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Taste Masking of Bitter Drugs for Incorporation into Orodispersible Tablets

Yana Zhekova Gvozdeva
Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University of Plovdiv, 4002 Plovdiv, Bulgaria
Research Institute at Medical University of Plovdiv, 4000 Plovdiv, Bulgaria

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ABSTRACT:
Oral drug delivery remains preferred route for various drugs administration. The taste of oral formulations especially orodispersible tablets is an important parameter governing compliance. There are many drugs, which are bitter in taste. A lot of taste masking techniques are developed which improve also the stability of the formulation and the performance of the products. Masking the bitter taste of drugs is necessary for the improvement of patient's compliance. This review describes various taste masking and taste evaluation methods.
KEYWORDS: orodispersible tablets, taste masking, precipitation method, spray drying, emulsion solvent evaporation technique, taste evaluation

I. INTRODUCTION

[15, 30]. Orodispersible tablets (ODTs) are known in the literature under various terms such as "Fast dissolve", "Quick dissolve", "Rapid melt", "Quick disintegrating", "Mouth dissolving", "Orally disintegrating", "Oro dispersible", "Melt - in-mouth" and others. They disintegrate or dissolve rapidly in the mouth after contact with saliva without the need for water or chewing. [38]. The USP defines ODTs as "a solid dosage form containing medicinal substances that disintegrates rapidly, usually within seconds when placed on the tongue". [37]. According to Ph. Eur 9 orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly within 3 min before swallowing. ODTs provide an advantage for pediatric and geriatric patients who have difficulty in swallowing conventional oral dosage forms.

[20]. The unpleasant taste of the drug is a leading problem in the development of orodispersible tablets. Taste masking achieves not only taste correction of the drug, which improves their organoleptic properties, but also protection from moisture and light, which leads to increased stability. Improved taste increases patient compliance and increases the therapeutic efficacy of the dosage form.

[34]. As a result of many years of research, the factors on which the choice of taste masking method depends are systematized. These are the degree of bitterness of the drug (intense, medium, or weak), as well as its dose and solubility. Also important are the shape and size of drugs particles, ionic characteristics and the release profile from the dosage form.

[20, 29]. A number of methods are developed, which include the use of various excipients and techniques to achieve masking of bitter taste. Some of the most commonly used methods are the addition of sweeteners and flavors, the use of lipophilic carriers, complexation with ion exchange resins, freeze-drying, microencapsulation by spray drying, polymeric coating of the drug, preparation of multiple emulsion, preparation of liposomes, taste masking by gelling and others. [3]. A number of methods require the use of appropriate excipients - polymers. Of great importance are their characteristics (chemical, biological and physical properties), their safety for the patient, and possible biodegradability.

[27, 29]. The choice of excipients is essential for successful taste masking. The addition of sweeteners and flavors is only one of the first ways of taste masking, which is used for liquid and children's dosage forms. It is applied for drugs that do not have an intensely bitter taste and high solubility in water or are combined with another method for taste masking. [9].There are two separate groups of sweeteners: natural sweeteners such as sucrose, glucose, fructose, mannitol, glycerol; and artificial sweeteners, which include aspartame, saccharin, acesulfame k, neotame. Cooling excipients such as menthol can help to reduce the sense of bitterness. [4].Regular studies on complexation with dextrins - maltodextrin, cyclodextrin as an approach to taste masking are

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known. [1].Opposing views have been published on the safety of cyclodextrins, especially when the dosage form is intended for children. Ion exchange resins are also used for taste masking while stabilizing some drugs and sustaining the release due to complexation. Sodium salts such as sodium chloride, sodium acetate and sodium gluconate are potential inhibitors of some bitter substances. A widely used method of taste masking is microencapsulation, achieved by spray drying, emulsion solvent evaporation technique, fluidized bed drying, and others. The drug may be incorporated into microcapsules and microspheres, into the core or into the polymer matrix, or bind to the polymer in a complex that is difficult to dissolve.

[3]. PH-sensitive polymers (soluble at pH<5) like polymethylmethacrylic polymers and ethylcellulose are widely used for taste masking. They are insoluble at neutral saliva pH and do not allow the release of the drug from the dosage form into the oral cavity. As a result, the drug does not come into contact with the taste buds and its bitter taste could not be observed.

