



INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH



FORMULATION STRATEGIES FOR TASTE-MASKING OF CHEWABLE TABLETS

Bhusnure O.G.¹, Shaikh F.E., Sugave B.K., Kavale B.S., Sayyed R.A., Hucche B.S.

Channabasweshwar Pharmacy College (Degree), Maharashtra, India.

ARTICLE INFO

Article history

Received 12/12/2015

Available online

31/12/2015

Keywords

Lubrication,
Disintegration,
Compatibility,
Stability,
Pediatric Patients,
Sweeteners.

ABSTRACT

Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. These tablets are intended to disintegrate smoothly in the mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Many active pharmaceutical ingredients (API) inherently possess a bitter taste. Nearly 20% of American adults surveyed complained of bad aftertastes or struggling to swallow when trying to take medication. If a medication is not palatable, the patient may opt to discontinue it. Failure to take medication as prescribed leads to increased morbidity, mortality, and potentially avoidable healthcare costs exceeding US\$100 billion annually in the US alone. While objectionable taste may be one of several reasons for poor adherence, every measure that minimises these reasons helps. With a recognised impact on patient healthcare outcomes and costs, the European Medicines Agency (EMA) has released guidelines promoting the development of medicines for paediatric use. The US FDA is promoting similar initiatives. Taste-masking is incredibly important for paediatric populations as well as Geriatric patients. Firstly, children are 3-4 times as sensitive to tastes as adults, with increasing tolerance to bitter tastes with age. Secondly, children, particularly infants, are unable to rationalise ingestion of an unpalatable medicine. The most popular oral dosage forms include liquids, powders, granules, orally disintegrating tablets (ODT), and chewable tablets. Each one has pros and cons, depending on the target age group. Liquids, powders, and granules provide the greatest flexibility in dosing, provided there is a simple way to meter the powders. For solid oral dosage forms like orally disintegrating tablets and chewable tablets, break-lines can be included in the tablet design to adjust dosing. As a result, chewable tablets has seen an increased interest from the pharmaceutical industry in taste-masking technologies.

Corresponding author

Dr. Bhusnure O.G

M. Pharm, Ph.D. Professor and Head
Department Of Quality Assurance,
Channabasweshwar Pharmacy College,
Kava Road, Latur-413512, Dist. Latur. (MS)
Tel: (+91)-2382-641008 (O), (+91)-2382-240008(O)
Fax: +91-2382-243855
omprakashbhusnure@gmail.com

Please cite this article in press as **Dr. Bhusnure O.G et al. Formulation Strategies For Taste-Masking of Chewable Tablets. Indo American Journal of Pharmaceutical Research.2015:5(12).**

Copy right © 2015 This is an Open Access article distributed under the terms of the Indo American journal of Pharmaceutical Research, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. These tablets are intended to disintegrate smoothly in mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Successful tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipient to perform a specific function in a tablet formulation such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic are one type of functional excipient commonly used in chewable tablet formulations to mask the unpleasant tastes and facilitate pediatric dosing. Ideally upon chewing, they are broken down in the mouth and release their ingredients in the process and therefore, do not have much lag time as required for the disintegration of tablets before absorption from stomach. Chewable tablet are often employed when the active ingredient is intended to act in a localized manner rather than systemically. Chewable tablet is one that is palatable and may be chewed and ingested with little or no water. Manufacturing of chewable tablet is generally done using either wet granulation process or direct compression. Increasingly, micronized and submicron forms of therapeutically and physiologically active substances are incorporated into tablet formulation to take advantage of the enhanced absorption characteristics of these forms. They are also used in the administration of antacids and carminatives. Mannitol is widely used as an excipient in chewable tablet for its non-hygroscopic nature for moisture sensitive drugs. As we know difficulty in swallowing (Dysphasia) is common among all age groups, especially in elderly and in also seen of swallowing of conventional tablets and capsules. Geriatric and pediatric patients and travelling patients who may not have ready access to water are most need of easy swallowing dosage forms like chewable tablets. The composition of chewable tablet consists of gum core, which may or may not be coated. The core is composed of an insoluble gum base like fillers, waxes, antioxidants, sweeteners, flavouring agents. The percentage of gum base varies from 30-60% depending upon the base used and its properties. A flavouring agent is included to make it more palatable. 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. A survey of American Association of Pediatricians reports unpleasant taste as the biggest barrier in the treatment of pediatric population. 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.

