

A Narrative Review on Formulation and Quality Attribute Considerations for Chewable Tablets

Monika*, Pragi, Varun Kumar, Amit Kumar, Deepak Garg, Preeti, Ashok Kumar

Department of Pharmacy, Jagannath University, Bahadurgarh, Haryana, 124507, India

Received: 01-06-2023 Revised: 15-07-2023 / Accepted: 21-08-2023

Corresponding author: Monika

Conflict of interest: Nil

Abstract

Recent advancements in novel drug delivery systems aim to improve the safety and therapeutic effectiveness of drug molecules by formulating a convenient or easy-to-administer dosage form. Patients with swallowing issues include those who are young, old, bedridden, crippled, and mentally ill. Oral administration is the most appropriate route for drug delivery because it has the highest compliance, especially in paediatrics and geriatrics. It has been cited as the most effective and secure way to administer medications. Chewable dosage forms include tablets, delicate pills, and gums. "Chewable squares" is a lengthy item in the drug specialist's toolbox. The purpose of the chewable tablet is to provide a unit dosage that may be given to toddlers, teenagers, or the elderly who could also have difficulty swallowing a whole pill. The benefits of chewable tablet formulations include stability, palatability, precise dosing, portability, and ease of delivery. Taste masking of bitter drug candidates can be done by the aid of sweeteners, flavoring agents and by utilizing taste masking techniques. Chewable tablets can be formulated by the use of tableting methods: dry granulation, wet granulation and direct compression.

Keywords: Chewable tablet, oral route, bioavailability, compressibility, taste-masking, granulation, formulation, palatability etc.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Even with the tremendous advancements in drug delivery systems, oral administration of medicinal agents continues to be the most common approach due to its low cost, ease of administration of the therapeutic agent, and compliance for patients. When compared with parenteral route, oral drug administration is often more comfortable for patients and less intrusive [1]. Due to their many benefits over alternative delivery methods, including efficacy, safety, cost-effectiveness, and patient compliance, oral dosage forms account for the bulk of drug delivery enterprises. Chewable tablets provide benefits over traditional tablets as a dosage form in terms of manufacturing, dosing precision, mobility, and long-term durability [2]. Oral dosage forms provide the most perfect dosage form characteristics out of all the different pharmaceutical dosage forms. The oral method is used to provide a variety of dose forms, including chewing gum, films, patches, wafers, and orally disintegrating pills. It's crucial to keep in mind that there must be a balance between the product's bioavailability, chemical and physical stability, and technical producibility when creating any pharmaceutical dosage form. Tablets and capsules are examples of unit dosage forms, in which one

typical dose of medication has been precisely positioned. In contrast, liquid forms like syrups, suspensions, emulsions, solutions, and elixirs are typically intended to contain one medication in 5-30ml; however, when the patient administers the medication themselves, dosage measurement error chances typically increase by a factor of 20–50% [3]. There are numerous distinct tablet varieties that may be created to meet certain therapeutic requirements.

Chewable tablets

Tablets that must be broken and chewed in between the teeth before intake are known as chewable tablets. These pills are provided to people suffering from dysphasia (trouble in swallowing) as well as children who face trouble in swallowing the whole tablet due to their small age group [1,2]. So, drugs that can be digested in the mouth prior to their ingestion are no longer designed to be swallowed whole. Due to some challenges associated with liquid & powder formulations like, chewable and disintegrating dose forms are more advantageous for individuals with dysphasia. The chewable tablet's function is to give a unit dose form of medication that can address the issue by allowing

patients to swallow the drug more easily. Tablets, gums and most recently chewy squares are examples of ingestible dose forms that have long been used. These tablets should have an acceptable taste and aroma [3,4]. Functional excipients including natural and artificial sweeteners are widely included in the manufacturing of chewable tablets to conceal undesirable flavors as well as taste and thus rationalize pediatric dose. They should dissolve in a short time and produce a cool-sweet taste. In order to produce chewable tablets, either the wet granulation technique or direct compression is typically used. These tablets consist of gum core and are composed of fillers, waxes, antioxidants, sweeteners, and flavoring agents. Mannitol, which is a non-hygroscopic compound, is considered as advantageous for preparation of moisture-sensitive medications. That's why it is utilized as an excipient in chewable tablet production. For the administration of pharmaceutical, nutraceutical, and veterinary products, these tablets are a commonly utilized dosage form. Therefore, this dosage form acts as a convenient way to administer medicines to children as well as to administer food products such as multivitamin chewable tablets. Additionally, they are employed in the administration of carminatives and antacids. Some examples of marketed products are listed in Table 57-10. According to a review report of Theresa M Michele and Barbara Knorr, more than 60 different chewable tablet formulations have received US approval [5]. A recommendation on quality attribute considerations for chewable tablets was released by the FDA in 2018 [6]. Table 4 provides a summary of these Qualities.

Advantages of Chewable Tablets

- Improved patient convenience and these tablets do not require water for swallowing.
- These show good bioavailability and thus absorption by bypassing the disintegration step.
- Greater patient acceptability (especially in pediatrics) as a result of the product's particular taste and pleasing flavor [7].
- It is appropriate for those who are bedridden, traveler or busy persons who do not always have access to water.
- Pre-adolescent children typically experience difficulties swallowing pills and capsules due to physiological and psychological reasons. So, chewable pills are preferred in these circumstances [7].
- It is possible to produce both a nice tongue feel and an efficient flavor concealing.
- Chewable tablets formulation is better option when larger size of dosage form is required to be administered.

- The medicinal agent's effectiveness is increased as the tablet's size decrease. So during mastication of these tablets their therapeutic efficacies increase.
- Aspiration risk is decreased, making it the perfect drug administration technique for those facing dysphasia.
- When a quick beginning of action is required, these tablets may be used in place of liquid dosage forms because they promote the flow of saliva in the mouth.