1.1 Taste masking by preparing drug-polymer complexes by the precipitation method

The precipitation method for taste masking of bitter drugs has been studied using cationic polymethacrylic polymers, which are available under the following commercial products - Acryl-EZE® (Colorcon); Acryl-EZEMP®, Eastacryl 30D® (Eastman chemical company); Eudragit® (Evonik GmbH); Collicoate MAE 30 D® (BASF fine chemicals). The main factor that affects taste masking is the amount of polymer that is included in the models. Therefore, the drug-polymer ratio is varied until the optimum is reached, whereby a lower concentration of the polymer achieves taste masking and a satisfactory drug loading.

[16]. The method is based on the preparation of saturated solutions of the drug and the polymer in 95% ethanol, which are mixed and the mixture is dropped into 0.1 N NaOH under constant stirring. The semi-solid material formed on the surface is extruded and allowed to dry at room temperature, after which it is finely triturated.

[17]. Khan and colleagues (2007) used the precipitation method to mask the bitter taste of ondansetron hydrochloride in orodispersible tablets. The drug has an intensely bitter taste, which requires its masking. Different models of drug-polymer complexes with variations of the drug: polymer ratio (Eudragit EPO®) have been prepared. It has been found that in models with a larger amount of polymer, no drug release in artificial saliva is observed.

[25]. In the study by Randale et al. (2010), the precipitation method was used to prepare polymer particles with metoclopramide hydrochloride, which are further included in orodispersible tablets. Models with different drug to polymer ratios have been prepared. The in vivo taste evaluation with healthy volunteers showed good taste masking of the bitter drug in some models.

[13]. In another study of orodispersible tablets with amlodipine besylate and Eudragit E® by the precipitation method, a taste masking of the drug was achieved at a drug: polymer ratio of 1: 2. The correction was realized with a very small amount of polymer. The result proves the successful application of the precipitation method for taste masking of bitter drugs.

1.2. Taste masking by microencapsulation

1.2.1 Microencapsulation by emulsion solvent evaporation technique

The method of the emulsion solvent evaporation technique is convenient to carry out in laboratory conditions, as no expensive equipment is required, such as for spray drying. The method requires maintaining an appropriate temperature and constant stirring, which ensure the production of a stable emulsion without affecting the activity of the drug. Particle size control is easier than other methods. Depending on the properties and solubility of the drug, different types of emulsions can be prepared - W/O (water in oil), O/W (oil in water), as well as multiple emulsions W/O/W, O/W/O.

[18]. The technique of evaporating the solvent from a prepared emulsion with a drug was developed in the late 1970s and was successfully applied to the preparation of microparticles with various polymers and drugs.

An organic solvent (e.g. dichloromethane) of polymer and drug is most commonly used to prepare the O/W emulsion. The reconstituted solution or suspension is added dropwise to an aqueous phase in which an emulsifier (Tween 20®, Tween 80®, sodium lauryl sulfate etc.) is included. The emulsifier concentration affects the particle size and shape. The stirring speed and the volume of the organic phase are also parameters on which the particle size and shape depend, as well as the reproducibility of the results.

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[21, 31]. There is evidence of successful microencapsulation by emulsion techniques of lipid-soluble drugs such as steroids, local anesthetics, bleomycin sulfate, doxorubicin, naltrexone, promethazine, and others. The main disadvantage of the method is the low efficiency of incorporation of water-soluble drugs, which separated from the organic phase and pass into the aqueous phase. Therefore for theophylline, caffeine and salicylic acid, the method is not applicable. There is a problem with drugs that dissolve in both water and an organic solvent. It is important to select a suitable polymer that could incorporate the drug into polymer structures to prevent release into another medium.

[21]. W/O type emulsions are more suitable for microencapsulation of water-soluble drugs. The polymer and the drug are dissolved in a polar solvent and are emulsified in a lipophilic phase (usually liquid paraffin or vegetable oil) in which a lipophilic emulsifier is dissolved. A critical step is to wash the solidified particles with an organic solvent to completely remove the oil phase from them. The parameters influencing the yield were found to be emulsifier concentration, stirring rate and medium volume.

