AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

An Update on Taste Masking Technologies for Orodispersible Tablets

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ABSTRACT

ODTS are solid unit dosage form which dissolve or disintegrate rapidly in mouth without water. So, acceptability of this dosage form mainly depends on its taste i.e. mouth feel. So it becomes necessary to develop such an ODT for that must be acceptable in taste to patient many techniques are available to mask the taste of drugs. These techniques not only serve as to mask the taste of drug but also to enhance the bioavailability of drug. Taste masking technology involves the development of a system that prevents the active substance interacting with the taste buds, thereby eliminating or reducing the bitter taste. This review describes the commonly used techniques that are adopted for masking the taste of bitter drugs and dosage form palatable. The common methods include addition of sweeteners, coating of drugs adjusting the pH values, granulation, freeze drying, forming complex with ion exchange resins etc.

Key words: orodispersible tablets (ODTs), taste masking.

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Received 24 February 2012, Accepted 9March April 2012

Please cite this article in press as: Snehalatha *et al.*, An Update on Taste Masking Technologies for Orodispersible Tablets. American Journal of PharmTech Research 2012.

INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easymanufacturing[1,2]. ODTs 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. ODTs 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. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets; as they may take up to a minute to completely disintegrate. When placed on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. ODTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms[3]. Taste-masking is of critical importance in the formulation of an acceptable ODT. Traditional tablet formulations generally do not address the issue of 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 or complement the bitter taste of the drug. ODTs are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste masking many bitter drugs. Most of the ODT technologies incorporate unique forms of taste masking as well. The primary methods of taste-masking include adsorption onto or forming complex with carriers and spray coating of solid dosage forms, which increase consumer choice, for the reason of rapid disintegrate/dissolve in oral cavity within seconds and swallowed without the need of water or chewing[4,5]. As tablet disintegrates in mouth this could enhance the clinical effect of the drug

through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase bioavailability by avoiding first pass metabolism[6].

TASTE MASKING TECHNOLOGIES

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers[7].Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted hydroxyl propyl cellulose) when coated with a water insoluble polymer (e.g. ethyl cellulose) masked the bitter taste of sparfloxacin[8]. The addition of low substituted hydroxyl propyl cellulose as disintegrant to the drug in cores, resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets[9, 10, 11].

1. Addition of Sweeteners and Flavors

Sugar-based excipients have a negative heat of dissolution, dissolve quickly in saliva, and provide a pleasing mouth feel and good taste-masking to the final product[12].Sweeteners are commonly used in combination with other taste masking technologies. They can be mixed with bitter taste medicaments to improve the taste of the core material which is prepared for further coating or may be added to the coating liquid. Taste masked lamivudine (antiretroviral drug) was prepared by using lemon, orange and coffee flavors [11].Synthetic sweeteners such as sucralose are commonly used in most taste masked products. Newer sweeteners derived from plant parts have been evaluated for taste masking efficiency. Sweeteners have been commonly used for the taste masking of pharmaceuticals. Artificial sweeteners such as sucralose, aspartame and saccharin have been used in combination with sugar alcohols such as lactitol, mannitol and sorbitol to decrease the after-taste perception of artificial sweeteners. Most of the products in the market use this kind of excipient to give pleasant mouth feeling. WOWTAB® used the so-called “smooth melt action” of sugar and sugar like (e.g., mannitol) excipients12. The Zydis® dosage form also uses sweeteners and flavors to mask an unpleasant taste[13].In the NuLev® DuraSolv® tablet, the low dose of hyoscyamine sulfate was sufficiently taste-masked by incorporating a sweetener and a flavor[14]. Flossesand small spheres of saccharides containing unpleasant drugs were mixed with sweeteners and flavors to provide taste masking [15].

2. Adjustment of pH Values

Many drugs are less soluble at pH different from the pH value of the mouth, which are around 5.9. Drug scan be insufficiently solubilized to be available to taste if the equilibrium concentration is below the tastethreshold[16]. After a solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules including a drug sildenafil dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone [17].

