major component for the successful development of oral solid dosage forms [8-11]. More specifically, a wide range of taste-masking technologies has been used to manufacture ODTs or thin-film platforms. An efficient taste-masking approach should prevent direct contact of the active substance with the taste buds present on the tongue surface. It is worth mentioning that selection of the appropriate masking technology depends on the active's physicochemical properties, such as water solubility, permeability, polymorphism, hydroscopicity, physical/chemical stability or mechanical properties such as compressibility. At the moment, taste-masking technologies focus on extremely bitter APIs such as macrolide antibiotics, non-steroidal anti-inflammatory drugs, analgesics, penicillins, antipsychotics, antihistamines and chemotherapeutics [12,13].

In this review, proprietary ODT and thin-film technologies are summarized and evaluated that have been used to improve oral dosage products, including the taste-masking approaches that have been utilized in each technology. In addition, taste-masking trends with commercial potential are also highlighted. A brief discussion of each approach, including product characteristics, performance attributes, limitations and cost efficiency, is included. The technologies described below are classified as lyophilized ODTs, compressed ODTs and heat-processed ODTs (**Figure 1**).

2. Lyophilized orally disintegrating tablets

Lyophilized ODT technologies have been largely developed to produce tablets with greater porosity, allowing for shorter disintegration times than orally disintegrating compressed tablets. At present there are three major technologies (**Table 1**) using similar basic formulation and process approaches with minor differences. The Zydis® (Catalent Pharma Solutions, US) technology is an example of lyophilized ODT products where the active substance is dispersed typically in a matrix that consists of a polymer (e.g., gelatine) and a saccharide (e.g., mannitol) dissolved in water [14,15]. The solution or dispersion containing the API is filled into preformed blister packs and then frozen rapidly under liquid nitrogen to produce a network of ice crystals. Subsequently, the product is lyophilized and the ice crystals are sublimed to produce a highly porous structure (**Figure 2A, B**). Finally, the dried aluminum blister packs are sealed while the produced tablets adhere slightly to the pack, ensuring minimum movement and friability during the transportation of the robust product. The *in vitro* disintegrating times are usually < 10 s owing to the quick disintegration of the porous-like structure, which allows almost immediate water penetration. Following administration and rapid dispersion on the tongue, the Zydis formulation efficiently regresses to the original API solution/suspension. Therefore, the Zydis ODT provides all the convenience of a solid oral-dose form with the advantages of a solution/suspension product.

The tablet disintegration time is controlled by the polymer grades, for example, the gelatine grade, which produces a strong glassy amorphous structure with rapid disintegration times. The polymer selection is not limited to hydrolyzed gelatine grades and hence hydrolyzed dextran, dextrin, polyvinyl alcohol, polyvinyl pyrrolidone and acacia grades can be included. The presence of mannitol ensures elegant appearance, rigidity, improved texture, taste and mouth feel, and most of all facilitates faster disintegration times. Owing to the rapid disintegration time of the Zydis products the active substance is exposed on the tongue, which could leave an unpleasant aftertaste. In this case the taste masking is achieved through complexation with ion-exchange resins or drug encapsulation approaches. However, taste-masking integrity and grittiness of large particles could be an issue, especially for high dose products. The active substance(s) are micronized to produce nanosized APIs and further stabilized in gelatine dispersions with rapid disintegration times for the produced tablet. Nano-milling processing can be easily used for acidic, basic and non-ionizable compounds to reduce the particle size of the active compounds.

The Zydis technology is particularly suitable for water-insoluble substances, and dose strengths can be