[21]. Of interest is also the method of preparation of multiple emulsions. Appropriate are some water-soluble peptides, proteins and macromolecules. The technique for preparing a W/O/W emulsion consists of dissolving the polymer in an organic solvent and emulsifying the aqueous solution of the drug in the organic solution of the polymer to obtain first a W/O emulsion. This emulsion is emulsified in another aqueous phase containing an emulsifier to obtain the multiple emulsion. The organic phase prevents the spread of the drug from the inner to the outer aqueous phase.

[22]. Many studies have been performed using the emulsion method for taste masking by varying different parameters, of which the drug-polymer ratio has the greatest influence. In a study by Malik et al. (2011), microparticles with Eudragit E 100® polymer and ofloxacin with different drug: polymer ratios were prepared. An emulsion of W/O type with Span 80® emulsifier was prepared. The results show that the amount of polymer determines the taste masking.

[19]. In a study by Kolhe et al. (2013) on orodispersible tablets with promethazine hydrochloride and Eudragit E 100®, it was also found that a major factor influencing taste masking is again the drug: polymer ratio.

[7]. A study by Dhoka et al. (2011) compared the ability to mask the bitter taste of cefpodoxime proxetil with Eudragit E 100®, hydroxypropylmethylcellulose (HPMC) and polyethylene glycol (PEG) to improve the taste characteristics of the resulting microparticles. All models use polyvinyl alcohol (PVA) as an emulsifier, and the emulsion is of O/W type. The evaluation of the taste by healthy volunteers shows the achieved taste masking in all models. This study focuses on the possibility of combining several polymers to achieve the desired characteristics of the microparticles.

[12]. Ethylcellulose has been successfully used in the emulsion technique as a polymer for taste masking. In the study by Gupta et al (2013), microspheres with aceclofenac and ethylcellulose were prepared. The emulsion of O/W type and is prepared with a 0.5% PVA emulsifier. The authors achieve bitter taste masking of aceclofenac thanks to the insoluble polymer in saliva - ethylcellulose. Ethylcellulose results in a delayed release of the drug in comparison with Eudragit E100®.

The presented studies prove that the method of emulsion solvent evaporation technique is successfully applied to mask the bitter or unpleasant taste of drugs. The selected polymers, emulsifiers and solvents, as well as the ratio between them, are of basic importance for the preparation of taste-masked particles.

1.2.2. Microencapsulation by spray drying

Spray drying is one of the most preferred methods for masking the bitter taste of drugs due to its high productivity. The disadvantage is the need for special equipment - spray dryer apparatus. On the pharmaceutical market, there are medicines obtained by the method of spray drying with improved taste - Mirtazapine ODT® - Teva pharmaceuticals; Zyprex Zydis® - Eli Lilly and others.

[20]. The interest of researchers and industry is focused on the spray drying conditions that affect the yield of the final product. The higher viscosity of the solution complicates the proper formation of drops. The lower the viscosity, the less energy and pressure are needed to form rounded particles. A high solids content (over 30%) is required to maintain proper spraying and to ensure proper droplet formation. The addition of a small amount of surfactant can significantly reduce the surface tension, which results in smaller droplet size and a higher drip rate. As the temperature of

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the spray solution increases, more energy is supplied to the system.

[20]. Spray drying can be used to control particle size, bulk density, degree of crystallization and amount of residual solvent. This method is used for taste masking by the ability to incorporate the drug into polymer microspheres that do not allow its release into saliva. Substances that are sticky and hygroscopic or slowly crystallize can be spray dried without any problem. The method is also suitable for thermolabile drugs, as the drying process is very short.

[11]. There is evidence in the literature for direct tableting after microencapsulation of a drug by spray drying. The implementation of the two methods one after the other leads to satisfactory properties of the obtained tablets due to reduced residual moisture, improved rheology of the tablet mixture and compactness by compression.

