Quality Attribute Considerations for Chewable Tablets

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/CMC

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Quality Attribute Considerations for Chewable Tablets Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides manufacturers of chewable tablets for human use with the Center for Drug Evaluation and Research's (CDER) current thinking on the critical quality attributes that should be assessed during the development of these drug products.[2] This guidance also provides recommendations about submitting developmental, manufacturing, and labeling information for chewable tablets that must be approved by CDER before they can be distributed. The recommendations in this guidance apply mainly to new drug applications (NDAs), abbreviated new drug applications (ANDAs),[3] and certain chemistry, manufacturing, and controls (CMC) supplements to these applications.[4] Some of the recommendations about the submission of developmental information may also apply to investigational new drug applications (INDs). The recommendations about assessing critical quality attributes apply to all chewable tablets for human use, including non-application products.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Products covered by these recommendations include over-the-counter (OTC) monograph products as well as products that must be approved by CDER before they can be distributed.

[3] This guidance applies to ANDAs to the extent that the applicable product, including its underlying design and other development determinations, can comply with the recommendations described in this guidance while maintaining compliance with the requirements that the product be the same as its reference listed drug (RLD), including as described in Section 505(j) of the Federal Food, Drug, and Cosmetic Act and its implementing regulation.

[4] This guidance should be considered for CMC supplements submitted for modifications that affect the formulation or other critical quality attributes of a chewable tablet.

II. BACKGROUND

Chewable tablets are an immediate release (IR) oral dosage form intended to be chewed and then swallowed by the patient rather than swallowed whole. They should be designed to have a pleasant taste and be easily chewed and swallowed. Chewable tablets should be safe and easy to use in a diverse patient population, pediatric, adult, or elderly patients, who are unable or unwilling to swallow intact tablets due to the size of the tablet or difficulty with swallowing. The availability of safe, easy-to-use dosage forms is important in clinical practice. Chewable tablets are available for many over-the-counter (OTC) and prescription drug products.

The United States Pharmacopeia (USP) recognizes and differentiates between two types of chewable tablets: (1) those that may be chewed for ease of administration, and (2) those that must be chewed or crushed before swallowing to avoid choking and/or to ensure the release of the active ingredient.[5] The concepts in this guidance are applicable to both types of chewable tablets.

Adverse events for chewable tablets can include gastrointestinal (GI) obstruction resulting from patients swallowing whole or incompletely chewed tablets, as well as tooth damage and denture breakage resulting from excessive tablet hardness.[6] A related potential adverse event that sponsors should also consider is esophageal irritation from chewable tablets. A review of numerous approved drug product applications for chewable tablets revealed that in certain cases critical quality attributes such as hardness, disintegration, and dissolution were not given as much consideration as may have been warranted. This was evidenced by instances of incomplete monitoring of all relevant critical quality attributes or the use of widely ranging values that were not justified as acceptance criteria. In addition, a wide variation in analytical procedures has been reported.[7,8,9]

This guidance describes the critical quality attributes that should be considered when developing chewable tablets and recommends that the selected acceptance criteria be appropriate and meaningful indicators of product performance throughout the shelf life of the product.

III. DISCUSSION

A variety of physical characteristics should be considered in the manufacturing process for chewable tablets. An ideal chewable tablet should be:

- Easy to chew
- Palatable (taste masked or of acceptable taste)

[5] USP 39-NF34 <1151> *Pharmaceutical Dosage Forms.*
[6] For general information on collection of Adverse Event Reports by FDA see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.
[7] USP 39-NF34 < 1217> *Tablet Breaking Force.*
[8] David ST, Augsburger LL. 1974. Flexure test for determination of tablet tensile strength. J Pharm Sci 63:933-936.
[9] Ambros MC, Podczeck F, Podczeck H, Newton JM. 1998. The characterization of the mechanical strength of chewable tablets. Pharm Dev Tech 3:509-515.

- Of appropriate size and shape[10]
- Able to disintegrate readily to minimize aspiration and facilitate dissolution.

Critical quality attributes for chewable tablets should include hardness, disintegration, and dissolution, as well as all factors that may influence drug bioavailability and bioequivalence. In addition, careful attention should be given to tablet size, thickness, and friability, as well as taste, which may impact the ability or willingness of a patient to chew the chewable tablet (i.e., a patient may swallow whole, rather than chew, a bad tasting tablet). No single quality characteristic should be considered sufficient to control the performance of a chewable tablet. Instead, the goal should be to develop the proper combination of these attributes to ensure the performance of the chewable tablet for its intended use.