Disadvantages of chewable tablets

There are, of course, certain drawbacks associated with chewable tablets and a few of them are listed:

- It might leave an unpleasant feeling and taste on the tongue if it is not correctly designed.
- Drugs with an awful taste cannot be formulated as chewable dosage form.
- Prolonged chewing of chewable tablet causes pain in facial muscles.
- To guarantee the integrity and durability of the product, proper packaging is necessary.
- Consumption of sweeteners like sorbitol and sucrose can result in nausea, vomiting and tooth cavities, respectively.
- Flavoring agent presence can cause ulcers in buccal cavity.
- Careful handling is required as these tablets do not have sufficient tensile strength.

Desirable Characteristics for chewable tablets [8-9]

- Chewable tablets should have acceptable bioavailability and bioactivity.
- These should have acceptable stability and quality.
- Improved overall palatability (Good taste and mouth feel).
- Should have desired size and shape.
- Should have sufficient mechanical strength.
- Should not leave any undesirable residue in mouth after oral administration.
- Ability to disintegrate readily to facilitate dissolution.
- Economical formula and process.

Elements like hardness, disintegration, dissolution and others that could impact the drug's bioavailability and bioequivalence are critical quality criteria for chewable tablets. Tablet flavor, size, thickness, and friability should also be carefully considered since these may influence a patient's ability or inclination to masticate a chewable tablet. Every quality characteristic is thought to be enough for regulating the effectiveness of a chewable tablet. Instead, the primary objective should be to create the ideal blend of these elements to guarantee that the

chewable tablet will work as intended (FDA, August 2018) [5].

Formulation Factors

Chewable tablets come in a range of forms and sizes. Some children's items are shaped like animals to appeal to this particular age group. Chewable tablets can have total weights that are higher than those used for traditional (swallow) tablets because they are chewed before gulping, and their weights are typically greater than 1000 mg. For instance, the total weight of antacid tablets frequently exceeds 1000 mg. There are various factors which are to be considered during the manufacturing of chewable tablets such as flow, lubrication, disintegration, organoleptic properties, compressibility, compatibility and stability [10].

Taste and flavour: The product should have a sweet flavour and taste. Taste is a physiological sensory signal that is produced when the tongue's taste receptors are chemically stimulated. Salty, sour, sweet, and bitter are the four basic flavours. The precise combined impression of taste and smell is typically referred to as an aroma. A well-formulated chewable orange-flavoured tablet, for instance, ought to have the unique sweet-sour flavor and aroma of a real orange.

Mouthfeel: This refers to the sort of taste or experience that chewing a tablet produces in the mouth. The overall mouth feel of the formulation is crucial for its effectiveness. In general, a gritty or sticky feel is undesired, but a calming and cooling sensation with a smooth texture is flavoured (such with mannitol).

After effects: The most frequent after taste of numerous chemicals are called as after effect. For instance, certain iron compounds have a "rusty" aftertaste, whereas saccharin in large doses often has a bitter aftertaste. A section of the entire surface of the tongue and mouth may go numb, which is another frequent side effect. This family of medications typically includes bitter antihistamines like promethazine hydrochloride and pyribenzamine hydrochloride.

Colouring: Chewable tablets are frequently colored for visual appeal and uniqueness of the product. Colorants can also be used to cover over unattractive natural colors that originate from a variety of basic materials. If the hue of the raw materials differs somewhat from the final result, colorants might be employed to ensure that batches are produced uniformly. Chewable tablet colors are often chosen to complement the flavor. Both organic synthetic dyes and natural pigments are accessible as colorants. Aqueous soluble dyes and lakes formed from these dyes are the most often used colorants in chewable tablets.

Chewability: The acceptance of chewable dose forms is influenced by the product's ability to be chewed. A chewable dosage form is said to be chewable if it can be easily consumed while tasting nice and pleasant cooling sensation in mouth without any undesirable gumminess, stickiness, chalkiness, or grittiness. Mannose and mixtures of sorbitol, fructose, sucrose, and mannitol are examples of excipients with these qualities.

Compressibility: In formulation of chewable tablets, the powder blend or granules should have desirable flow characteristics to get the final product. Powder/granules should possess optimum compressibility index to get final product of best quality. In addition to this, active pharmaceutical ingredients should be compatible with the excipients involves in the formulation of chewable tablets & further compatible to compression.

Taste- Masking

Taste- masking procedures must be followed to mask the bitter or unpleasant taste of active pharmaceutical ingredients/drugs to achieve patient acceptability, compliance and to avoid the considerable hurdle of pediatrics and geriatrics patients facing having swallowing issue [11-12]. Taste masking effectiveness is often a key determining factor for specialty dosage forms such as orally disintegrating tablets, films and chewable tablets.

The following organoleptic attributes of chewable pills should be taken into consideration: flavor, odor, consistency, mouthfeel, and aesthetic value of the product. The mechanism of taste-masking procedures rely on two main approaches: the first is sweeteners utilization during tablet formulation which is most straightforward method for resolving taste issue [73]. During formulation blends of sweeteners, like sugars or polyols, are frequently used to produce synergistic effects. And the is to prevent interaction of bitter/unpleasant drugs with taste receptors. The following are the taste masking techniques:

- Coating by Wet granulation [13-14]
- Microencapsulation [15-16]
- Solid dispersions [17-18]
- Inclusion complexation [19-20]
- Ion Exchange [21-22]
- Spray congealing and spray coating [23-24]
- Formation of different derivatives or salts [25-26]
- Use of amino acids and protein hydrolysates [27-28]
- Molecular complexes [29-30]
- Hot melt extrusion [24]
- pH modification [31]
- Development of liposomes [31]
- Viscosity modification [31]

- Prodrug approach [31]

Materials and Methods

The pharmaceutical industry is always seeking to meet the therapeutic demands of patients. In addition to active drugs and additives, inactive excipients are also crucial in the formulation process. Pharmaceutical excipients are substances excluding the pharmacologically active drug or prodrug which are incorporated in the manufacturing process or are contained in a finished pharmaceutical product dosage form [32-34]. In order to ensure no excipient-drug interaction, the formulator must diligently and thoroughly evaluate combinations of drug-envisioned excipients and must ensure the complies with existing standards and regulations. The screening of drug-excipient and excipient-excipient interactions should be done regularly in pre-formulation studies.