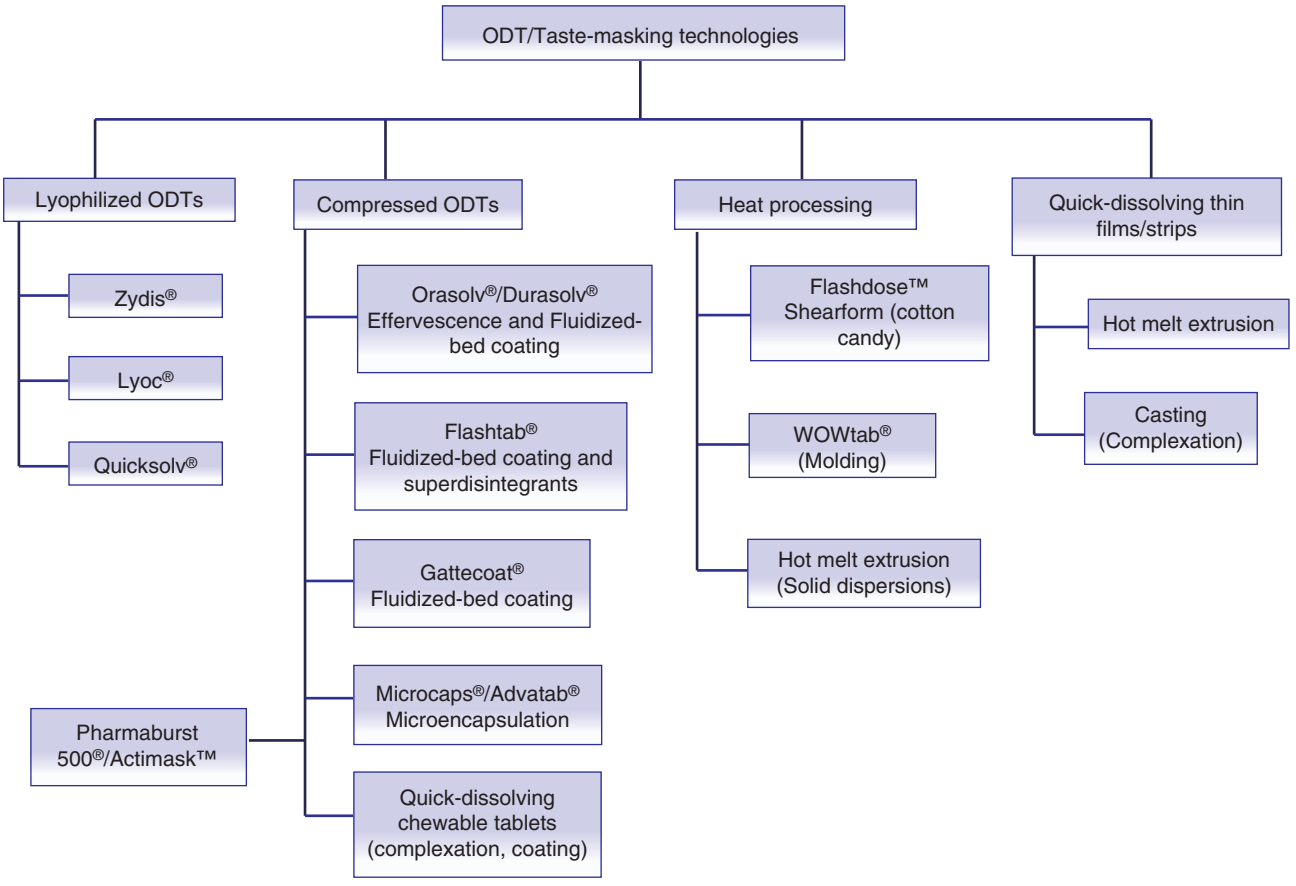

Figure 1. Current ODT/taste-masking technologies.
ODT: Orally disintegrating tablet.

accommodated for up to 400 mg. As none of the API is dissolved there is no risk of the drug forming a eutectic or amorphous material. Therefore, relatively high shelf temperatures can be used, which equals quicker drying time. By contrast, with a soluble API an amorphous/eutectic form is produced in the finished product. This results in reduced glass transition temperatures (T_g), and the drying conditions have to be carefully managed to prevent the product collapsing or melting. In every case the liquid dosing process ensures good dose uniformity and can allow extremely low dose strengths (micrograms). Further palatability improvement can be achieved by including pH-modifying agents, flavors and sweeteners.

The Zydis technology has been used in a wide range of clinical applications [16-18], such as bioequivalent products to conventional tablets or products suitable for pregastric (buccal and sublingual) uptake to enhance bioavailability and avoid first-pass metabolism. Its applicability is also extended to protein and peptide products or oral vaccines. More than 15 products are now commercially available, including Crazax and Claritin, as shown in **Table 1**.

Similarly to the above process, the Lyoc™ technology has been developed to produce tablets with fast disintegration speeds in the range 2 – 20 s. The Lyoc proprietary technology was originally developed by Chephalon, Inc., USA [19] and now is managed by the subsidiary Cima Labs, Inc., USA. The lyophilization manufacturing process encompasses freeze-drying of an aqueous solution, suspension, or emulsion of the drug compound and excipients. After this liquid homogeneous formulation is optimized, it is distributed into preformed blisters. The original approach involved the lyophilazation of an oil-in-water emulsion frozen at temperarratures from -20 to -50°C. The prepared emulsion consisted of the desired API, a lipid component (triglycerides), a stabilizer (non-ionic surfactant), a filler (mannitol) and a thickening agent (gums, celluloses). The last two components influence the formation of the porous structure of the end product and consequently play an important part in the release of the active pharmaceutical substance. The very low temperature freezing and the specific pressure conditions are then applied to the product, which results in water sublimation to obtain the finished product, which is a porous, stable solid tablet. The formulations using Lyoc technology also include flavors and sweeteners to mask the taste of bitter APIs. Similar to the previous lyophilization approach, the

Table 1. Summary of orally disintegrating tablet products.