Criteria for taste masked formulations

Both dissolution profile and taste profile contribute to the acceptability criteria for taste-masked formulations. However, each drug product will have different release profile requirements to meet an acceptable level of taste-masking depending on the dose strength and organoleptic response to the API. Ideally, the taste-masked dosage form should prevent release of the unacceptable tasting medicine until the API has left the mouth, then allow for immediate release once the dosage has been ingested. To determine the taste profile, while electronic tongue technology is advancing, taste panels remain the preferred methodology for determining efficacy of tastemasking. Patients may be able to tolerate different levels of release in the mouth for different APIs depending on the drug solubility and other ingredients such as flavours and sweeteners in the formulation. Some regulatory authorities have cautioned that the formulation cannot taste "too good" as a safeguard against mistaking the medication for candy. Taste profiles should aim for a neutral taste or one that is generally acceptable taste in the mouth. Specifically in the case of paediatric dosage forms, the goal for taste-mask coating aims for the minimum weight gain necessary to achieve robust functionality. However, effective weight gains will be dependent on the properties of the substrate. For instance, if the drug particle is very fine or has a broad particle size distribution, higher weight gains of the coating will be required for consistent taste-masking. In short, when it comes to successful taste-masking, understanding the properties of your coating substrate or drug really matter.

Strategies available for Taste-Mask Formulations

For most solid oral dosage forms (SODs) or tablets, the API is blended with a number of excipients, and a well designed film coating, such as Opadry® complete film coating system, often provides sufficient properties to adequately mask objectionable tastes for the brief residence time in the mouth before swallowing. Alternative dosage forms such as sachets, ODTs, and chewable dosage forms pose additional challenges in taste-masking due to increased contact surface area as well as residence time in the mouth, enhancing any unpleasant taste and/or lingering aftertaste. In these cases it is often necessary to create a barrier, such as a specific taste-mask coating, between the API and the taste buds in order to improve palatability and aid compliance. In a review of taste-masking technologies, coating was most highly rated, with inclusion of flavours and sweeteners a close second in terms of popularity.

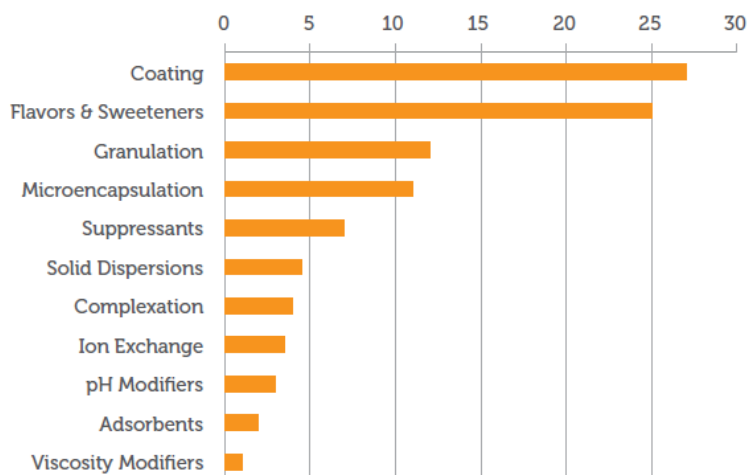


Figure 1: Breakdown of taste-masking technologies.

There are two main categories of coatings for taste-masking: pH-independent and pH-dependent. As an example of a pH-independent taste-mask coating, Colorcon's customers have been successful when a combination of Surelease® and Opadry® is applied. Surelease is an aqueous ethylcellulose dispersion and acts as the insoluble barrier membrane which prevents drug release in the mouth. Opadry acts as the soluble pore-former to promote immediate release in the stomach. Recent work at Colorcon has demonstrated the use of this combination for taste-masking acetaminophen (APAP) granules. Surelease:Opadry (85:15) was applied to APAP granules in a Glatt GPCG-2 fluid bed. Granules were coated to 10% weight gain of the Surelease:Opadry and compressed into a chewable tablet formulation. The dissolution profiles are shown in Figure 2, demonstrating that by using Surelease and Opadry for taste-masking we were able to match the release profile of a commercially marketed product and meet requirements for immediate release (no less than 75% released in 45 minutes). You may have noticed that the dissolution of the coated granules is quite different before and after compression into the chewable tablet. It is completely normal and expected for a partial rupture of the coating upon compaction pressure, and this can be accounted for in the design of the dosage form, as we have done here. The second category of taste-mask coating technology is a pH-dependent coating based on reverse enteric polymers which are insoluble at the relatively neutral pH of the mouth and become soluble once in the lower pH of the stomach. Included in this class of polymer are acrylic acid soluble polymers such as Kollicoat® SmartSeal, an aqueous dispersion of methylmethacrylate and diethylaminoethyl-methacrylate copolymer from BASF (Ludwigshafen, Germany).