[36]. Yi and team (2014) prepared microparticles with sildenafil citrate and Eudragit E 100® by spray drying. The drug-polymer ratio was varied and high yield and incorporation efficiency were achieved. To assess the masking of bitter taste, the authors use an "artificial tongue" device. The study shows that as the amount of polymer in the models increases, better masking of the bitter taste occurs. The taste was also assessed by healthy volunteers. The obtained results confirm the data from the in vitro test.

[35]. In the study of Xu and team (2008) for taste masking, microencapsulation by spray drying of an aqueous dispersion of famotidine and Eudragit EPO® was applied. The incorporation of famotidine into microspheres delays its release. Along with in vitro studies, in vivo studies in rats and humans were performed. In the selected optimal model of microspheres, the solids concentration was 34 mg/mL and the gas flow rate was 7 mL/min. The obtained microspheres are included in orodispersible tablets that disintegrate in 30 seconds in the oral cavity. Due to the delayed release of famotidine by its incorporation into polymer microspheres, its bitter taste could not be felt.

[5]. Another study compared three different polymers (Eudragit E 100®, Chitosan and Methocel E15 LV®) in their ability to mask the bitter taste of ondansetron hydrochloride by spray drying. Models with different drug: polymer ratios have been prepared. The difference between the polymers is that Eudragit E 100® does not affect the release rate, while Chitosan slows the release of the drug, which slows the action of the drug. Models with Methocel do not achieve good taste masking, and those with Chitosan are characterized by rapid swelling in the oral cavity, which does not create a pleasant feeling for the patient. This study demonstrates the advantages of Eudragit E 100® over other polymers.

The presented literature data show the successful application of the spray drying method for taste masking of drugs with bitter or unpleasant taste by combining suitable polymers and process parameters. The method is gentle on medicinal substances. High productivity, high yield and high encapsulation efficiency of the drug are achieved.

II. TASTE EVALUATION

[10]. Taste evaluation of the obtained product is very important by taste masking. The lack of an appropriate pharmacopoeial test to determine taste masking has led to a great variety of methods for taste assessment. Taste is a subjective perception. Depending on individual preferences, taste sensations vary widely. Various in vivo and in vitro taste evaluation methods are used. They are based on the amount of drug dissolved in artificial saliva, taste analysis using an Electronic tongue device, testing with experimental animals - rats and healthy volunteers.

2.1. In vitro taste evaluation – a spectrophotometric method

[10, 32]. Determination of the amount of drug dissolved in artificial saliva is a method of assessing masked bitter taste. The method is performed in vitro under conditions similar to the decomposition of the drug in the oral cavity. The dosage form is placed in contact with a small amount of enzyme-free saliva (10 to 50 ml) at pH 6.8-7.4 for 1 minute. After this time a sample is taken for quantitative analysis. The aim is to reproduce the conditions in the oral cavity as much as possible and to predict the possible taste sensation. Taste masking is achieved when no drug is released in the artificial saliva or the released drug amount is below the bitterness threshold of the selected drug. For example, the threshold of sensitivity of the tongue to the bitter taste of quinine hydrochloride is 0.00005%.

2.2. Electronic tongue

[14, 33]. The electronic tongue is an analytical tool containing a set of non-specific, low-selectivity chemical sensors with high stability and cross-sensitivity to various substances in solution. It is suitable for taste evaluation or

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multivariate calibration for data processing. The device allows reproducible results in multiple analyzes of pharmaceutical products by measuring and comparing flavors. The electronic tongue imitates human taste sensations, which allows the identification and classification of liquid forms according to their taste. The apparatus is not used for the selective detection of chemical compounds, but for the recognition of general properties of the sample, using a template system. The principle of measurement is different for different types of electronic tongues - potentiometry, voltammetry, amperometry. The application of such devices is not only for the detection of masked bitter taste, but also used in the analysis of foods - wine, beer, tea, plant products, coffee, milk, fermentation samples and even for water quality analysis. In the human body, taste signals are converted from nerves in the brain into electrical signals. Electronic tongue sensors generate electrical signals as potentiometric changes. The statistical software of the device interprets the sensor data in taste models. One of the first Electronic tongue devices was developed by Professor Fredrik Winkist of the University of Linköping, Sweden.[2]. Amelian and team (2017) evaluated the taste of cetirizine hydrochloride tablets using a spectrophotometric method, an electronic tongue and in vivo by the participation of healthy volunteers. Taste masked orodispersible tablets, obtained by the method of spray drying and by lyophilization, were studied. The electronic tongue is equipped with 16 ion-selective electrodes. The measurements are performed potentiometrically. The device presents the drug, the prepared models and the placebo model through photographs, by taking into account the distance between them, which corresponds to the respective taste sensations. The farther the image of a model is from cetirizine hydrochloride and the closer it is to the placebo model, the better its taste is masked. A correlation was found between the three methods used to evaluate the taste.