Excipients used for preparation of chewable tablets

Diluents: When a tablet's volume is insufficient, diluents, also known as fillers, are employed to make up the difference. This increases the volume of the dosage form. Examples include lactose, microcrystalline cellulose, mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium sulfate and calcium trisilicate, etc.

Binders: It provides cohesive strength to powdered materials and can be added either dry or wet form to form granules. An example includes Lactose,

cellulose derivatives- methyl cellulose, ethyl cellulose, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, starch, polyvinyl pyrrolidone (povidone), sodium alginate, carboxy methyl cellulose, acacia etc.

Disintegrators: It increases the rate of disintegration and dissolution. Examples include crospovidone, microcrystalline cellulose, modified corn starch, carboxy methyl cellulose, and sodium starch glycolate.

Sweeteners [35]: The sweetness profile is fine-tuned by the addition of desirable sweeteners. To make the formulation more palatable, particularly chewable dosage form, sweetening ingredients are added.

When the commonly used bearers, including lactose, sucrose, mannitol, and dextrose, don't completely veil the taste of the active medicine substance, sweeteners are typically added to chewable tablets. Pharmaceutical formulators are attempting to design their products without incorporating artificial sweeteners due to their potential carcinogenicity (e.g., cyclamates and saccharin) [35]. Examples of commonly utilized sweetening agents along with their relative sweetness are mentioned in table 2. In addition to relative sweetness, it's important to take into account the sweetness-response time curve. For instance, monoammonium glycyrrhizinate has a modest start but a long-lasting sweetness. Therefore, combinations of sweeteners may be employed to provide synergistic effects.

Table 1: Sweetening agents and their relative sweetness levels.

| Sr. No. | Materials | Relative sweetness |
|---------|---------------------|--------------------|
| 1. | Aspartame | 200 |
| 2. | Glycyrrhiza | 50 |
| 3. | Saccharin | 500 |
| 4. | Fructose(laevulose) | 1.7 |
| 5. | Lactose | 0.2 |
| 6. | Mannitol | 0.5-0.7 |
| 7. | Sorbitol | .5-.6 |
| 8. | Sucrose | 1 |
| 9. | Cyclamates | 30-50 |
| 10. | Dextrose(glucose) | 0.7 |
| 11. | Maltose | 0.3 |

Lubricating agents: These substances prevent clustering of ingredients and also prevent sticking of material with tablet punches. Examples: talcum powder, magnesium stearate, stearic acid etc.

Glidants: These are additive agents that are used to enhance the flowability by overcoming interparticle friction, surface charges, coherence, and adherence. Basically, glidants are employed in combination with lubricants. Examples: fumed silica, talc, magnesium carbonate etc.

Flavoring agents: Flavouring agents are key excipients of chewable tablets.

In addition to providing a delicious flavour, flavours can be used in combination with sweeteners to cover up the taste of the active components and increase the acceptability and palatability of the formulation.

Flavors are used on the basis of their desired characteristics & requirements.

Table 2: Flavor groups and their taste types

| Sr. No. | Flavor Groups | Taste Types |
|---------|---------------|--|
| 1. | Sweet | Vanilla, fruits, maple, stone fruits, berries, grape |
| 2. | Sour (Acidic) | Raspberry, anise, cherry, root beer, cherry, strawberry |
| 3. | Salty | Mixed citrus, butterscotch, maple, nutty, buttery, spice, mixed fruits, butterscotch |
| 4. | Bitter | Coffee, cherry, Liquorice, grapefruit, wine fennel, peach, mint |
| 5. | Metallic | Grape, burgundy, lemon-lime |
| 6. | Alkaline | Chocolate, Mint, cream, vanilla |

Colors: Colors are used to enhance the appearance and organoleptic profile of dosage form. FD&C (Food, Drugs and Cosmetics) and D&C (Drugs and Cosmetics) certified dyes and colorants are used. Depending on the manufacturing process, the type of colorant utilised in the production of chewable tablet varies. Dyes are generally used in chewable tablets manufactured by wet granulation method.

Manufacturing Methods

Manufacturing means proper incorporation of active pharmaceutical ingredient and all other excipients in appropriate quantity and manner, maintenance of correct moisture content, achievement of proper tablet hardness and to get a product of desired quality. The following techniques are used to make chewable tablets [34,36,37,38]:

1. Dry granulation (Non-Aqueous Granulation)
2. Wet Granulation (Aqueous Granulation)
3. Direct Compression

In this process, granules are formed when smaller, single-particle entities known as primary powder particles are forced to stick together. Granulation often entails the agglomeration of small particles into larger, multiparticle entities known as granules, which can range in size from 0.2 to 4.0 mm. Three methods are mainly used:

Dry Granulation: This technique is used for producing granules in a semi-automatic fashion. Any solid pharmaceutical product dosage can be prepared using this procedure. Dry granulation is a size-enlarging procedure that is also known as pre- or double-compression. It is thought to enhance the flow and compression properties of otherwise compressible powders. In this process, the powder mixture is compacted by applying a force to it, which usually results in significant size enlargement. If the employed ingredients are susceptible to flowability problems, this method can be considered. The formulation of tablets by a dry granulation method abolishes some unit operations but still involves milling, weighing, mixing, slugging, dry screening, lubrication, and compression of granules into tablets.

Dry granulation refers to the process of granulation without the using any liquid. In order to form granules by utilising the dry granulation method,

roller compaction or slugging methods are often used. Slugging is the process of compressing the main powder particles into substantial flat pallets using a tablet press or, more commonly, a sizable, powerful rotary press. The end product is subsequently pulverised using standard milling machinery. The milled product are subsequently passed through a sieve with the proper mesh size. After adding lubricating agents, granules are finally compressed into product (tablets).