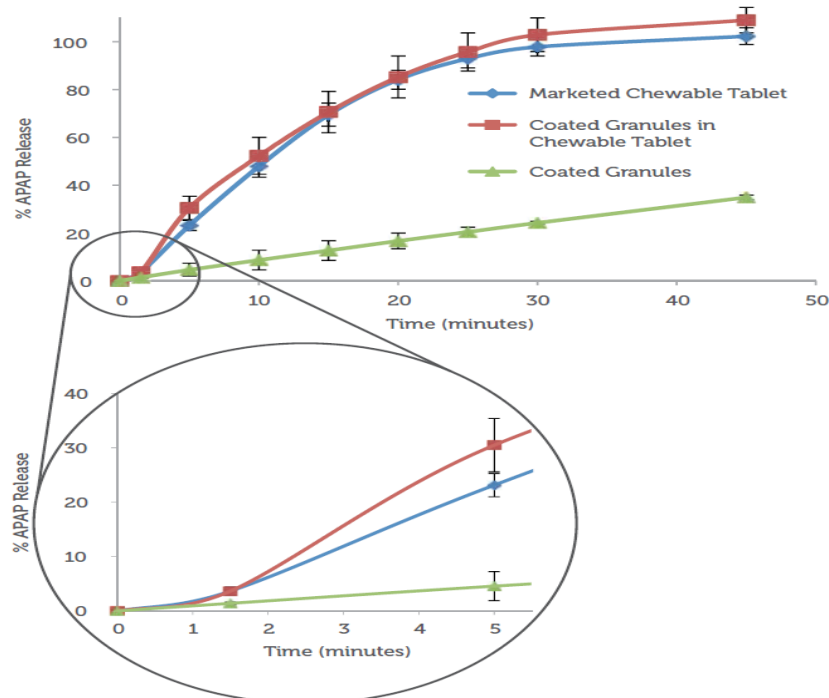


Figure 2: Drug release profiles of acetaminophen (APAP).

The granules coated with Surelease:Opadry (85:15) for the purposes of taste masking, formulated as granules and in a chewable tablet form, compared with a marketed chewable tablet. Top graph shows 50 minutes of data, with the first five minutes magnified in the lower graph. The product was developed specifically for taste-masking applications for orally administered pharmaceutical products, and is considered a best-in-class reverse enteric polymer. In 2014, Colorcon entered into a collaboration with BASF to develop a fully formulated coating system using Kollicoat SmartSeal. This relationship leverages BASF's expertise in polymer chemistry and Colorcon's long recognised leadership in fully formulated coating systems for pharmaceutical use. This collaboration aims to improve manufacturing speed and simplicity for the customer, enabling easy reconstitution of the film former while maintaining product functionality. Colorcon is excited to have expanded its taste-masking product portfolio with Kollicoat SmartSeal. This allows us to better serve the industry in providing solutions to improve adherence, particularly in the more challenging paediatric and geriatric spaces.

2. General Formulation Factors

Various factors involved in the formulation of chewable tablets. The major formulation factors are flow, lubrication, disintegration, organoleptic properties, compressibility, compatibility and stability, which are common to regular (swallowed) and chewable tablets; however, organoleptic properties of the active drug substances are primary concern here. A formulator may use one or more approaches to arrive at a combination of formula and process that result in product with good organoleptic properties. Such a substance must have acceptable flow, compressibility and stability characteristics.

i. Taste and Flavours

Physiologically, taste is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. There are four basic type of taste; salty, sour, sweet and bitter. Salty or sour tastes are derived from substances capable of ionizing in the solution. Many organic medicinal compounds stimulate a bitter response even though they may not be capable of ionizing in an aqueous medium. Most saccharides, disaccharides, some aldehydes and few alcohols give a sweet taste. Substance incapable of producing a sensory stimulation of the buds is known as tasteless. The term flavour generally refers to a specific combined sensation of taste and smell. For example, sugar has a sweet taste, but no flavour, whereas honey has a sweet taste and a characteristics smell.

ii. Aroma

Pleasant smells are generally referred to as aromas. For example, a well formulated, orange-flavoured chewable tablet should have a characteristic sweet and sour taste and aroma of fresh orange.

iii. Mouth-feel

This term is related to the type of sensation or touch that a tablet produce in the mouth upon chewing. As such, it has nothing to do with chemical stimulation of olfactory nerves or taste buds. However, for a formulation to be successful, the overall effect in the mouth is important. In general, gritty (e.g., calcium carbonates) or gummy texture is undesirable, whereas soothing and cooling sensation (e.g., mannitol) with smooth texture is preferred.

iv. After Effects

The most common after effect of many compounds is after taste. For example, some irons leave a "rusty" after taste; saccharin in high amounts tends to leave a bitter after taste. Another common after effect is a numbing sensation of a portion of the whole surface of the tongue and mouth. Bitter antihistamines like pyribenzamine hydrochloride and promethazine hydrochloride are typical of this class drugs.