Technology	Marketer	Active	Indication	Products
DuraSolv®	Wyeth	Loratadine	Allergy	Alavert®
OraSolv® (CIMA)	Organon	Mirtazapine	Depression	Remeron Sol Tabs®
	Alamo	Clozapine	Antipsychotic	Fazalco®
	Astra Zeneca	Zolmitriptan	Migraine	Zomig-ZMT®
	Shionogi Pharma	Prednisolone sodium phosphate	Asthma	Orapred ODT®
	Schwarz Pharma	Alprazolam	Anxiety disorder	Niravam®
		Hyoscyamine sulfate	Irritable bowel	NuLev®
		Levodopa/carbidopa	Parkinson's disease	Parcopa®
Lyoc (CIMA)	Cephalon	Piroxicam	Arthritis	Proxalyoc®
		Paracetamol	Pain	Paralyoc®
		Loperamide	Diarrhea	Loperamide-Lyoc®
		Phloroglucinol/trimethyl phloroglucinol	Abdominal pain	Spasfon-Lyoc®
Quicksolv	Janssen	Risperidone	Schizophrenia	Risperdal Quicklet®
Zydis (Catalent)	Schering	Loratadine	Allergy	Claritin Reditabs®
	Schering	Desloratadine	Allergy	Clarinex Reditabs®
	Merck	Rizatriptan benzoate	Migraine	Maxalt-MLT®
	GlaxoSmithkline	Ondansetron	Nausea and vomiting	Zofran ODT®
	Eli Lilly	Olanzapine	Schizophrenia	Zyprexa Zydis®
Flashtab (Ethypharm)	Boots	Ibuprofen	Pain	Nurofentabs®
	Pfizer	Paracetamol	Pain	Calpol FastMelts®
	Sanofi-Aventis	Prednisolone	Asthma	Solupred®
	MundiPharma	Oxycodone	Analgesic	OxynormOro®
Flashdose (Valeant/Biovail)	Reckitt Benckiser	Ibuprofen	Migraine/pain	Nurofen Meltlets®

drug loadings vary from 500 µg to 500 mg. Drug products based on Lyoc technology have been developed for drug molecules of varying physicochemical properties. At present, seven products that are utilizing Lyoc technology have been commercialized, as shown in **Table 1**.

The Quicksolv lyophilization process [20] developed by Janssen Pharmaceutica, a subsidiary of Johnson & Johnson (USA), is similar to the Zydis technology, where an aqueous dispersion of the API and matrix components (gelatine, mannitol) is first formed and then frozen. The water removal from the frozen matrix can be performed either by lyophilization or by submerging frozen product in alcohol (solvent extraction) to produce a dry unit. The porous structure obtained presents uniform porosity and adequate strength for handling. Efficient taste masking of bitter API is realized by drug encapsulation in a hydrophobic matrix such as fatty acid(s)/glycerides. The encapsulated active substance is added to an artificial flavor mixture and the resulting dispersion is transferred into molds.

3. Compressed orally disintegrating tablets

The manufacture of compressed orally disintegrating tablets is a promising approach that continues to grow rapidly owing to improved patient compliance. The utilization of conventional equipment offers reduced manufacturing cost and hence commercial value of these technologies.

Among the most established and successfully commercialized technologies are the Orasolv® (Cima Labs, Inc. USA) [21-23] and Durasolv® (Cima Labs, Inc. USA) [24,25] ODTs that have been marketed for immediate or sustained release oral dosage forms. Both technologies are manufactured by direct compression using conventional tableting equipment and they can be easily engraved. The tablets are placed in the patient's mouth and disintegrate rapidly by releasing the drug taste-masked particles. On swallowing, the microparticles reach the patient's gastrointestinal tract where complete dissolution and systemic absorption of the drug takes place. The Orasolv technology uses taste-masked drug microparticles that disintegrate rapidly by adding effervescent agents. The effervescent agents react to generate carbon dioxide on exposure to saliva. This causes a sensation in the mouth that is pleasant to the patient and tends to stimulate further saliva production, which also aids in disintegration. However, excipients such as disintegrants, flavors and sweeteners are usually added to develop the finish product. The technology has been developed for drug loadings of 1 – 750 mg and disintegration times of 10 – 40 s. The tablets are compressed to relatively low hardness of 6 – 25 N, resulting in friable ODTs in some instances. Similarly, the Dusrasolv technology combines formulations of taste-masked drug microparticles with or without low effervescence-containing materials. The main improvement is related to the addition of a non-direct compression filler (e.g., mannitol) and a relatively high lubricant content (1 – 2.5%). Owing to the design of these formulations, the drug loadings range from 125 to 500 mg with disintegration times from 10 to 50 s. However, Durasolv tablets are compressed to a greater hardness of

