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A Review on Taste Masking Technology in the Pharmaceutical Products

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Abstract

Taste masking technology plays a crucial role in the pharmaceutical industry, enhancing patient compliance and overall medication experience. It involves the development of techniques to disguise the unpleasant taste of certain medications, especially those targeted at pediatric and geriatric populations. By employing various approaches such as microencapsulation, complexation, and flavoring agents, pharmaceutical companies can mask the bitterness or unpleasant flavors of drugs without compromising their therapeutic efficacy. This innovation encourages patient adherence to medication regimens, particularly in populations sensitive to taste, ultimately leading to better treatment outcomes. The continual advancement of taste masking technology allows for the formulation of palatable medications that are easier to administer, ensuring patient comfort and improved healthcare delivery. Present review takes account of recent developments in taste masking technology.

INTRODUCTION

1.1 Taste Masking

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist **[1].** Taste-masking techniques are applied to mask or overcome the bitter or unpleasant taste of active pharmaceutical ingredients/drugs to achieve patient acceptability and compliance. Oral administration of bitter or unpleasant tasting drugs is often the biggest barrier for patient groups, such as pediatrics and geriatrics **[2].** A survey of American Association of Pediatricians reports unpleasant taste as the biggest barrier in the treatment of pediatric population **[3].** Unless the active ingredient is tasteless or does not have any unpleasant taste, taste-masking plays a key role in the success of a final solid oral dosage form. The efficiency of taste-masking is often a key determinant for the success of specialized dosage forms like orally disintegrating tablets and films, and chewable tablets. The mechanisms of taste-masking techniques often rely on two major approaches: the first is to add sweeteners, flavors, and effervescent agents to mask the unpleasant taste, and the second is to avoid the contact of bitter/unpleasant drugs with taste buds. In the past few years, significant progress has been made in the area of taste-masking by applying novel strategies and techniques, such as hot-melt extrusion and microencapsulation.

1.2 TASTE-MASKING TECHNIQUES

Taste-masking techniques often go hand in hand with the formulation technology. In short, they need to be mutually compatible **[4]**. For example, coated particles obtained after fluid-bed coating should be able to withstand the tablet compression process used for the final dosage form (tablet) manufacturing. The commonly used industrial techniques/methods of taste-masking include organoleptic methods, polymer coating, hot-melt extrusion, microencapsulation, complexation, and spray-drying.

Organoleptic Methods

This is the simplest and most convenient method of taste-masking. It involves adding a combination of sweeteners (sucralose, aspartame) and flavors (orange, mint) to mask the unpleasant taste of low to moderately bitter actives. In addition, effervescent agents (sodium bicarbonate, citric acid) can also be added to improve the mouth feel. Some formulations may include a bitterness blocking agent that masks the bitter taste or the perception of bitter on the tongue. Such bitter blockers may include adenosine monophosphate, lipoproteins, or phospholipids. These agents compete with the bitter active to bind to the G-protein coupled receptors on the tongue (receptor sites that detect bitter), thus suppressing the bitter taste **[5]**. It has also been found that sodium chloride can be added to a formulation to mask bitterness as in the preparation of pioglitazone hydrochloride orally disintegrating tablets **[6].**

Polymer Coating

The simplest option is direct coating that provides a physical barrier over the drug particles with a composition that is insoluble in the mouth. Hydrophobic or hydrophilic polymers, lipids, and sweeteners can be used as coating materials, alone or in combination to produce a single or multi-layer coat. Methacrylic acid and methacrylic ester copolymers (Eudragit E-100, RL 30D, RS 30D, L30D-55, and NE 30D) have been effectively used for taste-masking with polymer coat levels varying from 10% to 40%, depending on the drug bitterness **[7].** Fluid bed is often the technique of choice. Most recently, alternate approaches such as application of molten lipids [glyceryl palmitostearate (Precirol® ATO-5, Gattefosse, France) and glycerol behenate (Compritol® 888-ATO, Gattefosse, France)] on the surface of drug particles has been used as a solvent-free alternative.