3. Assessment of the Problems Regarding Formulation

Wherever feasible and practical, the first step in the formulation of chewable tablet is to obtain a complete profile of the active drug. This usually leads to the most efficient formulation of a stable and quality product as the drug usually dictates the choice of fillers, carriers, sweeteners, flavor compounds and other product modifiers. The drug profile ideally should contain information on the following:

i. Physical Properties

- Colour
- Odour
- Taste, after-taste and mouth-feel
- Physical form: crystal, powder, amorphous solid, oily liquid, etc.
- Melting temperature
- Polymorphism
- Moisture content Aqueous solubility
- Active drug stability
- Compressibility

ii. Chemical Properties

- Chemical structure and chemical class
- Major reactions
- Major incompatible compounds
- Drug dose

This active drug profile would eliminate potentially incompatible excipients, flavours and leading the use of excipients that would best compliment the drug physically, chemically and organoleptically. The choice of excipients and other product modifiers would involve balancing their cost with their functionality. The use of low-caloric and non sugar based excipients may represent a marketing advantage, especially with consumers concerned about caloric intake and dental caries.

iii. Need for the Development of Chewable Tablet

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

iv. Patient Related Factors

Approximately one-third of the patients need quick therapeutic action of drug, resulting in poor compliance with conventional the drug therapy which leads to reduced overall therapy effectiveness. A new dosage form, the immediate release tablets has been developed which offers the combined advantages of ease of dosing and convenience of dosing. These tablets are designed to release the medicaments with an enhanced rate. Chewable dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water.

- Very elderly patients who may not be able to swallow a daily dose of antidepressant
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup

v. Effectiveness Factors

Increased bioavailability and faster onset of action are a major claim of these formulations. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism.

4. Manufacturing and Marketing Related Factors

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value added product line extension and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations.

5. Physiology of Taste

Taste sensation can be expressed as a feeling by an individual when something is given into mouth in order to ascertain the whole component. There are generally four fundamental of taste:

- Sweet and salty, mainly at the tip of tongue
- Sour, at the side of tongue
- Bitter, at the back of the tongue

Generally Human tongue contains 50-100 number onion shapes structures called taste buds. Chemical from foods or orally ingested medicaments are dissolved by saliva via taste pores. They either interact with surface proteins known as taste receptors or ion-channels. These interactions cause electrical changes within the taste cells that trigger them to send chemical signal translate into neurotransmitters to the brain. Salt and sour responses are of channel type responses, while sweet and bitter are surface protein responses. Electrical responses, that send the signal to the brain, are result of varying concentration of changed atoms or ions within the taste cell. These cells normally possess negative charge. Tastants alter this taste by using varying means to increase the concentration of positive ions within taste cell. This depolarization cause taste cells to release neurotransmitters, promoting neurons connected to the taste buds to send electrical messages to the brain. In the case of bitter taste drug by binding to G-protein coupled receptors on the surface of the taste cell, prompts the protein subunit of alpha, beta and the gamma to split and activate enzyme. This enzyme then converts precursor within the cell into "second messenger". The second messenger causes the release of calcium ions from endoplasmic reticulum of the taste cell. The resulting build-up of calcium ion cells lead to depolarization and neurotransmitter release. The signals give a sense which is interpreted as bitter taste. Effective blocking of taste receptors can be accomplished by either coating the surface pore or competing with the channel themselves to reduce the effect of bitter stimuli firing.

i. Taste Masking

Taste masking is defined as a reduction of undesirable taste that would otherwise exist. Taste masking can be achieved using taste masking agents, specific flavours and sweeteners. Sweeteners are essential to complete the experience and produce a pleasant taste of the product. This is one of the major limiting factors in the formulation of oral dosage forms having unpleasant taste. Flavour masking and processing approaches are two primary methods to overcome this problem. Flavour masking generally include addition of flavour, sweetener, lipid and acids.

ii. Techniques for Taste Masking

Before formulation some common problems encountered: undesirable taste, bad mouth-feel. The desired product should prevent or minimize stimulation of the taste buds, contain a suitable flavour and sweetener and achieve good mouth feel and compressibility. The following techniques are used to solve these problems;

- Coating by Wet granulation
- Microencapsulation
- Solid dispersions
- Adsorbate Formulation techniques (Solvent method)
- Ion Exchange
- Spray congealing and spray coating
- Formation of different salts or derivatives
- Use of amino acids and protein hydrolysates
- Inclusion complexes
- Molecular complexes

TASTE-MASKING TECHNIQUES

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

6. 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. 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.