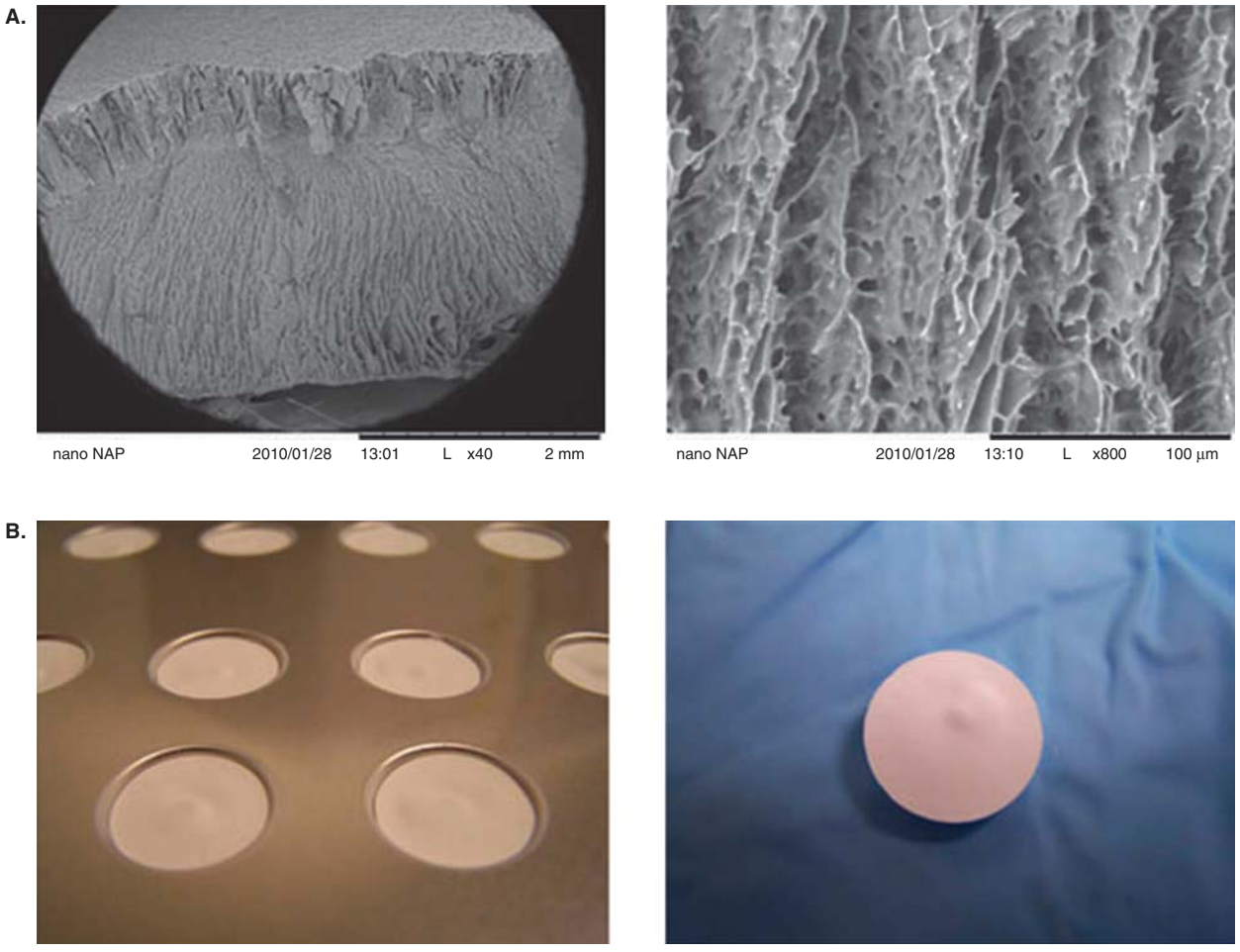

Figure 2. A. Electron scanning micrograph of a Zydis tablet. B. Zydis tablets containing ball-milled fenofibrate nanoparticles (provided by Catalent Pharma Solutions).

15 – 100 N, producing a more durable ODT with flexible packaging. The tablets can be packaged in traditional blister packaging or bottles. In both technologies drug molecules in the dose range 0.1 – 750 mg can be efficiently taste masked independent of the drug solubility. The taste-masking approaches include a variety of processes, such as solution layering, wet and/or dry granulation, suspension layering, alcoholic or hydroalcoholic solution layering and direct coating. Typical coatings are applied by using a fluid-bed particle coating (Wurster) with an appropriate selection of polymers, such as celluloses (ethyl cellulose, hydroxylpropyl methyl cellulose) or pH-dependent methacrylates (Eudragits®, Evonik Industries, Germany) [26]. Selection of the proper coating excipient is critical as the taste masking of the drug must provide the desired dissolution profile and the coating should withstand the compression forces.

A new-generation ODT platform called Flashtab® [27,28] that delivers efficient taste masking with rapid ODT disintegration times has been developed by Ethypharm, Inc. (France). The technology is a combination of wet and dry granulation before tablet compression. Taste-masked API microparticles are dry blended with conventional excipients (mannitol), superdisintegrants (crospovidone, croscarmellose sodium) and swelling agents (starch, microcrystalline cellulose) following direct compression. The taste-masking process includes fluidized-bed coating processing of granulated drug microcrystals. Initially, the API crystals are granulated by adding the API, a superdisintegrant (croscarmellose), an antistatic agent (SiO_2) and a sweetener (aspartame) in a fluidized bed and spraying a granulating ethanolic dispersion of coating agents (ethyl cellulose/hydroxypropyl methyl cellulose) and sweeteners. In the second step the API granules are coated with the coating solution to apply a physical barrier on the drug's surface. The coating solution can also comprise a water-soluble or swelling agent (mannitol, starch, or superdisintegrant) to facilitate solubilization of water-insoluble drugs. On this occasion the water-soluble agent crystallizes on the drug surface and in an acidic medium it solubilizes to leave pores that allow the physiological fluids to hydrate the coated particles. The presence of a swelling excipient can cause a complementary bursting effect. The

fluidized-bed coating approach ensures satisfactory taste masking and retains API's crystallinity as the drug is processed in the powdered form. It also enables high or low API contents or combinations of more than two active substances. The Flashtab ODTs deliver drug loading from 1 to 1000 mg with tablet hardness from 20 to 70 N. Depending on the actual drug loading, the disintegration times vary from 15 to 45 s. So far 15 marketed products have been developed using the Flashtab proprietary technology, indicating a robust and viable approach.

