

TASTE MASKED ORODISPERSIBLE TABLETS: A HIGHLY PATIENT COMPLAINT DOSAGE FORM

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*Received: 10 March 2016, Revised and Accepted: 19 March 2016***ABSTRACT**

Objective: Tablet is still most popular conventional dosage forms existing today, but the drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. For this reason, orodispersible tablets (ODT) that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. The main objective of this review is to explore various methodologies for masking the taste of obnoxious drugs, applications, evaluation and also the recent trends in taste masking technologies when prepare a ODT.

Methods: Pediatric and geriatric populations are the most sensitive to the bad taste of medicaments, thus in these cases patient compliance reduces. This reason is an initiative for the development of various taste masking technologies by which the characteristics of ODT is improved and good patient compliance is achieved.

Results: ODTs have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia.

Conclusion: In this review, various techniques discussed which can help to overcome bitter taste of active pharmaceutical ingredients as well as largely improve the product preference among patients. It will also enhance the quality of the treatment provided to patients, especially children and older patients. Furthermore, various techniques could be combined to develop palatable and cost-effective ODTs.

Keywords: Orodispersible tablet, Taste masking, Patient compliance.

INTRODUCTION

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. The tablet is still most popular conventional dosage forms existing today because of ease of self-administration, compact in nature, easy to manufacture and it can be deliver inaccurate dose [1]. One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is a common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which lead to poor patient compliance [2,3].

Difficulties in swallowing of tablet and capsule are also occurring when water is not available, in diarrhea, coughing during the common cold, allergy condition, and bronchial infection. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For this reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [4].

The United States Food and Drug Administration defined orodispersible tablet (ODT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed on the tongue."

But in ODTs, taste is a crucial factor that determines the palatability of oral dosage form and patient compliance. It also gives a unique identity to a product. The oral route is considered the most convenient and easy route of drug delivery. Yet, patient noncompliance, termed "intelligent noncompliance," due to feeling bitter, bad taste, etc., which is reasoned out by the patient but may not necessarily be wise, is one of the key causes of failure of oral dosage regimen [5]. Pediatric and geriatric

populations are most sensitive to the bad taste of medicaments. Furthermore, currently, there is a rising trend to formulate drugs in the form of orally disintegrating dosage forms due to their easy ingestion and absorption process [6]. Thus, in these cases, a good taste is indispensable to patient compliance. Moreover, high palatability gives a competitive advantage, especially in the case of over the counter products [7,8].

NEED OF TASTE MASKED ODTs

The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus, it is free of risk of choking and dissolves in saliva within a few seconds, and so-called true fast-dissolving tablets. Fast dissolving technology offers the following section [1,9].

- Improved compliance/added convenience
- No water needed
- No chewing needed
- Better taste/have a pleasant mouth feel
- Improved stability
- Suitable for controlled as well as fast release actives
- Allows high drug loading
- Ability to provide advantages of liquid medication in the form of solid preparation
- Adaptable and amenable to existing processing and packaging machinery
- Cost-effective.

CHARACTERISTIC OF TASTE MASKED ODT

This novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Traditional tablet formulations generally do not require taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars, and other sweeteners to overcome the bitter taste of the drug.

In fast-dissolving/disintegrating tablets include sweeteners and flavors for taste-masking, but many drugs are extremely bitter and that bitter taste cannot be masked by taste masking agent. In these cases, taste is masked by various technologies as given below then they are converted into FDT. Some other characteristics are as follows [1,7]:

- The taste masked ODT should not leave an unpleasant taste into the oral cavity
- It should disintegrate within the 15 seconds to 3 minutes without need of water
- It should have sufficient mechanical strength
- The particle size of drug candidate should be fine so that it provide better surface area for the absorption to enhance bioavailability
- Drug candidate should be absorbed throughout the GIT
- It should have good solubility for dissolution.

POLYMER AND TECHNIQUES USED FOR TASTE MASKING

- An appropriate taste masking technique can affect both product quality and process effectiveness. Following are various taste masking techniques along with their polymer that can be used to taste mask bitter active pharmaceutical ingredient.
- Sweetener, flavorant, and other excipient addition
- Complexation
- Coating
- Ion exchange resins
- Matrix entrapment
- Prodrug formation
- Salt formation
- Miscellaneous.