3. Coating or Encapsulation of Unpleasant Drugs

In some instances, sweeteners and flavors may not be sufficient to mask bitter drugs, so alternative methods of taste masking need to be employed. Frequently, the bitter-tasting drug powder is coated to inhibit or retard dissolution and solubilization of the drug. This allows time for all of the particles to be swallowed before the taste is perceived in the mouth[18]. When using a coating or encapsulation for taste masking, complete coating is necessary to prevent exposure of the taste buds to a bitter-tasting drug. It is important that the coating remains intact while the dosages form is in the mouth. The process of Microcaps® (Eurand) is also based on a microencapsulation technology i.e., deposition of a polymeric membrane on drug particles. This deposition is typically carried out in a liquid phase using the technique known as phase separation or coacervation. This process is also very useful in obtaining microcapsules for delayed or controlled release applications, in addition to taste masking. The typical size of microcapsule is 0.2–0.8mm [19-21]. The bitter taste of Linezolid was masked by a combination of microencapsulation by coacervation and subsequent functional membrane coating on the microcapsules with Eudragit L30D[22].Small particles such as crystals, granules, and pellets were coated with aqueous dispersions of methacrylic acid and methacrylic ester copolymers (Eudragit RL30D, RS 30D, L 30 D-55, and NE 30D) for taste masking and compressed into FDTs [23]. The FDTs were containing the taste-masked granules of pirenzepine HCl or oxybutynin HCl were prepared by coating the drugs with amino alkyl methacrylate co polymers (Eudragit E100) using the extrusion method[23]. Taste masked immediate release micromatrix powders were formed by spray drying the drug and cationic copolymer [24].Cima's taste-masking technology also uses coating of the active ingredient with material that delays the dissolution in the mouth of drugs with objectionable taste[25]. Taste-masked microcapsules were prepared by a phase separation approach. Fırst a polymeric material (water-insoluble) for microencapsulation of the drug is dissolved in a nonpolar organic solvent with a second polymeric material that promotes phase separation of the first polymeric material at a temperature where both polymers dissolve. As the

temperature is lowered, the first polymer forms a coating layer on the drug by phase separation, and a dispersion of microencapsulated drug is produced.

After removing the solvent and the second polymeric material from the dispersion, isolated taste-masked microcapsules were obtained [26]. The mouth feel of OraSolv® tablets is different from that of most other orally disintegrating tablets, because of the presence of an effervescent couple comprising an acidic compound and a carbonate or bicarbonate salt. In Micro Mask™ by KV Pharmaceutical, the taste masking system was prepared by casting or spincongealing melt dispersions or solutions of a drug in a molten blend of materials. A major amount of wax core material has a melting point within the range of50–200 °C. The taste masking process does not use solvents of any kind, and therefore leads to faster and more efficient production [27].Bite-dispersiontablets were prepared using a waxy material and phospholipid [28].Addition of fatty acid ester(s) and/or waxes (e.g., Witepsol H32) contributed to taste masking of drugs having an irritating taste [29].

When an active ingredient, such as acetaminophen, has a bitter taste, it can be encapsulated in a material such as partially hydrogenated cotton seed oil, corn oil, flavored oil, zein (corn protein), cellulose, or candied sugar. Encapsulation with one or more of these materials has been found to enhance the palatability of acetaminophen while the tablet is dissolving in the mouth. Flashtab® technology [30] involves the use of coated multiparticles of active ingredients for effective taste masking. Other coating techniques designed for protecting drugs can also be used for taste-masking purposes. In addition to coating bitter-tasting drug particles, drugs were simply blended with cyclodextrin. Blending with cyclodextrin without the conventional complex formation was shown to be effective in masking the unpleasant-tasting active ingredients in ODTs [31].