A. Hardness

The hardness of chewable tablets should be such that they withstand the rigors of manufacturing, packaging, shipping, and distribution, as well as be easily chewed by the intended patient population. Hardness is generally measured as the force needed to break the tablet in a specific plane. Tablet hardness may be measured and expressed in a variety of units. Applications submitted to FDA should use the same unit of measure in reporting results and specifications. including: kilopond (kp), kilogram-force (kgf), Newton (N), and Strong-Cobb Units(scu). 1 kp = 1 kgf = 9.8 N = 1.4 scu. Public standards also exist to ensure consistent measurement of the tablet hardness (Tablet Breaking Force[11]). Tablet hardness may be used to determine the chewing difficulty index (see Appendix I).

B. Disintegration

The time required for a tablet to break up into small particles is its disintegration time. For chewable tablets, disintegration time should be short enough to prevent GI obstruction in the event a tablet is not completely chewed by the patient. Usually, the presence of the correct type and amount of a disintegrant facilitates rapid disintegration of the tablet.[12] In vitro disintegration testing should be conducted using intact tablets in suitable medium using established disintegration equipment (such as USP Disintegration Apparatus) and methods.[13]

C. Dissolution

Drug absorption from chewable tablets depends on the release of the drug substance(s) from the intact or the chewed tablets; therefore, in vitro dissolution testing of chewable tablets should

[10] For tablets that may be chewed or swallowed whole, the FDA guidance for industry on *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* recommends that the largest dimension of a tablet intended to be swallowed whole should not exceed 22 mm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/defa ult.htm.

[11] USP 39-NF34 < 1217> *Tablet Breaking Force.*

[12] Gupta A, Chidambaram N, Khan MA. 2015. An index for evaluating difficulty of chewing the chewable tablets. Drug Dev Ind Pharm. 41:239-243.

[13] USP 39-NF34 <701> *Disintegration.*

follow the principles of dissolution testing of conventional IR tablets.[14] That is, the active pharmaceutical ingredient(s) of the chewable tablets should adequately dissolve out of the tablet with or without chewing.

For product characterization during development in vitro dissolution testing should be conducted on intact tablets in at least four media, such as water, aqueous media at pH 1.2, buffer pH 4.5, and buffer pH 6.8, with established dissolution methods using equipment such as USP Apparatus 1 (basket), USP Apparatus 2 (paddle), or USP Apparatus 3 (reciprocating cylinder).[15]

D. Performance in Simulated Physiological Media

Chewable tablets should also be evaluated using dissolution media such as simulated fasted and fed state gastric and intestinal fluids with enzymes (biorelevant dissolution media). Hardness should also be tested after brief (30-120 s) exposures to small quantities (1-2 mL) of human or simulated saliva. Such studies may provide a better understanding of in vivo performance of the chewable tablets.[16] In vitro testing in physiological media, consistent with the targeted patient population characteristics may support further characterization of the drug product and its critical quality attributes.

E. Biowaiver and Postapproval Considerations

The solubility and permeability characteristics of the drug substance may be used to determine where the drug fits within the Biopharmaceutics Classification System (BCS). Depending on the BCS classification of the drug substance, proposals for waiver of bioequivalence (BE) studies may be considered for chewable tablets.[17] Changes in the chemistry, manufacturing and controls after approval of the chewable tablets should be made in conformance with the principles outlined in the Scale-up and Post-Approval Changes Immediate Release (SUPAC IR) guidance document.[18]

IV. RECOMMENDATIONS

The following general and specific recommendations should be considered during the development phase of a chewable tablet.

Potential product design and development considerations should include: disintegrant(s) to facilitate release of the active ingredient, and sweeteners and flavoring agents for taste-

[14] See FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.
[15] USP 39-NF34 <711> *Dissolution.*
[16] Gupta A, Chidambaram N, Khan MA. 2015. An index for evaluating difficulty of chewing index for chewable tablets. Drug Dev Ind Pharm. 41:239-243.
[17] See FDA's guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.
[18] See FDA's guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.

masking.[19] The possibility of the interaction of excipients with each other and/or the drug substance(s), and their likely impact on the manufacturing process, should be explored.

The following information should be collected either during the conduct of pivotal clinical studies and reported in the subsequent NDA:

1. Were the chewable tablets swallowed intact (i.e., without breaking) or after being thoroughly chewed?

2. If swallowed intact, does the shape and size of chewable tablet pose a choking or bowel obstruction risk?[20]

3. If water was used to aid swallowing, what was the volume?

4. What was the subject's sensory experience (e.g., taste, mouth feel, and aftertaste)?[21,22]

For ANDA applications, general information such as subject's sensory experience (acceptability of taste, mouthfeel, and aftertaste) and ease of swallowing – in case of tablets swallowed intact – can be collected during the conduct of bioequivalence studies and reported in the subsequent ANDA submissions.