Sweetener, flavorant, and other excipient addition

This is one of the simplest techniques used in taste masking. Excipients such as sweeteners and flavorants can be added to taste mask bitter active pharmaceutical ingredients (API)/drug. Sweeteners, being highly water soluble, dissolve in saliva and coat the taste buds, thereby retarding the interaction of bitter API with taste buds. Flavorants enhance the formulation and give it a distinct taste. They are to be added in addition to primary taste masking agent. Certain cooling flavorants such as menthol numb the taste buds and retard bitter taste perception. In addition, other excipients such as bitterness inhibitors can also be added. Some examples of sweeteners and flavorants [1,10], i.e., aspartame, acesulfame potassium, cyclamate, glycyrrhizin, lactose, mannitol, saccharin, sucrose, and sucralose (Table 1).

Complexation

In complexation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. Complexation decreases the amount of drug particles, which are exposed to taste buds, thereby reducing the perception of bitter taste. Inclusion complex is a "host-guest" relationship in which the host is complexing agent and guest is the active moiety. The complexing agent is capable of masking bitter taste either by decreasing its oral solubility or decreasing the availability of drug to taste buds. Vander Waal forces are mainly involved in inclusion complexes. β -cyclodextrin is widely used complexing for taste masking of drugs due to its sweet taste and is nontoxic in nature [1,11], e.g., anethol- β -cyclodextrin complex and saccharin, hydroxypropyl β -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, and tannic acid.

Coating

The coating is one of the best methods of taste masking. It can involve coating of a tablet containing bitter API or coating of the bitter API particles themselves. Ideally, the polymers selected in coating should be such that they prevent API release in oral cavity and allow its release in the absorption window of the API. The coating material is classified into lipids, polymers, and sugars. These materials can either be used alone or in combinations, as a single layer or multiple layer coats to achieve taste masking of the bitter drugs. Hydrophobic polymers have been popularly used for coating of bitter drugs than hydrophilic polymers

to achieve taste masking. Sweeteners can also be incorporated in the coating solution of better taste masking [1,12] (Table 2).

Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a polymeric material or film. Types of microencapsulation include air suspension coating, coacervation phase separation, spray drying, spray congealing, solvent evaporation, pan coating, and interfacial polymerization. Of these processes, first four are mostly used techniques for achieving taste masking.

Ion exchange resins

Ion exchange resins are synthetic organic polymers inert in nature, consists of a hydrocarbon chain to which insoluble groups are attached, and they have ability to exchange their labile ions for ions present in the solution with which they are in contact.

Based on the charge of the functional groups present, ion exchange resins are classified into cation exchange resins and anion exchange resins. Within each category, they are classified into strong and weak depending on their affinity for counter ions. Cation exchange resins are exchangers of sodium, potassium or aluminum salts, and anionic resins are for chloride ions. The drugs are loaded onto the resins by column method and batch method [9] (Table 3).

Matrix entrapment

Matrix entrapment involves trapping of drug into bulky matrix and thereby retarding its contact with taste buds. The matrix may contain polymeric, resinous, gelling, or lipoidal materials [9,13].

Prodrug formation

Prodrugs are molecules that are initially inactive but, upon biotransformation, are converted to active forms. Prodrug formation leads to physicochemical modification of bitter loci and thereby inhibits/retards their interaction with taste receptors. Other advantages of prodrugs include change in aqueous solubility, increase lipophilicity, improved absorption, less side effects, and change in membrane permeability [14].

Salt formation

Salt formation usually retards the solubility of API in saliva and thereby retards its taste perception [15].

Table 1: Selection of flavors based on sensation of taste

Sensation	Flavor
Salt	Butterscotch, apple, apricot, peach, vanilla
Bitter	Wild cherry, walnut, chocolate, mint, passion fruit
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, liquorice, root bear, raspberry

Table 2: List of different types of polymers with examples

Type of polymer	Examples
Water soluble polymers	Cellulose acetate butyrate, PVP, hydroxyl ethyl cellulose
Water insoluble polymers	Ethyl cellulose, polyvinyl acetate, crospovidone, crosscarmellose
pH dependent Water insoluble polymers	Polycarbophil, polyacrylic acid
pH independent Water insoluble polymers	Cellulose ethers, cellulose ester, polyvinyl acetate
Reverse enteric polymers	Eudragit E 100, Eudragit EPO, methyl methacrylate, hydroxyl ethyl methacrylate, vinyl Pyridine
Enteric polymers	Phthalate, hydroxyl phthalates, acrylic acid esters
Spacing layer polymers	Ethyl cellulose: PVP