A similar taste-masking coating technology [29-31] has been developed by Gattfosse (France) and involves application of a molten lipid on the surface of the drug crystals through fluidized-bed coating. The Gattecoat™ hot melt coating is a solvent-free process in which molten lipid excipient is sprayed onto solid particles. The lipid film solidifies on cooling and coats the particles during fluidization in a fluid-bed coating device. A lipid layer of ~ 10 µm is formed around the particles, providing high drug loadings of 95%. The lipids used in this technology are naturally derived mixed glycerides such as glyceryl palmitostearate (Precirol® ATO-5, Gattfosse, France) and glycerol behenate (Compritol® 888-ATO, Gattfosse, France) with low melting points. One of the key features of the Gattecoat technology is the suitability for processing APIs at quite low temperatures (41°C), rendering it suitable for thermolabile or for low melting point active substances. The lipids provide acceptable taste masking (flavoring agents can be added), powder lubrication and sustained drug release owing to the amphiphilic properties. The obtained granules can be easily incorporated in ODT formulations. Although Gattecoat has been proved to be an effective taste-masking technology, there are no marketed products reported so far.

Taste masking of bitter APIs can be also achieved through microencapsulation technologies to apply a physical barrier on the drug surface. Such a technology, named Microcaps® [32,33], has been developed by Eurand (USA), which is used in combination or alone with the AdvaTab® ODT platform [34,35]. The encapsulated masked particles are produced by solvent coacervation by phase separation with a mixture of a water-insoluble polymer (e.g., ethyl cellulose, polyvinyl acetate or methacrylate polymers) and a gastrosoluble pore-former. The organic or inorganic pore-former is insoluble in water and saliva but is readily soluble under acidic conditions. In the solvent coacervation process the water-insoluble polymer is solubilized in an organic solvent while the drug and the pore-former are suspended in the heating tank (50 – 65°C). The produced polymer membrane provides adequate taste masking while the pore-former is uniformly distributed throughout the membrane under controlled cooling. On the other hand, the AdvaTab technology includes the formation of rapidly dissolving microgranules. In this process one or more sugar alcohols and/or saccharides are granulated to a high shear granulator following wet milling and drying in a fluidized-bed to produce microgranules with particle sizes < 400 µm. Both technologies are then combined by blending the taste-masked microparticles with the rapidly dispersing microgranules before tablet compression in a conventional rotary tablet press. Another important feature of the AdvaTab technology is the external lubrication system developed by Kyowa Hakko Kirin (Japan). This is an external lubrication system that pre-lubricates the dies and punches through a powder-spraying device called ExLub system [36,37]. The tablets manufactured by these technologies dissolve in 15 – 30 s (depending on dosage strength) and produce a smooth, pleasant-tasting mixture of API granules and carrier that is easy to swallow. The tablets have a friability of < 0.5%, and can be packaged in bottles or blister packs. However, the compression forces need to be applied cautiously to avoid membrane disruption, and thus compromising the taste-masking effect. A minor concern of Eurand's ODT platform is the levels of excipient required in the finished product, which are typically relatively high. At present, two licensed products for paracetamol and diphenhydramine HCl have been developed using Microcaps and AdvaTab technologies.

Taste-masking approaches have also been applied for manufacturing quick-dissolving chewable tablets (QDCTs) to mask the taste of active agents. Medichew® [38,39] is a well-known proprietary two-layer tablet platform developed by Fertin Pharma (Denmark). The technology comprises a bilayer tablet with a fast-dissolving layer and a second gum tablet layer. The API can be placed either in the fast-dissolving layer to obtain fast release or in the gum layer. The gum layer consists of a tailored gum base mixed with the active substance, flavors, syrup and sweeteners. The gum base contains artificial resins, waxes, elastomers, fats, emulsifiers and fillers. In the Medichew technology cyclodextrins (CDs) [40] are used to mask bitter APIs through the formation of 'inclusion complexes'. Cyclodextrins are cyclic oligosaccharides containing at least six D-(+)-glucopyranose units attached by α-(1,4)-glucosidic bonds with a bucket-shaped molecular structure of a hydrophobic cavity and hydrophilic exterior. As a result of their molecular structure and shape CDs have a unique ability to act as molecular containers by entrapping guest molecules. The inclusion complexes are formed in aqueous solutions when water molecules located within the lipophilic central cavity are replaced by a lipophilic drug molecule. In the case of hydrophilic active substances, the hydroxyl groups on the outer surface of the cyclodextrin molecule can form hydrogen bonds. Nevertheless, Medichew is a versatile technology, and efficient taste masking is also feasible through ion-exchange resin complexes [41]. The active substance can be either acidic or basic and binds to an ion-exchange resin to form a drug-resinate complex. Resins are polymers that contain appropriately substituted acidic groups, such as carboxylic and sulfonic for cation exchangers; or basic groups, such as quaternary ammonium group for anion exchangers. Ion-exchange resin complexes have been used to mask the taste of nicotine using cationic resins

Table 2. Summary of quick-dissolving chewable tablets and thin films.