A more straightforward, cost-effective, and efficient method of dry granulation is roller compaction. In this procedure, the components are moved between the two counter-rotating rollers, where the material is densified and combined to produce a sheet of solid material. In order to produce final product, compacts are then further processed, sized, lubricated, and compressed. Various steps are involved in dry granulation:

- Weighing of ingredients
- Mixing
- Compression of powder into slugs (Pre-compression)
- Milling and sieving
- Mixing with disintegrate and lubricant
- Compression of granules into tablets

Wet Granulation: This is most commonly used granulation method. In this method, an appropriate non-toxic and volatile granulating fluid, such as water, isopropanol, or ethanol, is used to agglomerate or bring together small particles of powder into larger, stronger, and more durable structures known as granules. A binder or granulating agent may be added to the granulating solution, or it may be utilized independently. The qualities of the materials to be granulated have a major role in the choice of the granulating fluid. This involves four key mechanism steps:

- Wetting and Nucleation
- Coalescence
- Consolidation
- Attrition or breakage

Mechanism of Wet granulation

Steps involved in the wet granulation method for tablet production are:

- Weighing and mixing of ingredients (excluding lubricants).

- Preparation of damp mass by the addition of binder solution.
- Screening of damp mass into granules & drying.
- Sizing of granules by dry screening.
- Lubrication of granules.
- Compression of granules into tablets.

Direct Compression: This is the method of compressing powder blends of the medicinal substance and excipients on a tablet machine without employing the process of granulation. Apart from a mixing step, this approach involves no mechanical treatment of the powder. This is ideal for moisture and heat sensitive APIs, removing wetting and drying processes and boosting stability, by decreasing undesirable consequences. The API is blended with excipients and lubricants, then compressed, making the product simple to handle.

There are only a few steps involved in producing tablets through direct compression, and they are as follows:

- Pre-milling of ingredients (API and ingredients)
- Mixing of all ingredients
- Compression

Recent advancements in granulation technology

Numerous technical advancements have been made to the granulation process to help increase the commercial production of pharmaceutical formulations, including [39]:

- Thermal adhesion granulation [40-41]
- Pneumatic dry granulation [42]
- Melt/thermoplastic granulation [43-44]
- Moisture activated dry granulation [45-46]
- Spray drying granulation [47-48]
- Fluidized bed granulation [49]
- Extrusion-spheronization granulation [50-51]
- Freeze granulation [52-53]
- Steam granulation [54-55]
- Foam binder granulation [56-57]

Evaluation: Various physical and chemical factors are taken into consideration while evaluating chewable tablets [58-60]. These are:

1. Physical appearance and organoleptic characteristics:

Consumer acceptability of these tablets depends on their general design, visual identity, and overall elegance. Chewable tablets are assessed for their size, shape, and organoleptic qualities including flavor, color, and aroma.

The tablet's flavor is an important consideration for patient acceptance. The API and excipients, particularly the flavoring and sweetening agents, may be responsible for the flavor. The tablet size and state can be checked and controlled dimensionally. This is done to evaluate their consistency of tablets from each batch, tablet dimensions can be estimated by Vernier Caliper scale.

2. Hardness: A hardness test is performed to measure the force required to break a tablet in a specific plane. Tablets must have a sufficient strength to withstand the severe stresses of manufacturing, packaging, shipping and distribution, but not so hard as to cause chewing problems.

Tablet hardness can be measured and expressed in different units. An index was developed that considers the hardness of a tablet versus the amount of force (load) required to break that tablet to create a numerical value that can be used to compare chewable tablets for ease of chewing (FDA, 2018). Tablet hardness is determined using a hardness analyzer that measures the force required to break the tablets.

3. Friability: Tablets friability can be evaluated by the Roche Friabilator. Firstly, 10 tablets are weighed and placed into it, which is then allowed to rotate at 25 rpm for 4 minutes. Then tablets are removed from it, dusted, and weighed once again.

Tablets that lose less than 0.5–1.0% of their weight are considered acceptable. Moreover, if capping occurs during testing, the tablets are to be discarded. The % friability of tablets can be calculated by formula,

$$\% \text{ Friability} = \frac{(\text{Initial Weight} - \text{Final Weight})}{(\text{Initial Weight})} \times 100.$$

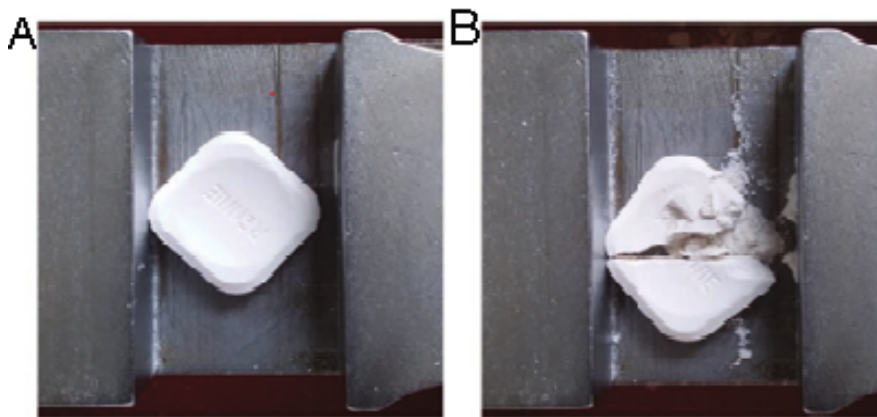


Figure 2: Tablet breaking force measurement configuration (a) tablet before applying the pressure; (b) tablet after the test [6,61].