4. Granulation

Taste masking by granulation is achieved by decreasing the surface area of the drug by increasing its particle size. The additional benefit obtained is ease of processing for tablet compression as the majority of drugs have a low bulk density. Additionally, polymers that serve as binders and taste-masking agents may be incorporated, which reduce the perception of taste. Granulation may be achieved with or without the use of a solvent. Dry granulation involves the use of forming compacts/slugs that are milled for blending [32].Wet granulation can be achieved by using the fluid bed process or high shear granulation. In the fluid bed process, the drug is suspended in the bed with air, and a binder is sprayed from the top. The granules formed are porous and not amenable to further processing like coating. In high-shear granulation, the granule formation occurs by spraying a liquid binder on to drug/mixture of drugs with excipients

that are being agitated by combined action of an impeller and chopper. The granules obtained are dense and maybe used directly or coated further in a fluid bed. This approach is suitable for high-dose drugs (>50 mg) with unpleasant taste [33].

5. Freeze drying process

This method is used to develop fast-dissolving oral technologies such as Zydis and Lyoc Technology. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds[3]. This is due to the high porosity produced by the freeze drying process.

The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure formers. The resultant mixtureis then poured into the preformed blister pockets of a laminate film and freeze dried [14].The two most commonly used structural excipients are gelatin and mannitol, although other suitable excipients can be used. This process is ideally suited to low solubility drugs such as these are more readily freeze dried.

6. Solid dispersions

Solid dispersions can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate[34].

7. Ion exchange resins

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets, and mask taste. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbate or resonates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins.

Ion exchange resins can be classified into four major groups:

Strong acid cation-exchange resin.

Weak acid cation-exchange resin.

Strong base anion-exchange resin.

Weak base anion-exchange resin.

Strong acid cation resins (sulfonated styrene divinylbezene copolymer product) function throughout the entire pH range and can be used for masking the taste of basic drugs. Weak acid cation exchange resins function at pH values above 6.0. Similarly, strong base anion-exchange resins function throughout the entire pH range and can be used for masking the taste of acidic drugs, while the weak base anion exchange resins function well below pH 7.0[35].Polystyrenematrix cation-exchange resins (Indion CRP-244, IndionCRP-254) have been reported to mask the bitter taste of chlorpheniramine maleate, diphenhydramine HCl, ephedrine HCl, noscapine HCl, and amphetaminesulphate[36].Amberlite IRP-69, a cation-anion exchange resin, is used to mask the bitter taste ofbuflomedil[37].Oral liquid products of quinolones (orbifloxacin) and/or their derivatives are formulated using ion exchange resins, such as methacrylic acidpolymer cross linked with divinylbenzene, as the carrier. The formation of a quinolone-resin complex (resinate) eliminates the extreme bitterness of thequinolones to make the liquid oral dosage form palatable. The preparation procedure involves dissolving the quinolone in an aqueous media followed by the addition of an ion exchange resin to form a drug/resin complex. The complex can be suspended directly into suitable vehicles with flavoring agents such as syrup base (malt extract) with the aid of an anticakingagent (colloidal silicone dioxide) and a preservative (sorbic acid) [38].To reduces the bitterness of erythromycinand clarithromycin, a polymer carrier system was developed by adsorption on Carbopol 934. Tastemasking was further improved by encapsulating the adsorbate particles with polymer coatings. Hydroxy propyl methyl cellulose (HPMC) phthalate (HP-55) provided the best combination of suspension stability, taste protection, and bioavailability[39].

CONCLUSIONS

ODTs rapidly disintegrate or dissolve in the saliva. Due to this; palatability plays an important role in accepting the dosage form. Most of the drugs have unpalatable taste and this is eliminated by many approaches like addition of sweeteners, coating of drugs adjusting the pH values, granulation, freeze drying, forming complex with ion exchange resins etc. So all the above approaches not only being used to mask the bitter taste of drug but also enhance bioavailability of drug.

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