Technology	Marketer	Active	Indication	Products
Medichew (Fertin Pharma)	Novartis	Nicotine	Nicotine replacement	Nicotinell®
	GlaxoSmithKline	Nicotine	Nicotine replacement	NiQuitin®
McNeil Consumer Healthcare	McNeil Consumer Healthcare	Acetaminophen	Cold/flu	Tylenol Meltaways®
OraVescent (CIMA)	Pfizer	Acetaminophen/ Dextromethorphan HBr/Pseudoephedrine HCl	Cough/sore throat	Triaminic Softchews®
	Bristol-Myers Squibb	Acetaminophen	Fever	Tempra Quicklets
Casting (Zengen)	Prestige Brands	Benzocaine	Sore throat/pain	Chloraseptic® Relief Strips™
Casting	McNeil Consumer Healthcare	Diphenhydramine HCl	Allergy	Benadryl quick dissolve strips
	Novartis	Diphenhydramine HCl/Phenylephrine HCl	Cold and cough	Triaminic Thin Strips®

by preparing aqueous slurry of nicotine/cation exchange resin and incorporating organic polyols (Table 2).

Conventional masking approaches, however, can also be used for masking purposes such as fluidized-bed coating [42,43] or coacervation [44] to prepare masking composition of QDCT platforms. Several taste-masked formulations, for example acetaminophen (Tylenol® Meltaways, McNEIL-PPC, Inc. USA) or Chlorpheniramine maleate/Dextromethorphan HBr (Triaminic® Softchews, Novartis Consumer Health Inc.), are incorporated in marketed QDCTs for administration to children.

An interesting platform has been developed by SPI Pharma (USA) that combines the Pharmaburst 500® co-processed directly compressible (DC) excipient system (Pharmaburst 500) and coating processes (Actimask™/Tasteshield™) to mask bitter active ingredients. The Pharmaburst 500 comprises a mixture of co-processed carbohydrates (e.g., mannitol, maltitol and sorbitol) that are spray-dried to produce a solid dispersion with a microcrystalline plate structure [45]. During the drying process the saccharides co-crystallize to produce a eutectic system with a single melting point. As a result the powder obtained shows excellent flow and compaction properties with a small percentage of fines. It can be used to formulate both low and high drug loading ODTs over a wide range of compression forces (10 – 30 kP). The Pharmaburst ODTs are manufactured by direct compression and disintegrate rapidly in < 30 s. For taste-masking purposes conventional methods such as fluidized-bed coating or coacervation are applied to coat micronized active substances. The smaller coated active particles can be used as individual coated particles or they can be assembled during the process into a multicore particle that has an overcoat. These masking approaches are also suitable for higher active dosages (e.g., acetaminophen) and produce uniformly coated particles that have a drug loading of 90% or higher, thus reducing the overall tablet weight. The masked particles are then blended with other excipients to produce ODTs with high content uniformity and smooth mouth feel.

4. Heat-processed orally disintegrating tablets

Heat exchange processes have been evolved to provide self-binding flowable matrices and subsequently ODT formulations. The matrices can be designed to present taste-masking and/or rapid disintegration properties.

Flashdose™, also known as Sheraform technology [46,47], developed by Bioavail Corp. (formely Fuisz Technologies, USA), utilizes a unique spinning mechanism to produce a floss-like crystalline structure called 'cotton candy'. The first step of the procedure is to mix an uncured shearform matrix and the active ingredient to prepare a molded dosage form. The term 'shearform matrix' means a matrix produced by subjecting a feedstock that contains a carrier material, mainly sugars (mono- and disaccharides), to flash-flow processing. The flash-flow processing can be accomplished by two main processes, called flash-heat and flash-shear. In the flash-heat process the feedstock material is heated sufficiently to create an internal flow condition that permits part of the feedstock to move at subparticle level with respect to the rest of the mass and exit openings provided in the perimeter of a spinning head. The centrifugal force created in the spinning head flings the flowing feedstock material towards the outside from the head to reform into a changed structure. The centrifugal force necessary to separate and discharge flowable feedstock is produced by the spinning head of a cotton candy machine. In the flash-shear process, a shearform matrix is formed by raising the temperature in the feedstock material, which includes a non-solubilized carrier, such as a saccharide-based material, until the carrier undergoes internal flow on application of a fluid shear force. The feedstock is advanced and ejected while in the internal flow condition and subjected to disruptive fluid shear force to form multiple parts or masses that have morphology different from that of the original feedstock. The multiple masses are cooled substantially immediately after contact with the fluid shear force and are