4. Weight variation [62]: As per USP weight variation research, the 20 tablet weight is regulated by computing the standard loads and comparing the single tablet load to the normal one. The results of the weight variety test are expressed in percentages. USP states that tablets pass the test if no more than

two of them deviate by more than the permitted percentage and if no tablet differs by more than twice the permitted percentage.

$$\text{Weight variation} = \frac{(\text{Initial weight} - \text{Average weight})}{\text{Average weight}} \times 100$$

Table 4: Weight Variation Limits [63].

| Sr. no. | Average weight tablets (mg) | Maximum % difference limits |
|---------|-----------------------------|-----------------------------|
| 1. | 130 or less | ± 10.0 |
| 2. | 130 to 324 | ± 7.50 |
| 3. | More than 324 | ± 5.0 |

5. Disintegration: The amount of time a tablet needs to disintegrate into smaller pieces is known as the disintegration time. Typically, the correct kind and quantity of disintegrant encourages quick breakdown and facilitates careful chewing of the tablet. Utilising intact tablets, disintegration apparatus (USP Disintegration Apparatus), and procedures, in vitro disintegration testing ought to be carried out [64].

water, aqueous medium at pH 1.2, buffered aqueous medium at pH 4.5, and buffered aqueous medium at pH 6.8 [64].

6. Dissolution: The release of the drug substance(s) from chewed or intact tablets determines how quickly a drug is absorbed from a chewable tablet. In vitro dissolution testing of chewable tablets should adhere to the guidelines for dissolution testing of conventional IR tablets [65]. Utilising the appropriate dissolution apparatus, such as USP Apparatus 1 (basket type), USP Apparatus 2 (paddle type), or USP Apparatus 3 (piston cylinder type), in vitro dissolution tests on intact tablets should be carried out in at least four media, such as

7. Drug content uniformity [66]: The formulation's drug content can be analysed using the HPLC method. 20 chewable tablets are ground up, and 100 mg of powdered medication is accurately transferred to 50 ml volumetric flasks. Add 5 ml of methanolic sulfuric acid to the above volumetric flask with thorough shaking. Methanol is used to prepare the final volume of up to 50ml. Then it is filtered through a filter (Whatman filter paper, 41 µm pore size) paper and the first 10 ml of filtrate is discarded. Then, 5 ml of the clear filtrate is pipetted out and transferred to 50 ml volumetric flasks, where methanol is used to bring the volume up to 50 ml. Separate injections of 2µl each of the sample preparations and the standard solution are administered into the column. Estimates are done at 254 nm while maintaining a flow rate of 2 ml/min.

Table 5: FDA guidelines for chewable tablets [6]

| Attributes | Recommendations |
|-----------------|---|
| Tablet Hardness | Less than 12kp; higher hardness levels may be taken into account (e.g. tablet rapidly softens or disintegrates after brief (<30 seconds) exposure to simulated saliva). |
| Disintegration | Typically, the same specifications as immediate-release tablets; important to determine since some individuals may swallow tablets without chewing. |
| Dissolution | Typically, the same specifications as immediate-release tablets. Does not apply to chewable modified release products. |

| | |
|--------|---|
| | In vitro dissolution testing should be conducted on intact chewable tablets since some people may take them whole without chewing. |
| Others | Specific to the individual product (e.g. tablet with functionally coated particles should not be adversely affected by chewing) Tablet size, shape, thickness, friability, palatability Chewing difficulty index is discussed in the guidance: however limits are not provided. |

Veterinary products

Chewable tablets are frequently used in veterinary formulations. The Simparica Trio pill is one such; it combines pig liver powder, hydrolyzed vegetable protein, sugar, and gelatin to satisfy the sensory needs of dogs [69]. Due to the variation in diets of various animal species, some of their sensory requirements differ from those of humans. For example, dogs prefer animal-based proteins. It may be necessary to employ complex feeds, such as blends of proteins, carbohydrates, and flavorings, in order to achieve voluntary acceptance (the animal's readiness to voluntarily take a product) [70,71]. Due to variances between animal species, the safety of the excipients that are to be incorporated into formulations must be taken into account, like xylitol, which is acceptable for human ingestion but very harmful to dogs [72].

Applications of Chewable tablet:

1. Local therapy: Chewable tablets can release the active ingredient over an extended period of time at a regulated pace, producing a durable local impact.

2. Pain: Quick absorption of the therapeutically active ingredient is required for the effective treatment of mild pains, headaches, colds, muscular aches, etc. Chewable tablets can be considered as an effective medication delivery method for treating mild pain since oral absorption has a quick beginning of action and lower risk of gastrointestinal side effects.

3. Systemic therapy: Chewable tablets make it easier to transport medications throughout the

body, particularly when the main constituent is absorbed through the buccal mucosa.

4. Smoking Cessation: As a smoking termination aid, chewing gum preparations including nicotine, lobeline, and silver acetate have undergone clinical testing.

5. Obesity: Caffeine, guarana, or chromium are included in a number of chewing gum anorectic formulations. It has been demonstrated that the central anorectic stimulants caffeine and guarana raise metabolic rate.

Marketed products of chewable tablets

Chewable tablets are the most popular dosage form which is easily available in market, used for delivering the active components. The marketed products of chewable tablets are listed in table 6.

Conclusion

In the modern era, chewable tablets are preferred over conventional dosage forms by pediatric, geriatric and bedridden patients due to difficulty in swallowing, lesser amount of water for swallowing medications as well as unable to tolerate the bitter taste of certain drugs. Chewable tablets are a versatile dosage form that combines the manufacturing and stability advantages of solid products while providing favorable organoleptic and administration benefits.

A formulator may use one or more approaches to arrive at a combination of formula and process that result in product with acceptable flow, compressibility and stability characteristics.