PVP: Polyvinyl pyrrolidone

Table 3: List of commonly used ion exchange resins

Type of resin	Functional group	Functional backbone	Commercial resins
Strong anion	-N+R ₃	Polystyrene-DVB	Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	-N+R ₂	Polystyrene-DVB	Amberlite IR 4B, Dowex 2
Strong cation	-SO ₃ H	Polystyrene-DVB	Amberlite IR 120, Dowex 50, Indion 244, Purolite C 100
Strong cation	-SO ₃ Na	Polystyrene-DVB	HMR, Kyron -T-154 Amberlite IRP 69, Indion 254, Tulsion-T-344
Weak cation	-COOH	Methacrylic acid-DVB	Amberlite IRC 50, Indion 204-234, Tulsion 335, 339, Purolite C 102DR, Kyron-T-104, Tulsion T 335, Doshion P544 (R)
Weak cation	-COOK	Methacrylic acid-DVB	Amberlite IRP 88, Indion 234, Tulsion T 339, Kyron-T-134

Miscellaneous

Other techniques such as granulating with polymeric material, adsorption, adding effervescent excipients, and rheological modification of liquid preparations can be used for masking the taste of bitter API.

Granulation, taste masking of a bitter taste drug can be masked by granulation process. Granulation is major and a common process in tablet production. In this approach, saliva-insoluble polymers are used as binding agents in the tablet preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets. Granulation of various drugs can be done by alginic acid, sugar alcohol solution, polycarbophil, microcrystalline solution, and castor oil, etc. [16].

Adsorption adsorbate of bitter tasting drug can be considered as less saliva soluble version of that drug. In this technique, adsorbates of the bitter drugs are prepared by adsorption process. This process involves the adsorption of the drug solution using insoluble materials such as silica gel, bentonite, and veegum. The adsorbate (resultant powder) is dried and used for the formulation of final dosage forms [17].

Taste suppressants and potentiators most of Linguagen's bitter blockers (adenosinemono phosphate) compete with bitter substances to bind with G-protein coupled receptors sites. In general, hydrophobic nature of these bitter substances has good binding affinity to the receptor sites. Lipoproteins are universal bitter taste blockers. Neohesperidine phospholipids have bitter taste suppression characteristics by chemically interacting with the taste receptors. Cooling and warming agents suppress unpleasant taste of medicament by subjecting taste receptors to extreme sensations to overcome/overpower the bitter taste so as to confuse the brain. Eucalyptol (cooling agent) and methyl salicylate (warming agent) mixture were used for suppression of the bitter taste of thymol [18-20]. Potentiators increase the perception of the taste of sweeteners and mask the unpleasant taste. Various potentiators include thauMATINE, neohesperidine dihydrochalcone and glycyrrhizin increase the perception of sodium or calcium saccharinates, saccharin, acesulfame, and cyclamates [19,21].

Recent developments in the field of taste masking

Stimuli-responsive drug delivery systems incorporating pH sensitive, ion-sensitive polymers have been developed for masking bitter API

taste [22]. Lycopodium derived microcapsules have been used to taste mask ibuprofen [23]. Techniques, such as nano hybridizing and wet spherical agglomeration, have also been used for taste masking [24,25].

TECHNIQUES USED FOR PREPARATION OF ODT

- Freeze drying/lyophilization
- Spray drying
- Molding
- Sublimation
- Mass extrusion
- Direct compression
- Phase transition process
- Cotton Candy Process
- Nanonization.

Freeze drying/lyophilization

Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drug in a water soluble matrix which is then freeze-dried to give highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in <5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs, i.e., thermolabile substances [26,27].

Spray drying

This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non-hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating and an acidic material (e.g., citric acid) and/or alkali material (e.g., sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium [28].

Molding

Tablets prepared by this method are solid dispersions. Molded tablets offer improved taste due to water soluble sugars present in dispersion matrix. The molding process is of two types, i.e., solvent method and heat method. The solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g., mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum [29].

Sublimation

In this method, a subliming material (such as ammonium bicarbonate, ammonium carbonate, urea, benzoic acid, naphthalene, and camphor) is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores, where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva [30].

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 [31,32].