The second alternative involves deposition of successive layers of an active compound onto inert starter seeds, such as sugar spheres or celpheres. The bitter drug is dissolved or dispersed in an aqueous or non-aqueous solvent along with a binder to allow the adherence of the drug particles to the inert substrate. Some commonly used binders include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), povidone, Eudragit E-100, and carboxymethyl cellulose. The drug-layered beads are then subsequently coated with a taste-masking polymer that retards drug dissolution in the oral cavity. Various polymers used for taste-masking purposes are Eudragit E-100, ethylcellulose, HPMC, HPC, polyvinyl alcohol, and polyvinyl acetate **[8].** The taste-masked coated beads can then be incorporated into the final dosage form, such as a capsule or a compressed tablet. CIMA LABS has extensive experience in this area in the form of their DuraSolv® and OraSolv® technologies.

A third approach involves granulating the drug and then coating the drug-loaded granules with a taste-masking polymer. Granulation decreases the surface area of the drug by increasing its particle size and thus

minimizing the amount of taste-masking polymer required. Granulation-coat approach is preferred over layer-coat for high doses as the granulation process can afford high drug loading. Regardless of the approach, fluid-bed coating remains the industrial process of choice to apply polymer coat for taste-masking. One of the challenges of taste-masking is evaluating the success or efficiency of the taste-masking technology. In the author's experience, dissolution testing can be used as a surrogate test for taste by evaluating the drug release from the taste-masked beads at earlier time points. The FIP/AAPS (Federation International Pharmaceutique/American Association of Pharmaceutical Scientists) guideline recommends multi-point dissolution testing within early points of analysis (eg, ≤ 5 min) as a means to address the taste-masking properties of the formulation.8 Data collected at these early time points may be used for in vitro evaluation of the taste-masking efficiency. Figure 2 shows the release comparison of Niravam tablets containing layer-coated taste-masked drug beads vs. the non-taste-masked Xanax tablets. A multi-point profile in neutral pH medium with early single point specification (NMT X% released at 5 or 10 min) is applied to determine the taste-masking efficiency.

Hot-Melt Extrusion

Hot-melt extrusion (HME) offers a relatively newer approach to taste-masking and provides advantages such as absence of organic solvents in the process, fewer processing steps, continuous operation, and scale-up capabilities **[9].** For the purpose of taste-masking, the bitter active is mixed with other ingredients in a dry state. The mixture is filled in a hopper, conveyed, mixed, and melted by an extruder. The process subjects the materials to a heating process under intense mixing to obtain the taste-masked extrudates. The extrudate can then be milled or micronized to obtain taste-masked granules or particles, which are then incorporated into a suitable dosage form. Twin screw extruders (Figure 3) are one of the most popular extruders and provide advantages such as short transit time, convenient material feed, high shear kneading, and less over-heating.

Microencapsulation

Microencapsulation is a technology with a long history in the pharmaceutical industry, and taste-masking represents an expanded area of its application. In principle, microencapsulation provides the opportunity to encapsulate the bitter active and thus prevent its contact with taste buds. Microcaps® is one such well-recognized technology that applies coacervation/phase separation to produce different encapsulated polymeric membranes. The process primarily consists of formation of three immiscible phases, formation of the coat, and deposition of the coat. The formation of the three immiscible phases is accomplished by dispersing the core particles in a polymer solution. A phase separation is then induced by change in the temperature of polymer solution; change in the pH, addition of a salt, non-solvent, or by inducing a polymer-polymer interaction. This leads to deposition of the polymer coat on the core material under constant stirring. The core particles coated by the polymer are then separated from the liquid phase by thermal, crosslinking, or desolvation techniques leading to rigidization of the coat **[10].** Microcaps are used in conjunction with Advatab® compressed ODT technology.

Complexation

Cyclodextrins have been extensively used for taste-masking bitter drugs by forming inclusion complexes with the drug molecule. Cyclodextrins are unique bucket-shaped cyclic oligosaccharides containing at least six D-

(+)-glucopyranose units attached by alpha-(1,4)-glucosidic bonds with a molecular structure of hydrophobic cavity and hydrophilic exterior. The formation of inclusion complexes and its type depends on several factors like drug properties, processes involved, the equilibrium kinetics, formulation excipients, and the desired final dosage form and delivery system. Taste-masking is achieved by the interaction of cyclodextrins with proteins of the taste buds or by inhibiting the contact of bitter drug molecules with taste buds.