Table 6: Marketed products of chewable tablets

| S. No. | Name of drug | Category | Method used | Result |
|--------|---------------|---------------------------------|--|--|
| 1 | Acetaminophen | Anti-pyretic | Direct compression | Good drug release with suppressed bitterness & low sweetness. |
| 2 | Levamisole | Anthelmintic | Wet granulation | less disintegration time & complied with all specified parameters. |
| 3 | Lamotrigine | Anticonvulsant or Antiepileptic | Melt granulation | Taste masked with 90% drug release within 1 hr. |
| 4 | Albendazole | Anthelmintic | Non-aqueous, Aqueous, Direct compression | Product with direct compression had faster dissolution rate |
| 5 | Albendazole | Anthelmintic | Wet granulation | All parameters were found acceptable within their limits. |
| 6 | Metformin HCL | Hypoglycemic agent | Wet granulation | All the parameters were |

| | | | | |
|----|------------------------------------|---|--|---|
| | | | | found to be satisfactory. |
| 7 | Paracetamol and Metoclopramide HCL | Analgesic, Antiemetic | Wet granulation | Formulation shown the satisfactory drug release with disintegration time of 56 sec. |
| 8 | Mebendazole | Anthelmintic | Non-aqueous, Aqueous, Direct compression | Product formulated by Direct compression had faster dissolution rate. |
| 9 | Montelukast sodium | Leukotriene receptor antagonists, to prevent and manage Asthma. | Direct compression | All parameters were found acceptable within their limits. |
| 10 | Albendazole | Anthelmintic | Direct compression | All satisfactory parameters. |

References

- Bhusnure O.G., Ekbal S.F., Mane J. Sarfaraz A.S., Hucche B.S. Formulation strategies for taste masking of chewable tablets. *Indo American J. Pharm. Res.* 2015; 5(12): 3836-3849.
- Taranum R, Mittapally S. Soft chewable drug delivery system: Oral medicated jelly and soft chew. *J. Drug Delivery and Therapeutics* 2018; 8(4): 65-72. DOI <https://doi.org/10.22270/jddt.v8i4.1784>.
- Thakur R.R, Narwal Sonia. Oral disintegrating preparations: Recent advancement in formulation and technology. *J. Drug Delivery and Therapeutics* 2012; 2(3): 87-96. DOI <https://doi.org/10.22270/jddt.v2i3.130>.
- Renu, Dahiya J., Jalwal P., Singh B. Chewable Tablets: A comprehensive review. *The Pharma Innovation Journal* 2015; 4(5): 100-105.
- Michele T. M., Knorr B., Elizabeth B. Safety of chewable tablets for children, 2002 Aug;39(5):391-403. DOI: <https://doi.org/10.1081/jas-120004032>.
- Quality Attributes Considerations for Chewable Tablets, Guidance for industry; U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Ahmedabad.
- Available from: <http://www.pharmaapproach.com>.
- Available from: [https://www.naturalproductsinsider.com/.../four tips to improve palatability-chewable tablets](https://www.naturalproductsinsider.com/.../four-tips-to-improve-palatability-chewable-tablets).
- William Stoltman. The new FDA Draft Guidance on chewables: Quality Attribute considerations for chewable tablets- Guidance for Industry (CDER, June 2016).
- Available from: [http://www.who.int/drug information](http://www.who.int/drug-information).
- Sohi H, Sultana Y, Khar R.K. Taste masking technologies in oral Pharmaceuticals: Recent developments and approaches. *Drug Delivery Ind Pharm.* 2004; 30(5): 429-448. DOI: <https://doi.org/10.1081/ddc-120037477>.
- Aynew Z, Puri V, Kumar L, Bansal A.K. Trends in Pharmaceutical taste-masking technologies: A pattern review. *Recent Patents on drug delivery and formulation* 2009; (3): 26-39. DOI: <https://doi.org/10.2174/187221109787158364>.
- Sajal J.K, Uday R.S, Surendra V. Taste masking in pharmaceuticals: An update. *J. Pharm. Res.* 2008; 1(2):126-130.
- Joshi S, Petereit H.U. Film coatings for taste masking and moisture protection. *Int. J. Pharm.* 2013; 457(2): 395-406. DOI: <https://doi.org/10.1016/j.ijpharm.2013.10.021>.
- Tripathi K, Parmar D, Patel U, Patel G, Daslaniya D, Bhimani B. Taste masking: A novel approach for bitter and obnoxious drugs. *J. Pharm Sci. and Bioscientific Res.* 2011; 1(3): 136-142.
- Al-Kasmi B, Bashimam M, El-Zein H, Alsirawan B. Mechanical microencapsulation: The best technique in taste masking for manufacturing scale- Effect of polymer encapsulation on drug targeting. *Int. J. Pharm. Sci.* 2017; 260: 134-141. DOI: <https://doi.org/10.1016/j.jconrel.2017.06.002>.
- Ozkan G, Franco P, Marco L.D, Xiao J, Capanoglu E. A review of microencapsulation methods for food antioxidants: Principles, advantages, drawbacks and applications. *Food chemistry.* 2019; 272: 494-506. DOI: <https://doi.org/10.1016/j.foodchem.2018.07.205>.
- Sobel R, Gundlach M, Su C.P. Chapter 33- Novel concepts and challenges of flavor microencapsulation and taste modification. *Microencapsulation in Food Industry.* 2014: 421-442. DOI: <https://doi.org/10.1016/B978-0-12-404568-2.00033-9>.
- Ye Q, Georges N, Selomulya C. Microencapsulation of active ingredients in functional foods: From research stage to commercial food products. *Trends in Food Sci. and Tech.* 2018; 78: 167-179. DOI: <https://doi.org/10.1016/j.tifs.2018.05.025>.
- Sang H, Moon C, Lee B, Oh E. Mesoporous pravastatin solid dispersion granules incorporable into orally disintegrating tablets. *J. Pharm Sci.* 2018; 107(7): 1886-1895. DOI: <https://doi.org/10.1016/j.xphs.2018.03.003>.