Direct compression

Direct compression represents the simplest and most cost-effective tablet manufacturing technique. The addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration [33].

Phase transition process

FDT were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 minutes. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol [34].

Cotton candy process

This process utilizes a unique spinning mechanism to produce floss-like crystalline structure. Cotton candy process involves the formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to improve flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength. However, high process temperature limits the use of this process [32,34].

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 [34]. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into mouth dissolving tablets. This technique is especially advantageous for poor 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 [31].

IMPORTANT PATENTED TECHNOLOGIES IN ODTs

Zydis

This drug delivery system consists of freeze-dried tablets having active drug designed to rapidly disintegrate in the mouth. The freeze-dried tablet is made by lyophilizing a suspension or solution of drug containing various excipients such as polymer, polysaccharides, preservatives, pH adjusters, flavors, sweeteners, and colors, which is then filled in blisters. Freeze drying occurs in the blisters, which are then sealed and further packaged. Some of the advantages of the zydis system include fast disintegration time. Some of the disadvantages include low throughput, high cost of goods, and limited taste masking [35].

OraSolv, DuraSolv, and PakSolv

The ingredients contained in the technology include polyols as fillers, disintegrant, which may include an effervescence couple, flavor, sweetener, and lubricant. The drug may be taste masked if required typically utilizing a fluid bed coating process. The tableting process includes direct compression, and can accommodate a wide range of potency from <1 mg to as high as 500 mg. Tablets manufactured with OraSolv technology should contain an effervescence couple along with microparticles of drug within a rupturable coat. The tablets manufactured are compressed at a low hardness that promotes fast disintegration. The dosage forms need to be packaged in aluminum foil blisters with a dome shape that impacts physical protection and impermeability to moisture [36].

Lyoc

This was the first freeze drying based technology introduced for ODTs. The process involves preparation of a liquid solution or suspension of the drug containing fillers, thickening agents, surfactants, non-volatile flavoring agents, and sweeteners. This homogenous liquid is then deposited in blister cavities and subjected to freeze drying [37].

Flashtab

Flashtab tablet matrix consists of a swellable agent (modified starch or microcrystalline cellulose) and a super disintegrant (crospovidone or croscarmellose). The system may also contain, depending on the need, a highly water-soluble polyol with binding properties such as mannitol, sorbitol, maltitol, or xylitol, instead of the swellable agent as mentioned before. The active is taste masked by direct coating. Tablets manufactured using this technology produce durable tablets in which the excipients are first granulated using wet or dry granulation process, then the coated drug is mixed with the excipient granules and compressed into tablets that can be handled and packaged using conventional processing equipment. Tablets for blister packaging can withstand the pressure used to push the tablet out of the lidding foil of the blister card. Tablets containing hygroscopic material can also be blister packaged, using high-quality polyvinyl chloride or aluminum foils, which provide a higher degree of moisture protection than ordinary polyvinyl chloride or polypropylene foils [38].

Flash dose

FlashDose tablets containing a matrix of these sugar fibers disintegrate very rapidly on contact with saliva, with disintegration times of a few seconds. The tablets produced by FlashDose are hydrophilic and highly porous, owing to relatively low compression during the pressing of the tablets. For taste masking, Fuisz uses its own patented, single-step, solvent-free process, termed "CEFORMTM technology," which produces uniform microspheres with a very narrow particle size distribution. The resulting tablets produced by this process are soft, friable, and highly moisture sensitive. They require specialized packaging materials and processes to protect them from external humidity and mechanical abrasion [39].

Wow tab

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. In this process, a combination of low mold ability saccharides with hardness 0-2 kg and high moldability saccharides with hardness more than 2 kg is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low moldability saccharide, e.g., lactose, glucose, and mannitol and granulated with a high mold ability saccharide, e.g., Maltose, Oligosaccharides and compressed into tablet [40].

Pharmaburst technology

Pharmaburst is a co-processed excipient system which involves a dry blend of a drug, flavors, and lubricant then followed by compression into tablets which then dissolve within 30-40 seconds. Tablets manufactured by this methodology have sufficient strength can be packed in blister packs and bottles [41].

FrostaTM

The technology incorporates manufacture of highly plastic granules using a plastic material, a material enhancing water penetration, and a wet binder. These granules can then be compressed into tablets at low pressure, thus enabling fast disintegration on administration. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 seconds depending on size of tablet [42].