The potential for buccal absorption of the drug substance should be evaluated and described in the NDA. The importance of any buccal absorption may depend on the solubility and permeability characteristics of the drug substance, its stability in saliva (over a pH range 6.0 to 7.5), and whether it undergoes extensive first-pass metabolism.

Stability in the buccal environment can usually be assessed in vitro. For example, studies at the applicable pH range over a short period of time (e.g., <5 min) showing minimal drug substance release or lack of degradation of the drug substance may be adequate to demonstrate short-term stability in the buccal environment.

A. Critical Quality Attributes

The hardness, dissolution, and disintegration of the chewable tablet should be established early in development. FDA recommends that multiple attributes be studied to address the performance of the chewable tablet and incorporated in the product specification. Reliance on only one attribute should be avoided.

For drug products that require filing of an application with the Agency, the development information should be provided in section 3.2.P.2 (Pharmaceutical Development) of a common

[19] See FDA's guidance for industry on *Q8(R2) Pharmaceutical Development*.
[20] See footnote 9.
[21] See footnote 9.
[22] European Medicines Agency. 2006. Reflection Paper: Formulations of choice for the pediatric population. EMEA/CHMP/PEG/194810/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf.

technical document (CTD) formatted submission. The information on tablet hardness and chewing difficulty index (see Appendix I) should be provided in section 3.2.P.3.4 (Control of Critical Steps and Intermediates) or section 3.2.P.5.1 (Specification) of a CTD formatted application.[23]

The Agency encourages manufacturers of currently approved chewable tablets and nonapplication chewable tablets to reevaluate the critical quality attributes and ensure appropriate specifications are in place. Should the Agency have reason to determine that a marketed chewable tablet poses a particular risk to public health because it is difficult to chew (e.g., causes damage to the teeth or dental prosthetics, or GI obstruction), appropriate action will be taken to alleviate the risk to public health.

- **Hardness**

  - Based on the review of applications and literature sources, the Agency recommends that hardness for chewable tablets be kept low (e.g., < 12 kp).

  - A higher hardness value (e.g., ≥12 kp) may be considered if brief (approximately 30 seconds) exposure to saliva before chewing results in significant disintegration and/or reduction in hardness of these tablets. The study may be performed in vivo using human volunteers or in vitro for 30 seconds exposure, using 1 mL of simulated salivary fluid (see Appendix II).

  - In all other cases, the sponsor should provide justification for the proposed hardness, including studies demonstrating that the tablet can be safely chewed by the intended population without damage to teeth, dentures, or other adverse effects related to chewing these tablets.

  - In addition to evaluating the hardness of chewable tablets, the sponsor should consider evaluating the tablets for the chewing difficulty index (see Appendix I) both before and after exposure to human saliva.

- **Disintegration and Dissolution**

  - Chewable tablets should typically meet the same disintegration and dissolution specifications as IR tablets.

  - In vitro dissolution testing should be conducted on intact chewable tablets since it is possible that some patients might swallow the tablets without chewing. Crushing of the chewable tablets prior to conducting in vitro dissolution testing generally is not recommended since there is no reported validated method for this process to date. Furthermore, this approach would be unlikely to result in experimental conditions simulating a range of chewing patterns that might be observed in different patient populations. However,

[23] ICH Harmonised Tripartite Guideline. The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1). September 2002.

additional dissolution assessments may be needed on a case-by-case basis[24] based on product-specific information.

- It is possible to use other methods, as long as the proposed methods are demonstrated to be equivalent or superior to the existing approaches.

- **Other Critical Quality Attributes**

  - Other critical quality attributes applicable to a particular chewable tablet should be evaluated using Agency recommended methods or using methods that are demonstrated to be equivalent or superior to the existing approaches.

B. Nomenclature and Labeling

As previously stated, the USP recognizes and differentiates between two types of chewable tablets: (1) those that may be chewed for ease of administration, and (2) those that must be chewed and/or crushed before swallowing to avoid choking and to ensure the release of the active ingredient.[25] These two types of chewable tablets are differentiated by the way they are named and labeled.

- The format "[DRUG] Tablets" will be used for tablets that MAY be chewed or swallowed in their entirety. The labels and labeling for these products will also include a labeling statement indicating that the tablets MAY be chewed.

- The format "[DRUG] Chewable Tablets" will be used for tablets that MUST be chewed and for which there is no alternative route of administration. The labels and labeling for these products will also include a labeling statement indicating that the tablets MUST be chewed.