permitted to continue in a free-flow condition until solidified. In the shearform process the sugar product is a substantially amorphous sugar, which results from subjecting sugar to heat and shear sufficient to transform crystalline sugar to amorphous sugar without the use of a solution. Taste masking of the active floss produced is conducted by fluidized-bed coating using the appropriate masking polymers (ethyl cellulose, hydroxypropyl methyl cellulose). The active floss is then blended with the sugar floss and other excipients before tableting. The Flahsdose technology has been incorporated into the commercial Ibuprofen Meltlets. However, one of the disadvantages is the increased amounts of excipient in relation to the active ingredient.

Tablet molding is another technology that involves heat processing for the manufacture of ODT taste-masked dosage forms. The WOWtab® developed by Astellas Pharma (Yamanouchi, Japan) is a platform of compression molding ODTs [48,49]. The tablets are composed of water-soluble ingredients such as saccharides (e.g., lactose, mannitol, glucose, sucrose or xylitol) that are granulated by fluidized-bed with another saccharide of low melting point (e.g., maltose, trehalose, maltitol, sorbitol) before tableting. It is also possible to add a water-soluble polymer (e.g., ethyl cellulose or hydroxypropyl methyl cellulose) in the coating solution to act as binder. The active substance can also be coated by the saccharide or separately with waxes or saturated fatty acids, by fluidized-bed coating [50]. The powdered material is then compressed under low pressure using a conventional tablet press to retain the shape of a tablet. The produced tablets are heated (80 – 180°C) until the saccharide melts and becomes amorphous. They are then humidified at 20°C/75%RH (24 – 36 h) and dried at 30°C/40%RH (3 h) to produce highly porous ODTs with certain moisture content. At the end of the humidification and drying process the amorphous sugar irreversibly changes to the crystalline state, thus enhancing product robustness. Further improvement of the manufactured tablets can be obtained by applying extra heat at higher temperature (140°C) for short time periods [49]. Nevertheless, the tablet molding process can be cost-ineffective and time-consuming for certain applications. In addition, the required conditioning steps render the technology unsuitable for moisture active substances.

Hot melt extrusion (HME) is another process [51-53] that can be used successfully for taste masking of active substances and the manufacture of several pharmaceutical dosage forms. In principle, HME engages pumping of raw materials with a rotating screw under elevated temperatures through a die into a product of uniform shape. HME offers several advantages over traditional pharmaceutical processing techniques, including the absence of solvents, few processing steps, continuous operation, high production yields and scale-up capabilities. In addition, the extrudates produced are in the form of granules, pellets, spheres, mucoadhesive/sublingual films [54], or even tablets. To achieve effective taste masking the active substance is embedded in a polymer matrix under intensive mixing to facilitate various interactions. These interactions include: i) solubilization of the drug molecules in the polymer; ii) interaction of an anionic active substance with a cationic polymer [55]; and iii) interaction of a drug salt with an anionic polymer [56]. In the first case the drug is dispersed at a molecular level due to drug-polymer complexation, where drug molecules occupy the interstitial space between the polymer chains.

Similarly, molecular dispersions have been observed in the latter cases of oppositely charged drug–polymer interactions. For example, Ibuprofen was successfully masked when extruded with a methacrylate copolymer (EUDRAGIT® EPO) [57]. The EPO polymer is used for protective coatings and taste masking [58] because it dissolves quickly by means of salt formation with acids in the stomach. The possible taste-masking mechanisms are attributed to the intermolecular ionic interactions between the Ibuprofen's carboxylic and the EPO's dimethylamino groups. The deprotonation of -COOH facilitates the formation of a carboxylate salt and consequently builds a taste-masking effect. By selecting the appropriate polymeric material the dissolution rate of the active substance can be increased further in addition to the masking effect. Generally, drug release from the polymer matrix can be modulated by the incorporation of other functional excipients.

The incorporation of low melting point plasticizers may lower the processing HME temperatures, thus reducing drug and carrier degradation. As a result, HME can process heat-sensitive active compounds, providing stable products with improved physical and mechanical properties. The obtained extrudates are micronized and the collected granules can be incorporated further into ODT platforms by adding extragranular materials. Further HME advantages include co-processing of different APIs [59] or control of the tablet porosity [60] (addition of sodium carbonate) and thus control of the drug dissolution rates.

HME is also a viable alternative for the production of flexible thin films as it can overcome common problems of solvent casting methods. The advantages of thin films prepared by HME include excellent mechanical properties [61], increased drug loadings (15 – 30%), tuned release patterns, bioadhesion [62] and product stability [63].