21. Ma X, Williams R.O. Characterization of amorphous solid dispersions: An update. *J Drug Delivery Sci. and Tech.* 2019; 50: 113-124. DOI: <https://doi.org/10.1016/j.jddst.2019.01.017>.
22. Wan H, Ni Y, Li D. Preparation, characterization and evaluation of inclusion complex of steviolbioside with γ -cyclodextrin. *Food Bioscience.* 2011; 26: 65-72. DOI: <https://doi.org/10.3390/molecules26237227>.
23. Abou-Okeil A, Rehan M, El-Sawy S.M, El-bisi M.K, Ahmed- Farid O.A, Abdel-Mohdy F.A. Lidocaine/ β -cyclodextrin inclusion complex as drug delivery system. *European Polymer J.* 2018; 108: 304-310. DOI: <https://doi.org/S0014305718315519>
24. Tan Thiam D.C, Jianming J, Gokhale R, Heng P.W. Hot melt extrusion of ion-exchange resin for taste masking. *Int. J. Pharmaceutics.* 2018; 547(1): 385-394. DOI: <https://doi.org/10.1016/j.ijpharm.2018.05.068>.
25. Llic I, Dreu R, Burjak M, Homar M, Kerc J, Srcic S. Microparticle size control and glimepiride microencapsulation using spray congealing technology. *Int J. Pharmaceutics.* 2009; 381(2): 176-183. DOI: <https://doi.org/10.1016/j.ijpharm.2009.05.011>.
26. Chauhan R. Taste masking: A unique approach for bitter drugs. *J. Stem Cell Bio. Transplant.* 2017;1(2). DOI: <https://doi.org/10.21767/2575-7725.100012>
27. Akitomi H, Tahara Y, Yasuura M, Kobayashi Y, Toko K. Quantification of tastes of amino acids using taste sensors. *Sensors and Actuators B: Chemical.* 2013; 179: 276-281. DOI: <https://doi.org/10.1016/j.snb.2012.09.014>.
28. He W, Yang R, Zhao W. Effect of acid deamidation-*alcalase* hydrolysis induced modification on functional and bitter masking properties of wheat gluten hydrolysates. *Food Chemistry.* 2019; 277: 655-663. DOI: <https://doi.org/10.1016/j.foodchem.2018.11.004>.
29. Liu, Tingting, Wan, Xiaocao, Zhang Z, and Chao. A donepezil/cyclodextrin complexation orodispersible film: Effect of cyclodextrin on taste masking base on dynamic process & *in-vivo* drug absorption. *Asian J. Pharm. Sci.* 2018. DOI: <https://doi.org/10.1016/j.ajps.2018.05.001>.
30. Haung, Tianhe, Zhao Q, Su Y, Ouyang. Investigation of molecular aggregation mechanism of glipizide/cyclodextrin complexation by combined experimental and molecular modeling approaches. *Asian J. Phar. Sci.* 2018. DOI: <https://doi.org/10.1016/j.ajps.2018.10.008>.
31. Patel C.J., Tyagi S, Mangukia D, Mangukia I, Gupta A.K., Malik J, Shree N, Paswan S.K. Pharmaceutical taste masking technologies for bitter drugs: A concise review. *J. Drug Del. & Therapeutics.* 2013; 1(5): 39-46. DOI <https://doi.org/10.22270/jddt.v6i2.1224>.
32. Patel H, Shah, Upadhyay V. New Pharmaceutical excipients in solid dosage forms. *Int. J. Pharm. & life Sciences* 2011; 2(8). DOI: <https://doi.org/10.1002/chin.20123226>.
33. Available from: www.Pharmaguideline.com/2013/02/Pharmaceutical_excipients_and_their_suggested_quantity.html: Pharmaceutical guidelines.
34. Orally disintegrating tablet and film technologies. Second Edition, 2004:177.
35. Sohi H, Sultana Y, Khar RK. Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches. 2004;30(5):429-48. DOI: 10.1081/ddc-120037477.
36. Surbhi G, Seema S, Singh G, Rana A. Industrial process validation of Tablet dosage form: An overview. *Int. Res. J. Pharm.* 2012; 3(3): 49-51.
37. Lachman L, Liberman H.A., Schwartz J.B. *Pharmaceutical dosage forms.* New York marcel dekker Inc.1989, 2(1).
38. Lachman L, Liberman H, Kanig J. *The theory and Practice of Industrial Pharmacy.* 3rd Edition. 1986; p. 1-909.
39. Solanki H.K., Bosuri T, Thakkar J.H., Patel C.A., Recent advances in granulation Technology. *Int. J. Pharmaceutical Sci. Review and Research* 2010; 5(3): p. 48-49.
40. Lin H, Ho H, Chen C, Yeh T.S, Sheu M.T. Process and formulation characterizations of thermal adhesion granulation process for improving granular properties. *Int. J. Pharmaceutics.* 2008; 357(1-2): 206-121. DOI: 10.1016/j.ijpharm.2008.02.002.
41. Narang A.S, Badawy Sherif I.F. "Handbook of Pharmaceutical wet granulation", Chap.- 25, Emerging paradigms in pharmaceutical wet granulation". 2019; p. 825-840.
42. Verma R, Patil M, Paz C.O. "Handbook of Pharmaceutical Wet Granulation", Chap. 7, Current Practices, 2019; p. 203-259.
43. Kittikunakorn N, Listro T, Zhang F, Sun C.C. Effects of thermal binders on chemical stabilities and tablility of gabapentin granules prepared by melt granulation. *Int. J. Pharmaceutics.* 2019; 559: 34-47. DOI: 10.1016/j.ijpharm.2019.01.014.
44. Patel A.V, Caudhari D.V, Pranav J, Shah S.A. Hot melt granulation method for preparation of floating matrix tablets of tolperison hydrochloride. *Future J. Pharm. Sci.* 2018; 4(2): 139-149. DOI:10.1016/j.fjps.2017.12.002.