Quicksolv technology

In the Quicksolv formulation, the matrix compositions are dissolved in the solvent (usually water), and then this solution is frozen. At the temperature, the first solvent will remain in the solid form, and then the frozen solution contacts the second solvent which is usually, ethanol,

menthol, or acetone. Thus, the first solvent is removed after a few hours of contacting the second solvent to result in a usable matrix. The final product disintegrates almost instantly. This method is claimed to prevent or to reduce the incidence of cracking during the final preparation, having uniform porosity and also the adequate strength for handling [43].

Nanocrystal technology

Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled into blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug [44].

Ziplets advatab

It utilizes water-insoluble ingredient combined with one or more effective Disintegrants to produce ODT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles [45].

EVALUATION OF ODTs

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using Vernier Calliper [46].

Weight variation

About 20 tablets were selected randomly from the lot and weighted individually to check for weight variation as per I.P.

Friability

Friability attempts for decreasing the disintegration time increase the friability of ODTs than the conventional tablets. Dosage forms like zydys are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre-weighed tablets are placed in the friabilator. Friabilator consists of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least

Table 4: Ideal candidates for taste masked ODTs

Year	Author	Contribution	References
1997	Koizumi	New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material.	[30]
2006	Mishra <i>et al.</i>	Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets	[28]
2008	Shah and Mashru	Development and evaluation of artemether taste masked rapid disintegrating tablets with improved dissolution using solid dispersion technique	[1]
2009	Kumar <i>et al.</i>	Development and characterization of melt-in tablets of Haloperidol by sublimation technique	[31]
2009	Malke <i>et al.</i>	Novel melt granulation using sugars for metoclopramide hydrochloride orally disintegrating tablet	[50]
2010	Shishu <i>et al.</i>	Development of taste masked oral formulation of ornidazole	[7]
2010	Torne <i>et al.</i>	Fast disintegrating tablets of ondansetron hydrochloride by direct compression technique	[51]
2010	Dahima and Sharma	Formulation and <i>in vitro</i> evaluation of taste masked ODT of metoclopramide hydrochloride using indion 204	[52]
2010	Pandey <i>et al.</i>	Formulation and evaluation of taste masked fast disintegrating tablets of lisinopril	[53]
2010	Puttevar <i>et al.</i>	Formulation and evaluation of ODT of taste masked doxylamine succinate using ion exchange resin	[54]
2011	Douroumis <i>et al.</i>	Development and evaluation of cetirizine HCl taste masked oral disintegrating tablets.	[2]
2011	Masareddy <i>et al.</i>	Development of orodispersible tizanidine HCl tablets using spray dried coprocessed excipient bases	[29]
2012	Meghana <i>et al.</i>	Development and evaluation of mouth-dissolving tablet of taste masked amlodipine besylate for the treatment of hypertension	[55]
2012	Remya <i>et al.</i>	Formulation and evaluation of fast disintegrating ODTs of ondansetron hydrochloride	[56]
2013	Thakare <i>et al.</i>	Development of metoclopramide hydrochloride orodispersible tablets using taste masking tulsion 339	[57]
2014	Ahmed <i>et al.</i>	Taste-masked ODTs of cyclosporine self nanoemulsion lyophilized with dry silica	[4]
2014	Deshmukh <i>et al.</i>	Formulation and evaluation of taste masked fast disintegrating tablet of tramadol HCl	[58]
2014	Gupta <i>et al.</i>	Fast disintegrating combination tablet of taste masked levocetirizine dihydrochloride and montelukast sodium:	[59]
2015	Alshehri <i>et al.</i>	Formulation design, development, and characterization of Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology	[8]
2015	Tripathi and Mayle	Formulation and evaluation of taste masked ODT of levocetirizine dihydrochloride	[60]

ODT: Orodispersible tablets

4 minutes [46]. At the end of test, tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100$$

Hardness (crushing strength)

Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm² is considered to be satisfactory for uncoated tablets [46].

Water absorption ratio

A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured [46]. The wetted tablet is then reweighed. Water absorption ratio, R is determine by using following formula:

$$R = 100 \times (W_a - W_b) / W_b$$

Where, W_b is the weight of tablet before water absorption

W_a is the weight of tablet after water absorption.

Uniformity of dispersion

Keep the two tablets in 100 ml water and stir gently for 2 minutes. The dispersion is passed through 22 meshes. The tablets will consider passing the test if no residue remained on the screen.