Ion exchange resins provide an alternative to cyclodextrins to achieve taste-masking by complexation **[11].** Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. The preparation of the taste-masked complex involves suspending the resin in a solvent in which the drug is dissolved. The drug-resin complex formed is referred to as drug-resinate, which prevents direct contact of the drug with taste buds, thus providing taste-masking during administration. Upon ingestion, the resin exchanges the drug with the counter ion in the gastrointestinal tract, and the drug is released to be absorbed. Commercially available ion exchange resins that may be used for taste-masking are based on methacrylic acid – divinyl benzene polymer and styrene – divinyl benzene polymer.

Spray-Drying

Spray-drying provides an alternate approach to taste-masking by applying a physical barrier coating. The bitter drug is either dissolved or dispersed along with the polymer in a suitable solvent followed by spray-drying. The process usually consists of three different steps: (1) atomization of feed into a spray, (2) spray-air contact (mixing and flow) followed by drying, and (3) separation of dried product from the air. The process provides the option of using aqueous and non-aqueous solvents. The dried product often includes granules or beads containing taste-masked encapsulated drug. The amount of polymer coat can sometimes retard the drug release, and therefore requires careful polymer selection and process design to afford taste-masking. Also, the formulation and processing can affect whether or not the polymer is "coated" on the surface or dispersed. The quality of taste-masking depends on providing a coat, not a dispersion. Some of the advantages of spray-drying include (a) less processing time being a single step process, (b) scale-up capability, and (c) wide variety in the choice of solvent and polymer.

RECENT ADVANCES

Alyami et al. (2023). In the present study, taste masked PMZ nanocapsules (NCs) were prepared using an interfacial polycondensation technique. A one-step approach was used to expedite the synthesis of NCs made from a biocompatible and biodegradable polyamide based on l-arginine. The produced NCs had an average particle size of 193.63 ± 39.1 nm and a zeta potential of −31.7 ± 1.25 mV, indicating their stability. The NCs were characterized using differential scanning calorimetric analysis and X-ray diffraction, as well as transmission electron microscopy that demonstrated the formation of the NCs and the incorporation of PMZ within the polymer. The in vitro release study of the PMZ-loaded NCs displayed a 0.91 ± 0.02% release of PMZ after 10 min using artificial saliva as the dissolution media, indicating excellent taste masked particles. The in vivo study using mice revealed that the amount of fluid consumed by the PMZ-NCs group was significantly higher than that consumed by the free PMZ group ($p < 0.05$). This study confirmed that NCs

using polyamides based on l-arginine and interfacial polycondensation can serve as a good platform for the effective taste masking of bitter actives **[12].**

Siddiqui et al. (2023). The study is based on preparing taste-masked oral suspension of azithromycin using ion exchange resins Kyron T135 and Doshion-P542 AB. The complexation process was optimized through Design of Experiment (DOE), and the resins-complexes were characterized by bitterness score, differential scanning calorimetry (DSC), fourier transform infra-red spectrophotometry (FTIR) and powder x-ray diffraction (PXRD). The complexes were further formulated and optimized through Central Composite Design (CCRD) into oral suspension using xanthan gum, hydroxypropyl cellulose, tri-basic sodium phosphate, and sucrose. To obtain the optimized product, the trial batches were tested for sedimentation ratio and viscosity in comparison to the reference product followed by assay and studies of drug-release kinetics. To perform bioequivalence of the optimized formulations against the reference product, an LC-MS/MS based bio-analytical method was developed and validated followed by a three-period cross over study. The pharmacokinetic parameters C*max*, T*max*, AUC0-t and AUC *0*-∞ were obtained through non-compartmental analysis (NCA) using log-transformed data. Moreover, physiologically based pharmacokinetic (PBPK) modelling of the *in-vitro* data was carried out to predict the pharmacokinetics of the optimized formulations in the intended paediatric population. Kyron T-135 yielded the best loading efficiency at a drug resin ratio of 1:1.35 and Doshion-P542 AB at 1:3.25, while stirring and swelling time of 30 min for Kyron T-135 yielded optimum drug loading. In case of Doshion P-542 AB the optimum time was 22.5 and 30 min for stirring and swelling respectively. The bitterness score proved the tastelessness of the drug resin complex. The optimized formulation with Kyron (formulation code K4) and Doshion (formulation code D6) were selected as optimum on the basis of similar quality attributes to the reference product. The drug dissolution kinetics revealed first order drug release. The developed bioanalytical method was found to be sensitive and linear in the range of 2–500 ng/mL showing accuracy within 101.32–106.68%. Both optimized formulations (K4 and D6) were found to be bioequivalent with geometric mean ratio of C*max*, T*max*, AUC0-t and AUC *0*-∞ within 90% C.I. *in silico* PBPK based predictive pharmacokinetics in the paediatric population was successfully estimated for the developed formulations **[13].**