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 [9]. 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 cephers. 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 3:- Fluid –Bed Coater & 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 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 Internationale 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[10]. 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.

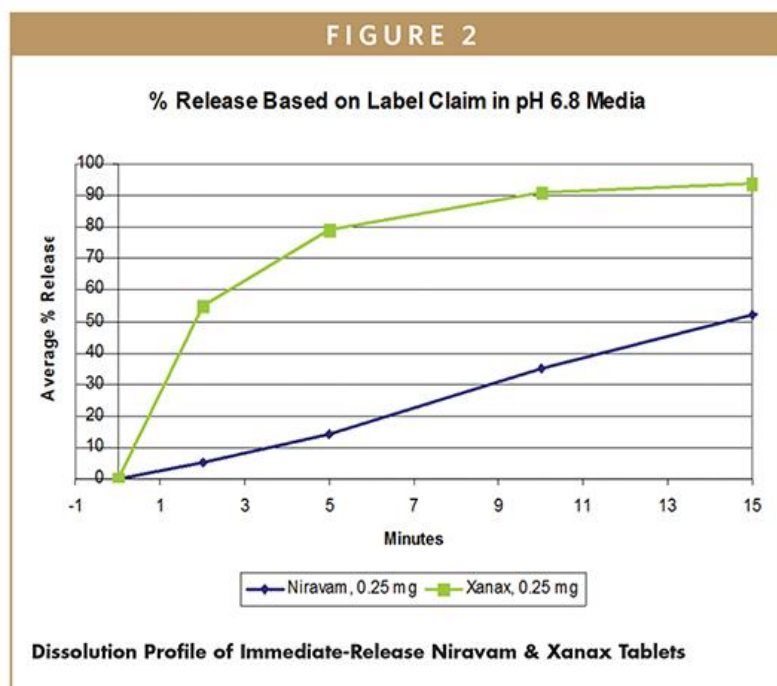


Figure 4 :- Dissolution profile immediate release Niravam & Xanax Tablet.

7.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. 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 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 5:-Hot –Melt Extruder.

8. 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. Microcaps are used in conjunction with Advatab[®] compressed ODT technology.

9. 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. 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.

10. 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.

GENERAL EXCIPIENTS USED IN THE FORMULATION OF CHEWABLE TABLETS

Special consideration, however, needs to be given to those materials that form the basis for chewable tablet formulation. The acceptability in the formulation of chewable tablets will be primarily determined by taste and to a lesser degree, appearance. Therefore, appropriate selection and use of components that impact on these properties are of extreme importance. Of course, the formulator must not become as concerned with these properties as to lose sight of other pharmaceutical and biomedical considerations; the resultant product must be as pure, safe, efficacious, and stable as any other. The wet granulation, dry granulation, direct compression and direct compaction processes are as applicable to chewable tablets as to any other type of tablet. The concern such as moisture content and uptake, particle size distribution, blending and loading potentials, flow and compressibility is no less important, and must be addressed by the formulation/process development pharmacist as for any product. However, in the case of chewable, the new concerns of sweetness, chew-ability, mouth-feel and taste must also be considered. Major excipients, such as fillers or direct compaction vehicle have the major role in the outcome of these concerns; process, a lesser (but certainly not minor) role.

Many of the sweeteners are commonly used in the tablet formulation are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chew-ability. In general these all excipients fall under the sugar category, although a combination of bland excipients with artificial sweeteners may provide a satisfactory alternative. Some common chewable tablet sweeteners are Brown sugar, Compressible sugar, Honey, Dextrose/fructose, Lactose, Mannitol, Sorbitol. Few of them need further explanation as follows:

11. Sweetners

i. Dextrose

Dextrose is the sugar obtained through the complete hydrolysis of starch. Its sweetness level is approximately 70% that of sucrose, and is available in both anhydrous (but hygroscopic in nature) and monohydrated form.

ii.Lactose

Lactose is the monosaccharide that produced from whey, a byproduct of the processing of cheese. Although generally acknowledged as the most widely used pharmaceutical excipient in the world. Its applicability to chewable tablets is minor at best, due to its extremely low sweetness level (15% sucrose). This deficiency requires the addition of an artificial sweetener of sufficient potency to overcome lactose's blandness. For wet granulation applications, regular pharmaceutical grades (hydrous fine powders) are available. For direct compression, an anhydrous powder having good flow and compressible characteristics is available as lactose.