Disintegration time

According to the European pharmacopoeia the fast disintegrating or ODTs should disintegrate within 3 minutes without leaving any residue on the screen. However, it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus, the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. To overcome these problems, several new methods have been proposed [46].

In vivo disintegration time

In vivo disintegration time is determined using a panel of healthy human volunteers. The disintegrating time noted by the volunteers by placing the tablet in mouth [46].

Dissolution test

The dissolution method for oral disintegrating tablets is the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used. The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets [46].

IN VITRO CHARACTERIZATION OF TASTE MASKED ODT

In vitro methods such as spectrophotometry involve mixing of formulation to 10ml distilled water and then analyzing API concentration. If API concentration is below the threshold, sufficient taste masking is considered to be achieved.

The spectrophotometry method is not an absolute taste evaluation test. Another *in vitro* test involves usage of the electronic (e) tongue to evaluate taste. The e-tongue emulates the three levels of biological taste recognition: The receptor level (taste buds in humans, probe membranes in the e-tongue), the circuit level (neural transmission in humans, transducer in the e-tongue), and the perceptual level (cognition in the thalamus in humans, computer and statistical analysis

in the e-tongue). In e-tongue, the formulation or API is evaluated against standard (e.g., quinine hydrochloride) and the software generates taste patterns that form the basis of evaluation [15,47].

IN VIVO CHARACTERIZATION OF TASTE MASKED ODT

In vivo tests such as human panel testing and frog taste nerve responses can be used to evaluate taste of formulations. In human panel testing, large groups of healthy volunteers are asked to take bitter drug and then the taste-masked formulation. They are then asked to comparatively rate the formulation on various organoleptic properties. In frog taste nerve responses, glossopharyngeal nerve of bullfrogs is connected to AC amplifier and responses to bitter drug and formulation are taken. The peak height obtained is used to assess taste masking [48,49] (Table 4).

CONCLUSION

ODTs have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. In this review, various techniques discussed which can help to overcome bitter taste of API as well as largely improve the product preference among patients. It will also enhance the quality of the treatment provided to patients, especially children and older patients. Furthermore, various techniques could be combined to develop palatable and cost-effective ODTs.

REFERENCES

- Shah PP, Mashru RC. Development and evaluation of artemether taste masked rapid disintegrating tablets with improved dissolution using solid dispersion technique. *AAPS Pharm Sci Tech* 2008;9(2):494-500.
- Douroumis DD, Gryczke A, Schminke S. Development and evaluation of cetirizine HCl taste-masked oral disintegrating tablets. *AAPS Pharm Sci Tech* 2011;12(1):141-51.
- Noorjahan A, Amrita B, Kavita S. *In vivo* evaluation of taste masking for developed chewable and orodispersible tablets in humans and rats. *Pharm Dev Technol* 2014;19(3):290-5.
- Ahmed SZ, Bader MA, Mahmoud M, Tamer MS. Taste-masked orodispersible tablets of cyclosporine self nanoemulsion lyophilized with dry silica. *Pharm Dev Technol* 2014;9(8):1-8.
- Drewnowski A, Gomez-Carneros C. Bitter taste, phytonutrients, and the consumer: A review. *Am J Clin Nutr* 2000;72(6):1424-35.
- Rodgers S, Busch J, Peters H, Christ-Hazelhof E. Building a tree of knowledge: Analysis of bitter molecules. *Chem Senses* 2005;30(2):547-57.
- Shishu, Kamalpreet, Kapoor VR. Development of taste masked oral formulation of ormidazole. *Indian J Pharm Sci* 2010;72(2):211-5.
- Alshehri SM, Park JB, Alsulays BB, Tiwari RV, Almutairy B, Alshetaili AS, *et al.* Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology. *J Drug Deliv Sci Technol* 2015;27(3):18-27.
- Vummaneni V, Nagpal D. Taste masking technologies: An overview and recent updates. *Int J Res Pharm Biomed Sci* 2012;3(2):510-9.
- Sonawane V, Saiffee M, Shinde N, Hawaldar A, Pawar A. An update of taste masking methods and evaluation techniques. *Der Pharm Let* 2010;2(1):1-15.
- Vummaneni V, Nagpal D. Recent taste masking technologies: An overview and updates. *Int J Res Pharm Biomed Sci* 2012;3(2):510-24.
- Sharma D, Kumar D, Singh M, Singh G, Rathore M. Taste masking technologies: A novel approach for the improvement of the organoleptic property of pharmaceutical active substance. *Int Res J Pharm* 2012;3(2):108-16.
- Sharma S, Lewis S. Taste masking technologies: A review. *Int J Pharm Pharm Sci* 2010;2(1):6-13.
- Rafik K. Computationally designed prodrugs for masking the bitter taste of drugs. *Drug Des Open Access* 2012;4(1):120-9.
- Thoke S, Gayke A, Dengale R, Patil P, Sharma Y. Review on: Taste masking approaches and evaluation of taste masking. *Int J Pharm Sci* 2012;4(2):1895-907.
- Tripathi A, Parmar D, Patel U, Patel G, Daslaniya D, Bhimani B. Taste masking: A novel approach for bitter and obnoxious drugs. *J Pharm Sci Biopharm Res* 2011;1(1):136-42.

