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TASTE-MASKING - Pharmaceutical Taste-Masking Technologies

INTRODUCTION

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.[1] A survey of American Association of Pediatricians reports unpleasant taste as the biggest barrier in the treatment of pediatric population.[2] 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. The following presents an overview and current status of the industrial approaches and platforms used for taste-masking in oral dosage forms.

TASTE-MASKING TECHNIQUES

Taste-masking techniques often go hand in hand with the formulation technology. In short, they need to be mutually compatible.[3] 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.[4] 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.[5]

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.[6] 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.

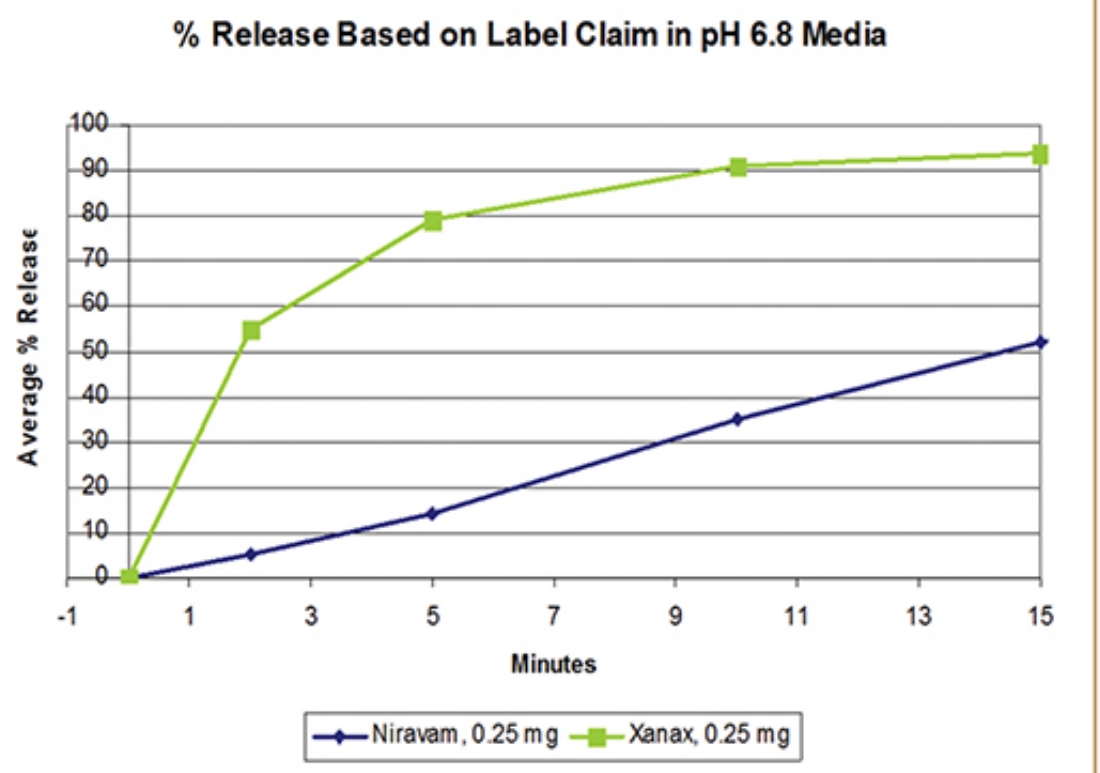
The second alternative involves deposition of successive layers of an active compound onto inert starter seeds, such as sugar spheres or celpheres. The bitter drug is dissolved or dispersed in an aqueous or non-aqueous solvent along with a binder to allow the adherence of the drug particles to the inert 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.[7] 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.

FIGURE 1

A) Fluid-Bed Coater & B) Wurster Setup for Taste-Masking

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 (Figure 1) 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.

FIGURE 2



Dissolution Profile of Immediate-Release Niravam & Xanax Tablets

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.

FIGURE 3

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.

SUMMARY

In summary, a variety of taste-masking technologies are available and used in the pharmaceutical industry today with new platforms being researched and developed constantly. The type of technology used depends largely on the physical and chemical properties of the drug substance and the desired final dosage form. Advances in taste-masking technologies throughout the past few years have enabled the pharmaceutical industry to provide commercial products with improved patient acceptability and compliance, especially with pediatric and geriatric populations; along with enhanced convenience for patients on the go. More companies are turning to taste-masking expertise to complement their product portfolios for oral dosage forms.

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