iii.Mannitol

Mannitol is a white, crystalline polyol approximately 50% as sweet as sucrose. It is freely soluble in water and, when chewed or dissolved in the mouth, imparts a mild cooling sensation due to its negative heat of solution. This combined with an exceptionally smooth consistency has made mannitol the excipient of choice for chewable tablet formulations.

iv.Sorbitol

Sorbitol is slightly sweeter and considerably more hygroscopic isomer of mannitol. For direct compression, it is available commercially as Sorb-Tab and crystalline Tablet Type.

Table 1: Approximate Relative Sweetness of different Sweeteners.

Materials	Relative sweetness
Saccharins	450
Sucrose	1
Mannitol	0.5-0.7
Maltose	0.3
Lactose	0.2
Aspartame	200
Glycyrrhizin	50
Sorbitol	0.5-0.6
Dextrose	0.7
Fructose	1.7

v. Flavouring Agents

From the perspective of consumer acceptance, taste is almost certainly the most important parameter of the evaluation of chewable tablets. Taste is a combination of the perceptions of mouth-feel, sweetness and flavour. Mouth-feel is affected by heat of solution of the soluble components, smoothness of the combination during chewing and hardness of the tablet. These factors are directly and almost entirely related to the active ingredient and major excipients. Sweetness, at an appropriate level, is a necessary background to any flavour. The primary contributors to sweetness in a chewable tablet are the drug, natural sweeteners and artificial sweetness enhance that may be incorporated in the formulation. Flavouring agents are available in a variety of physical forms from a large number of suppliers specializing in these materials. Virtually all offer technical support services, which will be addressed in the section on flavour formulation. Various forms available include water-miscible solutions, oil bases, emulsions, dry powders, spray-dried beadlets, and dry adsorbates. A typical flavour having the capability of producing several hundred combinations for a given application.

vi.Flavour Selection and Formulation

Initially, the inherent taste of the active drug must be evaluated to determine its probable contribution to the formulation and a final decision must be made relative to formulation components that would impact on both the pharmaceutical properties and organoleptic characteristics of the tablet. Throughout in formulation development, these considerations must be maintained and eventually optimized. The goal must be a baseline formulation having acceptable properties such as hardness, friability, and dissolution, while providing a suitable mouth-feel and sweetness background for flavouring. Having in the preparation of one or more unflavoured bases,. These should be designed to narrow the flavour focus to one or more groups of flavor preferred by decision makers within the company. Various group of flavour for general baseline taste types are tabulated below in table 2:

Table 2: Flavour groups for general Baseline taste types.

Sweet	Grape, berries, honey, vanilla
Sour (acidic)	Citrus, liquorice, strawberry, cherry
Salty	Buttery, spice, mixed citrus, mixed fruit
Bitter	Liquorice, wine, mint, nut, fennel, grapefruit

Manufacturing

For chewable tablets, manufacturing means proper incorporation of the colouring agent, maintenance of correct moisture content, and achievement of proper tablet hardness.

All of these are the routine responsibility of the manufacturer in the department once the parameters have been established during development. The process development and scale up considerations be thoroughly studied in order to ensure the of proper specifications. If colour is added as a lake for direct compression blend, then the blending operation consists of the addition of coloured powder to white granules. So, coloured powder will uniformly coat the white granules. However, during compression, the granules release fresh white material to the surface, resulting in white spots on a coloured background or "speckling".

GENERAL METHODS OF MANUFACTURING CHEWABLE TABLETS

The Chewable tablets were prepared by using the following methods:

1. Non aqueous Granulation/Dry granulation
2. Aqueous Granulation/Wet granulation
3. Direct compression

Granulation

Granulation is the process in which primary powder particles are made to adhere to form larger, multi-particles entities called granules. Pharmaceutically granules have size range between 0.2 to 4.0 mm. Granulation is used to improve flow and compressibility of powders and to prevent segregation of the blend components. Granulation is mainly done by using two techniques.

i. Dry granulation

It is the novel method for semi-automatic production of granules. The method is applicable to any solid dosage pharmaceutical products. Dry granulation method replaces existing solid dosage form development and manufacturing technologies offering more rapid development and better quality. In this process, the powder mixture is compressed without the use of heat and solvent. Two methods are used for dry granulation. The more widely used is slugging where the powder is recompressed and the resulting tablet are milled to yield the granules.