5. Quick-dissolving thin films

The concept of quick-dissolving thin-film technologies is a relatively new area of interest for the pharmaceutical industry. Thin-film approaches to delivering lidocaine from polymer matrices for dental applications have been known since the 1970s [64]. Although not exactly an ODT, the thin-film or strip platforms provide an alternative to conventional tablets for rapid release of active agents. These intraoral thin films are usually dissolved quickly to release the active substance but can be modified to retard drug release depending on their thickness and the selection of the matrix polymer. The thin films are usually manufactured by a liquid casting process

that controls thickness and weight variability. The film drying takes place by passing through ovens to evaporate the remaining solvents. At the end, the dried films are cut into single unit doses following packaging in single or multi-dose containers. Taste-masking selection includes the use of sweeteners, flavors, cyclodextrins and ion-exchange resin complexes. Several thin-film technologies have been developed and commercialized by pharmaceutical companies such as Pfizer, Inc., Zengen, Inc. and McNeil-PPC, Inc. Some of these technologies, incorporating new manufacturing approaches, are selectively described below.

For the first time a new technology was introduced by Zengen, Inc. [65,66] for the delivery of an active substance such as benzocaine (3 mg) and menthol (3 mg) in Chloraseptic® Relief Strips™. The formulation comprised a bilayer film with a substrate active layer and a second dry layer. The dry layer is usually applied by spray coating methods. Each layer is composed of water-soluble bioadhesive polymers such a cellulose or pullulan, a flavoring agent (cherry flavor), plasticizer (glycerin) and sweetener (sucralose).

Thin-film patented technologies have been developed by McNeil-PPC to deliver active agents under the trade names of Triaminic Thin Strips® and Benadryl® quick dissolve strips [67,68]. Taste masking in these technologies (**Table 2**) is carried out by the formation of drug-resin complexes. The active substances (e.g., Dextromethorphan HBr) are mixed with ionic resins (AMBERLITE™ IRP69) in a hot aqueous solution to facilitate drug-resin complexation. The complex produced is blended with film-forming ingredients, poured on a mold and cast to form a film of a desired thickness.

Quick-Dis™ and Slow-Dis™ are examples of a unique intraoral delivery system (IODS) technology based on a unique casting process [69] developed by Lavipharm Group. The formulation of the active substance and water-soluble hydrocolloids are completely dissolved in water in a mixing tank to form a homogenous viscous solution. The solution is then metered onto a moving web and dried in temperature-controlled multizone ovens to produce dried films that are die-cut and packaged. The technology can be used to manufacture bilayer films where similarly the viscous active solution is degassed under vacuum and coated on a non-treated casting film. This latter approach was used to prepare intraoral nicotine bilayer films [70]. The films dissolve rapidly depending on the composition and the thickness, and present excellent bioadhesion properties. Several clinical studies were conducted to prove the efficacy of the film technology using therapeutic medications for erectile dysfunction, ulcer, and smoking cessation. For the erectile dysfunction medication, Quick-Dis was found to be superior to conventional tablets in terms of bioavailability of the active ingredient, whereas for smoking, cessation showed shorter t_{max} when compared with conventional marketed products. Taste masking is usually achieved by complexation of the active substance with a masking agent such as glycyrrhizin [71] or by creating a drug solid dispersion.

6. Expert opinion

In this review, various taste-masking technologies have been introduced that have been combined with ODT or thin-film platforms. The continuing need for improved compliance and convenience of taking medications by the patients has resulted in a tremendous increase of new quick-dissolving and chewable formulations, which do not require drinking water or swallowing tablets or capsules. Many of these platforms have been introduced as commercial products for improved patient convenience of dosing and product line extensions. In addition, some of them are opening new market opportunities owing to the unparalleled taste masking, dose flexibility, clinical outcomes and reduced manufacturing cost.

The capabilities of the technologies described above vary in terms of tablet taste, mouth feel, stability, dose capacity, disintegration times, manufacturing process and cost efficiency. However, it appears that taste masking, disintegration time and dose capacity are the three important factors that influence patient acceptance. Thus, lyophilized ODTs have been successfully commercialized with a wide range of approved products. Although freeze-dried ODTs are fragile and have higher costs for equipment/packaging, the lyophilized finished products are the most successful (e.g., Zofran®, Zyprexa®). In addition, the lyophilized ODTs have proved versatile through a range of clinical applications, enabling companies to exploit new patient populations.

On the other hand, compressed ODTs are also an attractive alternative because of the effective taste masking, use of conventional equipment and reduced manufacturing costs. A key aspect of the compressed ODTs is the tablet size resulting from drug loading limitations and increased excipient amounts, which could affect patient acceptance. Apparently, the utilization of conventional microencapsulation approaches (e.g., Cima Labs, Ethypharm, Inc.) renders compressed ODTs quite competitive.

HME is an emerging technology that can efficiently address taste masking, drug loading and release profiles of a wide range of active substances. It can also be used to improve the bioavailability of drug substances, especially those having low water solubility. HME is a viable approach for the development of solid dosage forms such as taste-masked ODTs or thin films because of the consistent and repeatable nature of continuous processing. Thin-film technologies have also attracted interest owing to the unique delivery advantages, but the drug loading limitations still need to be resolved. Another challenge of thin-film technologies is the limitations in the delivery of proteins or peptides owing to poor permeability and low bioavailability.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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