17. Jha Kumar JS, Sharma RU, Surendra V. Taste masking in pharmaceuticals: An update. *J Pharm Res* 2008;1(2):126-30.
18. Mashkevich OB. *Drug Delivery Research Advances*. New York: Nova Science Publishers; 1998. p. 117-52.
19. Sharma S, Lewis S. Taste masking technologies: A review. *Int J Pharm Pharm Sci* 2010;2(2):6-13.
20. Vijay D, Shyam V. Taste masking methods and technologies in oral pharmaceuticals: Current perspectives. *J Pharm Res* 2009;2(6):1049-54.
21. Wadhwa J, Puri S. Taste masking: A novel approach for bitter and obnoxious drugs. *Int J Biopharm Toxicol Res* 2011;1(1):47-60.
22. Yoshida T, Lai TC, Kwon GS, Sako K. pH and ion sensitive polymers for drug delivery. *Int J Biopharm Toxicol Res* 2013;1(1):46-58.
23. Diego AT. Protein free microcapsules obtained from plant spores as a model for drug delivery: Ibuprofen encapsulation release and taste masking. *J Mater Chem* 2013;1(3):707.
24. Kaushik D, Dureja H. Recent patents and patented technology platforms for pharmaceutical taste masking. *Recent Pat Drug Deliv Formul* 2014;8:37-45.
25. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. *Drug Dev Ind Pharm* 2004;30(5):429-48.
26. Virely P, Yarwood R. Zydis a novel, fastdissolving dosage form. *Manuf Chem* 1990;61:36-7.
27. Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. *J Pharm Pharmacol* 1998;50(1):375-82.
28. Mishra DN, Bindal M, Singh SK, Vijaya Kumar SG. Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets. *Chem Pharm Bull (Tokyo)* 2006;54(1):99-102.
29. Masareddy R, Kokate A, Shah V. Development of orodispersible tizanidine HCl tablets using spray dried coprocessed excipient bases. *Indian J Pharm Sci* 2011;73(6):392-6.
30. Koizumi K, Watanabe Y, Morita K, Utoguchi N, Matsumoto M. New method of preparing highporosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. *Int J Pharm* 1997;152(1):127-31.
31. Kumar R, Patil MB, Patil SR, Paschpura MS. Development & characterization of melt-in tablets of haloperidol by sublimation technique. *Int J Pharm Pharm Sci* 2009;1(1):65-73.
32. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth dissolving tablets: An overview of formulation technology. *Sci Pharm* 2009;77(1):309-26.
33. Bhowmik D, Chiranjib B, Pankaj K, Chandira RM. Orodispersible tablet: An overview. *J Chem Pharm Res* 2009;1(1):163-77.
34. Kuno Y, Kojima M, Ando S, Nakagami H. Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. *J Control Release* 2005;105(1-2):16-22.
35. Kearney P, Wong SK. Method for making freeze dried drug dosage forms. U. S. Patent 5, 631, 023; 1997.
36. Wehling F, Schuehle, S, Madamala N. Effervescent dosage form with microparticles. U. S. Patent 5, 178, 878; 1993.
37. Katzner L, Jones B, Khattar J, Kosewick J. Blister package and packaged tablet. U. S. Patent 6, 155, 423; 2000.
38. Pebley WS, Jager NE, Thompson SJ. Rapidly disintegrating tablets. U. S. Patent 5, 298, 261; 1994.
39. Robinson J, Ginity J. Effervescent granules and method for their preparation. U. S. Patent 6, 488, 961; 2002.
40. Mizumoto T, Masuda Y, Fukui M. Intrabuccally dissolving compressed moldings and production process there. U. S. Patent 5, 576, 014; 1996.
41. Khankari R, Hontz J, Chastain S, Katzner L. Rapidly dissolving robust dosage form. U. S. Patent 6, 981, 024; 2000.