ii. Wet granulation

Wet granulation is the most commonly used granulation method. This process involves wet massing of powder blend with a granulating liquid, wet sizing and drying. The granulating liquid contains a solvent which must be volatile so that it can be removed by drying and must be non-toxic in nature. Typical liquid include water, ethanol and Isopropyl alcohol. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are subsequently dried.

iii. Direct Compression

Direct compression is the most popular choice because it provides the shortest, most effective and least complex way to produce tablets. This method is mainly used when a group of ingredients can be blended. This is more suitable for moisture and heat sensitive APIs since it eliminates wetting and drying steps and increase the stability of active ingredient by reducing detrimental (harmful) effects. In this process, API mixed with the excipients and lubricant, followed by compression which makes the product easy to process.

EVALUATION PARAMETERS FOR CHEWABLE TABLET

The variety of evaluation parameters must be kept in mind during the formulation of chewable tablets. These are given as follows:

In-process Organoleptic evaluation

This evaluation takes place at various stages in the development of a chewable tablet. These are as follows:

Evaluation of drug itself:

It involves characterization and comparison of the substance in an absolute amount or against a known reference standard.

Evaluation of coated drug:

It involves comparison against the pure drug as well as different coating treatment.

Evaluation of unflavoured baseline formulation:

It involves comparison among different vehicles, proportion of vehicles or other formulation variables in presence of coated drug.

Evaluation of flavoured baseline formulation:

It involves comparison among different flavoured formulations.

Evaluation of final selection and product acceptance test:

It involves comparison between two formulations or competitive product.

Chemical Evaluation

It involves the following:

1. Assay of drug content
2. Dosage uniformity
3. *In vitro* and *In vivo* Evaluation

Physical Evaluation

It involves the following:

1. Tablet physical appearance
2. Hardness
3. Friability
4. Disintegration
5. Dissolution

APPLICATION OF CHEWABLE TABLETS**Local therapy:**

Chewable tablet can release an active substance at a controlled rate over an extended period of time providing a prolonged local effect.

Pain:

Successful treatment of minor pains, headaches, pains of cold, muscular aches, etc. requires rapid absorption of therapeutic doses of the active substance. Chewable tablet as a drug delivery system could be beneficial in minor pain treatment, when buccal absorption results in fast onset of action and reduces the risk of gastrointestinal side effects.

Systemic Therapy:

Chewable tablet provides benefits to systemic drug delivery, especially if the active substance is absorbed through the buccal mucosa.

Smoking Cessation:

Chewing gum formulations containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation.

Obesity:

Several chewing gum formulations containing caffeine, guarana or chromium are available. Caffeine and guarana are central stimulating anorectic agents that have proved to increase the metabolic rate.

ADVANTAGES OF CHEWABLE TABLETS

Chewable tablets are generally chewed in the mouth prior to swallowing and are not expected to swallow intact. Main purpose of chewable tablet is to provide proper unit dosage form of medication which can easily be administered to children or to the elderly who have difficulty in swallowing a tablet intact. Chewable tablet have some specific advantages:

- Better bioavailability through bypassing disintegration (that increase dissolution)
- Improved patient acceptance (especially pediatric) through pleasant taste
- Patient convenience; need no water for swallowing
- Possible to use as a substitute for liquid dosage forms where rapid onset of action is needed
- Absorption of drug is faster
- Product distinctiveness through marketing prospective
- The large size of the dosage form is difficult to swallow.
- In such cases chewable tablet offers advantages over it
- Effectiveness of therapeutic agent is improved by the reduction in size that occurs during mastication of tablet before swallowing

DISADVANTAGES OF CHEWABLE TABLETS

- There are, of course some limitations to the use of chewable tablets having bad tasting drugs and extremely high dosage level. Some common disadvantages of chewable tablet are:
- It contains sorbitol which causes diarrhoea and flatulence
- Flavouring agents present in chewable tablet may causes ulcer in oral cavity
- Prolonged chewing of chewable tablet results in pain in facial muscles
- They are hygroscopic in nature, so must kept in dry place
- They show the fragile, effervescence granules property
- Since these tablets have insufficient mechanical strength, so careful handling is required
- They require proper packaging for safety and stabilization of stable drugs

CONCLUSION

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.

CONFLICT OF INTEREST:-

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS:-

Authors are thankful to Dr. Thonte S.S., principal, Channabasweshwar Pharmacy College (Degree), Latur for providing constant inspiration and all kinds of motivation to contribute organizational resource for fulfilling & developing profession needs.