To help prevent patients from swallowing intact "[DRUG] Chewable Tablets," it is strongly recommended that the principle display panel of the container label and the carton labeling (if applicable) prominently state the following:

> Chew or crush tablets completely before swallowing.

If space permits, it is recommended that the following statement be displayed with lesser prominence to reinforce the importance of chewing the tablets:

> Do not swallow tablets whole.

Additionally, language similar to the previously mentioned statements should appear in the professional labeling (Highlights of Prescribing Information; Section 2 Dosage and Administration, and Section 17 Patient Counseling Information), as well as in any accompanying patient information or Medication Guide, if applicable.

[24] See FDA's draft guidance on *Lanthanum Carbonate*. August 2011, Revised November 2013.
[25] USP 39-NF34 <1151> *Pharmaceutical Dosage Forms.*

APPENDIX I: CHEWING DIFFICULTY INDEX

Tablet hardness[26] is the force required to cause the tablets to break in a specific plane. It may be used to determine the tensile strength, which is a more fundamental measure of the tablet's ability to withstand rupture. Mathematically it takes into account the shape and size of the tablet. For flat-faced round tablets, the tensile strength (σ_h) is calculated using the following equation:[27]

$$\sigma_h = \frac{2F_h}{\pi DH} \qquad \text{Equation 1}$$

where "F_h" is the load required to break the tablet, "D" is the tablet diameter and "H" is the tablet thickness (see Figure A).

The tablet breaking force (F_f) may also be measured by applying the force by means of a straight edge to an unsupported midpoint of the top face of a tablet supported at the two extremes of the lower face. The tensile strength (σ_f) in this case may be calculated as:[28]

$$\sigma_f = \frac{3F_f L}{2DH^2} \qquad \text{Equation 2}$$

where "L" is the constant distance between the two lower supports and the other terms are as defined earlier (see Figure B).

The tensile strength values determined from the two test methods have been shown to be proportional to each other. Thus,

$$\sigma_f = k\sigma_h \qquad \text{Equation 3}$$

where "k" is the proportionality constant.

Substituting equations 1 and 2 in equation 3, gives

$$\frac{3F_f L}{2DH^2} = k\frac{2F_h}{\pi DH} \qquad \text{Equation 4}$$

Rearranging Equation 4 gives the relationship between the forces F_f and F_h as

$$\left(\frac{3\pi L}{4k}\right)F_f = F_h H \qquad \text{Equation 5}$$

Since "$3\pi L/4$" is an experimental constant, while "k" is a proportionality constant between the two tensile strengths, Equation 5 may be viewed as defining the Chewing Difficulty Index, a measure of the difficulty of breaking/chewing the chewable tablets, as

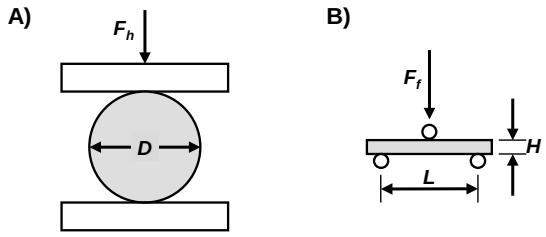
$$\text{Chewing Difficulty Index} = F_h H \qquad \text{Equation 6}$$

[26] USP 39-NF34 < 1217> *Tablet Breaking Force.*

[27] Fell JT, Newton JM. 1970. Determination of tablet strength by the diametral-compression test. J Pharm Sci 59:688–691.

[28] ASTM Standard D 0790-10. 2010. Standard Test Methods for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials. ASTM International. West Conshohocken, PA.

FIGURES



APPENDIX II: SIMULATED SALIVARY FLUID COMPOSITION

Currently, there is no official standard for the composition of simulated salivary fluid. Different compositions have been proposed in the literature.[29] An example of simulated salivary fluid (pH 6.8) is presented below.[30]

Ingredient	Concentration (mg/L)
Magnesium chloride, anhydrous ($MgCl_2$)	100
Calcium chloride, dihydrate ($CaCl_2 \cdot 2H_2O$)	220
Sodium phosphate dibasic, heptahydrate ($Na_2HPO_4 \cdot 7H_2O$)	1350
Potassium phosphate monobasic (KH_2PO_4)	680
Potassium chloride (KCl)	750
Urea ($CO(NH)_2$)	600
Sodium chloride (NaCl)	600
De-ionized water	*q.s.*

[29] Gal JY, Fovet Y, Adib-Yadzi M. 2001. About a synthetic saliva for in vitro studies. Talanta 53:1103-1115.
[30] Gupta A, Chidambaram N, Khan MA. 2015. An index for evaluating difficulty of chewing index for chewable tablets. Drug Dev Ind Pharm. 41:239-243.