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Chewable Tablets: A Comprehensive Review

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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. 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. 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.

Keywords: chewable tablet, gum core, antioxidant, compressibility etc.

1. 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. [1] 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. [2,3] 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. [4] 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. [5] 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.

1.1 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

1.2 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

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.

2.1 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.

2.2 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.

2.3 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.

2.4 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, flavour compounds and other product modifiers. The drug profile ideally should contain information on the following:

3.1 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

3.2 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.

4. 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.

4.1 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

4.2 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.

4.3 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 ^[6, 7, 8, 9]

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.

5.1 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.

5.2 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

6. General Excipients Used In the Formulation of Chewable Tablets ^[10, 11]

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:

6.1 Sweeteners

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.

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.

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.

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 1.1: Approximate Relative Sweetness of different Sweeteners

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

6.2 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.

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 succeeded in the preparation of one or more unflavoured bases, the development pharmacist should next prepare several basic flavoured preferences samples. These should be designed to narrow the flavour focus to one or more groups of flavour preferred by decision makers within the company. Various group of flavour for general baseline taste types are tabulated below in table 2:

Table 1.2: 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

6.3 Colour Integration

The final aspect of taste psychology requires that the flavour and colour match. A mismatch may detract from consumer acceptance.

Colourants

Colourants are used in the manufacture of chewable tablets for the following reasons:

- ❖ To increase aesthetic appeal to the consumer
- ❖ To mask non uniform colour of raw materials
- ❖ To complement and match the flavour used in the formulation
- ❖ To aid in product identification and differentiation

The Food drug and cosmetic Act of 1938 created three categories of the colourants of which only first two are applicable to the manufacture of chewable tablets. These are discussed as follows:

- ❖ **FD& C colours:** These are colourants that are certifiable for use in foods, drugs and cosmetics.
- ❖ **D&C colours:** These are dyes and pigments considered safe for use in drugs and cosmetics when in contact with mucous membranes or when ingested.
- ❖ **External D&C:** These colourants, due to their oral toxicity, are not certifiable for use in products intended for ingestion but are considered safe for use in products applied externally.

Dyes and lakes are two main form of colourants used in the manufacture of chewable tablets depending on whether the process of manufacture is by wet granulation or direct compression.

Dyes

These are chemical compound that exhibits their colouring power or tinctorial strength when dissolved in a solvent. They are usually 80 to 93% (rarely 94 to 99%) pure colourant material. Dyes are soluble in propylene glycol and glycerine.

Lakes

Lakes have been defined by the FDA as the “aluminium salts of FD&C water soluble dyes extended on a substratum of alumina. Lakes prepared by extending the calcium salts of FD&C dyes are also permitted. Lakes also must be certified by FDA.

7. Manufacturing ^[12, 13, 14]

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 establishment 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”.

7.1 Methods of Manufacturing

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.

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.

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.

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 API's 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.

8. Evaluation Parameters for Chewable Tablet ^[15]

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

8.1 In-process Organoleptic evaluation

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

1. **Evaluation of drug itself:** It involves characterization and comparison of the substance in an absolute amount or against a known reference standard.
2. **Evaluation of coated drug:** It involves comparison against the pure drug as well as different coating treatment.
3. **Evaluation of unflavoured baseline formulation:** It involves comparison among different vehicles, proportion of vehicles or other formulation variables in presence of coated drug.
4. **Evaluation of flavoured baseline formulation:** It involves comparison among different flavoured formulations.
5. **Evaluation of final selection and product acceptance test:** It involves comparison between two formulations or competitive product.

8.2 Chemical Evaluation

It involves the following:

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

8.3 Physical Evaluation

It involves the following:

1. Tablet physical appearance
2. Hardness

3. Friability
4. Disintegration
5. Dissolution

9. Application of Chewable Tablets

1. **Local therapy:** Chewable tablet can release an active substance at a controlled rate over an extended period of time providing a prolonged local effect.
2. **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.
3. **Systemic Therapy:** Chewable tablet provides benefits to systemic drug delivery, especially if the active substance is absorbed through the buccal mucosa.
4. **Smoking Cessation:** Chewing gum formulations containing nicotine, lobeline and silver acetate have been clinically tested as aids to smoking cessation.
5. **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.

10. Some Marketed Formulations of Chewable Tablet

Today Chewable Tablet is one of the most popular dosage form, used for delivering the many active components. Some marketed products of chewable tablet are given below in table 1.3:

Table 1.3: Marketed Formulations of Chewable Tablets

S. No.	Brand Name	Active Ingredient	Application
1.	Claritin	Loratadine	Anti-histamine
2.	Montair	Montelukast	Asthma
3.	Lamictal	Lamotrigine	Seizures
4.	Mylanta Gas	Simethicone	Gastric relief
5.	Natecal D3	Natecal D3	Osteoporosis
6.	Imodium Advanced	Loperamide Hydrochloride	Anti-diarrhoeal
7.	Alzol	Albendazole	Anthelmintic
8.	Tylenol	Acetaminophen	Analgesic

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