ABBREVIATIONS:-

- API – Active pharmaceutical ingredients
- %- Percentage
- \$- Doller
- US- united state
- EMA- European Medicines Agency
- US FDA- United state Food and Drug Administrative
- ODT- orally disintegrating tablets
- SODs- solid oral dosage forms
- min-minute
- APAP- Acetyl-para-aminophenol
- BTMT- Breakdown of taste-masking Technologies
- HPC- hydroxypropyl cellulose
- HPMC-hydroxypropyl methylcellulose
- NMT-non masked tested
- HME-Hot-melt extrusion
- PH-Potential of hydrogen

REFERENCES

1. Patil J, Vishwajith V, Gopal V. Formulation Development and Evaluation of Chewable Tablets Containing Non- Sedating Antihistamine. *Journal of Pharmaceutical and Scientific Innovation*. 2012; (3):112-17.
2. Lachmann L, Liberman HA, Schwartz JB. *Pharmaceutical Dosage Forms*. New York: Marcel Dekker Inc, 1989, (1):2
3. Udaykumar M, Nageswarao ABN, Kumar VTVS, Giri VV. Fast Dissolving Tablets: New Fangled Drug Delivery System, A Comprehensive Review. *International Journal of Research in Drug Delivery*. 2012; (3):15-18.
4. Patel Y, Shukla A, Saini V, Shrimal N, Sharma P. Chewing Gum as a drug delivery system. *International Journal of Pharmaceutical Sciences and Research*. 2011; (2):748-57.
5. Bansal et al, "Trends in Pharmaceutical Taste Masking Technologies: A Patent Review". *Recent Patents on Drug Delivery and Formulation*, 2009,(3) :26-39.
6. 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.
7. Vummaneni V, Nagpal D. Taste-Masking Technologies: An Overview and Recent Updates. <http://ijrpbsonline.com/files/11-3185.pdf>.
8. Okochi K, Koyama H, Shingaki A. Oral Preparation Comprising Pioglitazone. WO2007136129 (2007).
9. Lehmann K, Petereit HU, Dreher D. Fast Disintegrating Controlled Release Tablets from Coated Particles. *Drugs Made In Germany*. 1994;37(2):53-60.
10. Busson P, Schroeder M. Process for Preparing a Pharmaceutical Composition, US 2003;45(9):516
11. 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.
12. Lachman L, Lieberman H, Kanig, J. *The Theory and Practice of Industrial Pharmacy*. 3rd ed. 1986:420.
13. 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.
14. 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.
15. 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.

16. Lachman L, Liberman HA, Kanig LJ. Theory and Practice of Industrial Pharmacy, Vargese Publication House, , 199,(3): 293-336.
17. Smith DV, Margolskee RF. Making sense of taste. Scientific America 2001; 284(3):36.
18. Nanda AR, Garg KS. An update on taste masking technologies for Oral pharmaceuticals. Indian journal Pharma. sci. 2002; (1):64
19. Roche. Roto-granulations and taste masking coatings for preparation of chewable pharmaceutical tablets. US Patent 5 260 072 9 November, 1993.
20. Khar RK, Sohi H. Taste masking technologies in oral pharmaceuticals: Recent development and approaches. Drug. Dev. Ind. Pharma 2004; (30):429,448.
21. Patel H, Shah V, Upadhyay U. New pharmaceutical excipients in solid dosage forms. International Journal of pharmacy and life sciences. 2011, (8)2.
22. Orally Disintegrating Tablet and film technologies. Second edition, 2004, 177.
23. Solanki HK, Bosuri T, Thakkar JH, Patel CA. Recent Advances in granulation technology. International Journal of Pharmaceutical Sciences Review and Research. 2010; 5(3):48-49.
24. Surbhi G, Seema S, Singh G, Rana AC. Industrial Process Validation of Tablet Dosage Form: An Overview. International Research Journal of Pharmacy. 2012; 3(3):49-51.
25. Ray C, Arora V, Sharma V. Fast dissolving tablets-A Novel drug delivery system for pediatric and geriatric patient. International bulletin of drug research, 1(2), 55-70.
26. Kathiresan K, Vijin P, Moorthi C, Manavalan R. Formulation and Evaluation of loratadine chewable tablets. Research Journal of pharmaceutical, Biological and chemical sciences. 2010; 1(4):765.





Submit your next manuscript to **IAJPR** and take advantage of:
Convenient online manuscript submission
Access Online first
Double blind peer review policy
International recognition
No space constraints or color figure charges
Immediate publication on acceptance
Inclusion in **ScopeMed** and other full-text repositories
Redistributing your research freely

Submit your manuscript at: editorinchief@iajpr.com