Rawat, S et al. (2023). Biodegradable polymers could be employed for developing medicated straws with customized properties with the advance-ment of three-dimensional printing technology. Edible straws could be another futuristic approach so pediatrics could eat the straw after use. The edible straws could be loaded with probiotics and immunity boosters for potential therapeutic assistive effects. Adequately addressed regulatory aspects of medicated straws may prove as an innovative drug delivery system for the pediatric patient population. In conclusion, medicated straws are innovative drug delivery systems to accurately deliver drugs, minerals, vita-mins, probiotics,etc., to pediatric patients for better compliance and therapeutic efficacy **[14].**

CONCLUSIONS

The importance of this study is to review the research work done in the recent years on Taste Masking Technology in Pharmaceutical Products and thereby conclude the importance of developing new

pharmaceutical products in the future. This study will throw a light on how important Taste Masking Technology can be and its value in pharmaceutical development.

REFERENCES

1. Sohi, H., Sultana, Y., & Khar, R. K. (2004). Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches. In Drug Development and Industrial Pharmacy (Vol. 30, Issue 5, pp. 429–448). Informa UK Limited. https://doi.org/10.1081/ddc-120037477
2. Sohi H, Sultana Y, Khar RK. Taste-masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm. 2004;30(5):429-448.
3. Ayenew Z, Puri V, Kumar L, Bansal AK. Trends in pharmaceutical taste-masking technologies: a patent review. Recent Patents on Drug Delivery and Formulation. 2009;3:26-39.
4. Fu Y, Shicheng Y, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Crit Rev Thera Drug Carrier Syst. 2004;21(6):433-475.
5. Vummaneni V, Nagpal D. Taste-Masking Technologies: An Overview and Recent Updates. http://ijrpbsonline.com/files/11-3185.pdf.
6. Okochi K, Koyama H, Shingaki A. Oral Preparation Comprising Pioglitazone. WO2007136129 (2007).
7. Lehamann K, Petereit HU, Dreher D. Fast Disintegrating Controlled Release Tablets from Coated Particles. Drugs Made In Germany. 1994;37(2):53-60.
8. Busson P, Schroeder M. Process for Preparing a Pharmaceutical Composition, US Patent No. 6,534,087. March 18, 2003.
9. Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, McGinity JW, Martin C. Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm. 2007;33(9):909-926.
10. Lachman L, Lieberman H, Kanig, J. The Theory and Practice of Industrial Pharmacy. 3rd ed. 1986:420
11. Jeong SH, Park K. Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes. Int J Pharm. 2008;353:195-204.
12. Alyami, H. S., Ali, D. K., Jarrar, Q., Jaradat, A., Aburass, H., Mohammed, A. A., Alyami, M. H., Aodah, A. H., & Dahmash, E. Z. (2023). Taste Masking of Promethazine Hydrochloride Using l-Arginine Polyamide-Based Nanocapsules. In Molecules (Vol. 28, Issue 2, p. 748). MDPI AG. https://doi.org/10.3390/molecules28020748
13. Siddiqui, F., Shoaib, M. H., Ahmed, F. R., Qazi, F., Yousuf, R. I., Usmani, M. T., Saleem, M. T., & Ahmed, K. (2023). Formulation development and optimization of taste-masked azithromycin oral suspension with ion exchange resins: Bioanalytical method development and validation, in vivo bioequivalence study, and in-silico PBPK modeling for the paediatric population. In Journal of Drug Delivery Science and Technology (Vol. 79, p. 104048). Elsevier BV. https://doi.org/10.1016/j.jddst.2022.104048
14. Rawat, S. S., Rai, A., Rathi, R., Sharma, A., Huanbutta, K., Sangnim, T., & Singh, I. (2023). Medicated straw: an innovative drug delivery system for paediatrics. In Expert Opinion on Drug Delivery (Vol. 20, Issue 3, pp. 313–314). Informa UK Limited. https://doi.org/10.1080/17425247.2023.2171013