42. Jeong SH, Fu Y, Park K. Frosta: A new technology for making fast-melting tablets. *Expert Opin Drug Deliv* 2005;2(6):1107-16.
43. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. *Crit Rev Ther Drug Carrier Syst* 2004;21(6):433-76.
44. Kaushik D, Dureja H, Saini TR. Orally disintegrating tablets: An overview of melt-in mouth tablet technologies and techniques. *Tablets Capsules* 2004;2(1):30-6.
45. Dobbetti L. Fast Disintegrating tablets. P. C. T Patent 99, 445, 8; 1999.
46. Mohammad Y, Mohammad I. Drug food interactions and role of pharmacist. *Asian J Pharm Clin Res* 2009;2(4):1181-6.
47. Rachid O, Simons FE, Rawas-Qalaji M, Simons KJ. An electronic tongue: Evaluation of the masking efficacy of sweetening and/or flavoring agents on the bitter taste of epinephrine. *AAPS Pharm Sci Tech* 2010;11(2):550-7.
48. Miyana Y, Inoue N, Ohnishi A, Fujisawa E, Yamaguchi M, Uchida T. Quantitative prediction of the bitterness suppression of elemental diets by various flavors using a taste sensor. *Pharm Res* 2003;20(2):1932-8.
49. Katsuragi Y, Kashiwayanagi M, Kurihara K. Specific inhibitor for bitter taste: Inhibition of frog taste nerve responses and human taste sensation to bitter stimuli. *Brain Res Brain Res Protoc* 1997;1(1):292-8.
50. Malke S, Shidhaye S, Kadam V. Novel melt granulation using sugars for metoclopramide hydrochlorideorally disintegrating tablet. *Asian J Pharm Clin Res* 2009;2(1):68-73.
51. Torne S, Sakarkar DM, Pawar SR, Abdul R. Fast disintegrating tablets of ondansetron hydrochloride by direct compression technique. *Int J Pharm Tech Res* 2010;2(1):433-7.
52. Dahima R, Sharma R. Formulation and *in vitro* evaluation of taste masked orodispersible tablet of metoclopramide hydrochloride using indion 204. *Int J Chem Tech Res* 2010;2(1):447-53.
53. Pandey S, Viral D, Manish G. Formulation and evaluation of taste masked fast disintegrating tablets of lisinopril. *Int J Pharm Tech Res* 2010;2(2):1639-43.
54. Puteewar TY, Kshirsagar MD, Chandewar AV, Chikhale RV. Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. *J Kin Saud Univ Sci* 2010;22(1):229-40.
55. Meghana SK, Krupal KV, Pravin P, Rohini PC. Development and evaluation of mouth dissolving tablet of taste-masked amlodipine besylate for the treatment of hypertension. *Int J Pharm Chem Bio Sci* 2012;3(1):55-62.
56. Remya PN, Damodharan N, Sharma L. Formulation and evaluation of fast disintegrating orodispersible tablets of ondansetron hydrochloride. *J Pharm Sci Res* 2012;4(5):1810-13.
57. Thakare VM, Umesh TJ, Bharat WT, Kundan PC, Piyush M. Development of metoclopramide hydrochloride orodispersible tablets using taste masking tulsion 339. *J Adv Pharm Educ Res* 2013;3(4):480-7.
58. Deshmukh BA, Chaudhari SP, Jagadale S. Formulation and evaluation of taste masked fast disintegrating tablet of tramadol HCl. *Am J Pharm Tech Res* 2014;4(5):418-29.
59. Gupta MM, Gupta N, Chauhan BS, Pandey S. Fast disintegrating combination tablet of taste masked levocetirizine dihydrochloride and montelukast sodium: Formulation design, development, and characterization. *J Pharm (Cairo)* 2014;2014:568320.
60. Tripathi GK, Mayle S. Formulation and evaluation of taste masked orodispersible tablet of levocetirizinedihydrochloride. *Bull Pharm Res* 2015;5(1):31-4.