2.3. In vivo taste evaluation with experimental animals

[8, 26]. A number of studies have proven the similarity between the taste sensations of humans and rodents. Devantier and team (2008) compared the taste sensations of mice and humans to quinine, ciprofloxacin, clarithromycin, and nystatin. Rudnitskaya and co-authors (2013) conducted a test to evaluate the taste of 8 drugs (azelastine hydrochloride, caffeine, chlorhexidine digluconate, potassium nitrate, 18-naratriptan hydrochloride, paracetamol, quinine hydrochloride and sumatriptan). These studies compared the results of the number of lickings of solutions of these drugs from rats and the results of the panel method performed with healthy volunteers. [24]. A study by Noorjahan et al. (2014) developed a method for evaluating taste based on the withdrawal behavior of rats by unpleasant taste, as well as based on the frequency of lickings of solutions with the drug. Rats show similar reactions to repelling unpleasant taste sensations as humans. Initially, rats tested solutions with different concentrations of the drug in water. The aim is to determine the concentration at which the bitter taste is detected. Rats were left without water for 24 hours. Then count the number of lickings per bottle of water for 5 minutes as standard. The number of licks per bottle of drug solution compared to water is also determined. The number of lickings of the solutions of the taste-masked particles for a certain time is noted and the licking frequency is determined. Behavioral reactions of rats such as repulsion, avoidance at the end of the cage, washing of the face and paws when they feel an unpleasant taste are also reported. It has been found that as the concentration of the bitter drug increases, the licking frequency decreases.

2.4. Taste evaluation by healthy volunteers

[23]. To determine the taste masking of drugs, studies often compare the results obtained by in vitro analysis and in vivo taste evaluation by healthy volunteers. A panel method is used, forming a group of healthy people who participate in the trial voluntarily. Healthy volunteers do not ingest the drug and the prepared dosage form. The taste evaluation is done very quickly with subsequent rinsing of the oral cavity with water. The taste evaluation by healthy volunteers is always performed according to the principles and requirements of the Declaration of Helsinki - a declaration of ethical principles developed by the World Medical Association as a guide for doctors and others involved in human medical research.

[6]. A study to determine the taste of azithromycin orodispersible tablets by Chaudhari et al. (2016) was performed. The study involved 10 healthy volunteers. First, they determined the taste of the pure drug-azithromycin and then the resulting microparticles. A taste rating scale is preset: 3 - very bitter, 2 - bitter, 1 - slightly bitter, 0 - tasteless (normal). [28]. In another study with 20 healthy volunteers aged 20-25 years to determine the taste of tramadol hydrochloride, a scale with 8

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degrees (0 - tasteless, 0.5 - very slightly bitter, 1.0 - slightly bitter, 1.5 - slightly to moderately bitter, 2.0 - moderately bitter, 2.5 - moderately to very bitter, 3.0 - very bitter, 4.0 - very strongly bitter) was used. The mentioned studies show that each research team determines the design of the panel study and the scale for taste evaluation, which may be different in each experiment.

III. CONCLUSION

Taste masking of bitter drugs improved the quality of treatment provided to patients, especially children. The methods described in this review could be suitable for taste masking of bitter drugs and its taste evaluation. Applying different approaches to mask the bitter taste of drugs for the preparation of orodispersible tablets with desired characteristics is a challenge. The study requires the need for special equipment, research of the influence of various variables, optimization of the production conditions, as well as the application of appropriate methods for taste evaluation.

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