45. Moravkar K.K, Ali T.M, Pawar J.N, Amin P.D. Application of moisture activated dry granulation (MADG) Process to develop high dose immediate release formulations. *Advanced Powder Technology*. 2017; 28(4): 1270-1280. DOI:10.1016/j.apt.2017.02.015.
46. Taka saki H, Yonemachi E, Messerschmid R, Wada K, Terada K. Importance of excipient wettability on tablet characteristics prepared by moisture activated dry granulation. *Int. J. Pharm.* 2013; 456(1): 58-64. DOI:10.1016/j.ijpharm.2013.08.027.
47. Kaur G, Singh M, Matsoukas T, Kumar J, Nopens I, Two-compartment modeling and dynamics of top-sprayed fluidized bed granulator. *Applied Mathematical Modelling*. 2019; 68: 267-280. DOI:https://doi.org/10.1016/j.apm.2018.11.028.
48. Figueroa C.E, Bose S. Spray granulation: Importance of process parameters on in-vitro & in-vivo behavior of dried nanosuspensions. *European J. Pharm. & Biopharm.* 2013; 85(3): 1046-1055. DOI: 10.1016/j.ejpb.2013.07.015.
49. Gupta R. Fluid bed granulation and drying, Predictive modeling of pharmaceutical unit operations. 2017; p. 137-158.
50. Muley S, Nandgude T, Podder S. Extrusion-spheronization a promising palletization technique: In-depth Review. *Asian J. Pharm. Sci.* 2016; 11: 684-699. DOI:10.1016/j.ajps.2016.08.001.
51. Sriamornsak P, Nunthanid J, Luangtana-anan M, Puttipipatkachorn S. Alginate-based pellets prepared by extrusion spheronization: a preliminary study on the effect of additive in granulating liquid. *European J. Pharm. & Biopharm.* 2007; 67(1): 227-235.
52. Stuer M, Zhao Z, Bowen P. Freeze granulation: Powder processing for transparent alumina applications. *J. European Ceramic Society.* 2012; 32(11): 2899-2908. DOI:10.13140/RG.2.2.15985.02402.
53. Chou K.S, Liu H.L, Kao L.H, Yang C.M, Haung S.H. A novel granulation technique using a freeze-thaw method. *Ceramics I*. 2014; 40(6): 8875-8878. DOI:10.1016/j.ceramint.2013.12.149.
54. Cavallari C, Abertini B, Marisa L, Rodriguez L. Improved dissolution behavior of steam granulated piroxicam. *European J. Pharm. And Biopharm.* 2002; 54(1): 65-73. DOI: 10.1016/s0939-6411(02)00021-8.
55. Suresh P, Sreedhar I, Vaidniawaran R, Venugopal A. A comprehensive review on process and engineering aspects of pharmaceutical wet granulation. *Chemical Engg. J.* 2017; 328: 788-815.
56. Melvin X.L, Karen P.H. Foam granulation: Binder dispersion and nucleation in mixer-granulators. *Chemical Engg. Res. And Design*. 2011; 89(5): 526-536.
57. Melvin X.L, Karen P.H. Foam granulation: liquid penetration or mechanical dispersion. *Chemical Engg. Sci.* 2011; 66(21): 5204-5211.
58. Jagdale S., Gattani M., Bhavsar D., Kuchekar B., Chabukswar A. Formulation and evaluation of chewable tablet of levamisole. *Int. J. Res. Pharm. Sci.* 2010;1(3): 282-289.
59. Available from: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.html>.
60. Farheen F, Bhardwaj S. Formulation and evaluation of chewable tablets of mebendazole by different techniques. *PharmaTutor*. 2014; 2(6): 183-189.
61. Agarwal SP, Ragesh Khanna. "A REVIEW ON CHEWABLE TABLET". CBS Publishers and distributors, 2nd edn,2000, 247.
62. Md. Sahab Uddin, Abdullah. Md. Asaduzzaman, *Journal of Pharmaceutical Research Int.*, 2, 1(2015); DOI: 10.9734/BJPR/2016/22044.
63. Sameer Shakur S., Rahul P G., Amir A.S., Yogesh D P. and Bhushan D.G. Solubility Enhancement of Etodolac Chewable Tablet Using Honey, and Evaluation with (Doe) Design of Experiment *Acta Scientific Pharmaceutical Sciences*. 2(6), 2018; p. 199-205.
64. Available from: www.usp.org/harmonization-standards/pdg/general-methods/disintegration
65. United States pharmacopoeia (USP 29-NF 24), The Official Compendia of Standards Twin Brook Parkway, Rockville. Asian Edition; 60-62, 2006, 2007, 27, 3, 2675, 2505.
66. Kumar S., Kedarnagalakshman M, Sharma M. The role of Chewable tablets: An overview: *Asian Journal of Pharmaceutical Research and Development*, 9(4), 2021. DOI <https://doi.org/10.22270/ajprd.v9i4.1005>.
67. Mendes R.W., Anaebonam O., and Daruwaia B., "Chewable Tablets," in *Pharmaceutical Dosage Forms: Tablets: Vol 1*, H.A. Lieberman, L. Lachman, and J.B. Schwartz, Eds. (Marcel Dekker, New York, NY, 2nd ed., 1989), pp. 367-417.
68. Nasser N., Samantha N.K., Chewable tablets: A review of formulation considerations. *Pharmaceutical Technology North America*. 44(11), 2020; p. 38-44.
69. EMA/CVMP/EWP/206024/2011, Guideline on the Demonstration of Palatability of Veterinary Medicinal Products, (2014), www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/07/WC500170030.pdf. accessed April 14, 2020.
70. Aleo M. et al., *Open J. Vet. Med.* 8, 107-118, 2018.

71. Fahmy R., Danielson D., and Martinez M. "Formulation and Design of Veterinary Tablets," in *Pharmaceutical Dosage Forms: Tablets: Vol 2*, Augsburger L.L. and Hoag S.W., Eds. (Informa Healthcare, New York, NY, 3rd ed., 2008; p. 383-431.
72. Nyamweya N., Kimani N., "Chewable Tablets: A Review of Formulation", *Pharmaceutical Technology*. 44(11), 2020; p. 38-44.