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# Quality Attribute 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)**

**August 2018  
Pharmaceutical Quality/CMC**

# Quality Attribute Considerations for Chewable Tablets Guidance for Industry

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## **Quality Attribute Considerations for Chewable Tablets Guidance for Industry<sup>1</sup>**

This guidance represents 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 office responsible for this guidance as listed on the title page.

### **I. INTRODUCTION**

This guidance provides manufacturers of chewable tablets<sup>2</sup> 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.<sup>3</sup> This guidance also provides recommendations for sponsors/applicants regarding the submission of developmental, manufacturing, and labeling information for chewable tablets in applications. The recommendations in this guidance apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs),<sup>4</sup> and certain chemistry, manufacturing, and controls (CMC) supplements to these applications.<sup>5</sup> 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 immediate release (IR) 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.

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<sup>1</sup> 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.

<sup>2</sup> This guidance applies only to chewable tablets and not other chewable dosage forms.

<sup>3</sup> Products covered by these recommendations include over-the-counter (OTC) monograph products as well as prescription and OTC drug products that must be approved by CDER before they can be distributed.

<sup>4</sup> With respect to the applicability of this guidance to ANDAs – including recommendations for underlying design and other development determinations – is that Section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act requires a generic product to be the “same” as its reference listed drug in a number of relevant ways. These requirements further may inform acceptable quality attributes for a proposed generic product in addition to the recommendations in this guidance.

<sup>5</sup> This guidance should be considered for CMC supplements submitted for modifications that affect the formulation or other critical quality attributes of a chewable tablet.

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### **II. BACKGROUND**

Chewable tablets are an oral dosage form intended to be chewed and then swallowed by the patient rather than swallowed whole. They should be designed to be palatable and be easily chewed and swallowed. Chewable tablets should be safe and easy to use in a diverse patient population of pediatric, adult, or elderly patients who are unable or reluctant 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.<sup>6</sup> The concepts in this guidance are applicable to both types of chewable tablets.

Adverse events reported for chewable tablets include gastrointestinal (GI) obstruction resulting from patients swallowing whole or incompletely chewed tablets, and tooth damage or denture breakage resulting from excessive tablet hardness, and other esophageal irritation.<sup>7</sup> In light of these reported adverse events, the Agency reviewed approved drug product applications for chewable tablets and found that in certain cases critical quality attributes such as hardness, disintegration, and dissolution were not consistently evaluated. 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.<sup>8,9,10</sup>

This guidance describes the critical quality attributes that should be considered when developing chewable tablets and recommends selection of acceptance criteria that are 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

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<sup>6</sup> USP-NF <1151> *Pharmaceutical Dosage Forms*.

<sup>7</sup> For general information on collection of Adverse Event Reports by FDA, see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

<sup>8</sup> USP-NF < 1217> *Tablet Breaking Force*.

<sup>9</sup> David ST and LL Augsburg, 1974, Flexure test for determination of tablet tensile strength, *J Pharm Sci*, 63:933-936.

<sup>10</sup> Ambros MC, F Podczeczek, H Podczeczek H, JM Newton, 1998, The characterization of the mechanical strength of chewable tablets, *Pharm Dev Tech*, 3:509-515.

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- Palatable (taste masked or of acceptable taste)
- Of appropriate size and shape<sup>11</sup>
- Able to disintegrate readily to 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 is 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. Public standards exist to ensure consistent measurement of the tablet hardness (Tablet Breaking Force<sup>12</sup>). Tablet hardness may be measured and expressed in a variety of units.<sup>13</sup> Applications submitted to FDA should use the same unit of measure in reporting testing results and specifications.

An index has been developed that factors tablet hardness with the load to break that tablet to create a numerical value that can be used to compare chewable tablets for their ease of being chewed.<sup>14</sup> See Appendix I of this document for the description and rationale for this index (Chewing Difficulty Index). We encourage sponsors/applicants to accumulate and submit Chewing Difficulty Index data during product development.<sup>15</sup>

### **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

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<sup>11</sup> For tablets that may be chewed or swallowed whole, the guidance for industry *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. While this guidance was created for ANDA applicants, we believe that the size recommendations are reasonable for all marketed drug products. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>12</sup> See footnote 8.

<sup>13</sup> Units for hardness are expressed as: kilopond (kp), kilogram-force (kgf), Newton (N), and Strong-Cobb Units (scu). 1 kp = 1 kgf = 9.8 N = 1.4 scu.

<sup>14</sup> Gupta A, Chidambaram N, Khan MA. 2015. An index for evaluating difficulty of chewing the chewable tablets. *Drug Dev Ind Pharm.* 41:239-243.

<sup>15</sup> The Agency intends to evaluate submitted Chewing Difficulty Index data and update this guidance in the future as appropriate.

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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. In vitro disintegration testing should be conducted using intact tablets in suitable medium using established disintegration equipment (such as USP Disintegration Apparatus) and methods.<sup>16</sup>

### **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 follow the principles of dissolution testing of conventional IR tablets.<sup>17</sup> That is, the active pharmaceutical ingredient(s) of the chewable tablets should adequately dissolve out of the tablet.

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, buffered aqueous media at pH 4.5, and buffered aqueous media at 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).<sup>18</sup>

### **D. Performance in Simulated Physiological Media**

A sound understanding and assessment of the factors impacting the in vivo performance of drug products is needed during drug development. Utilizing in vitro methods that use simulated physiological media such as saliva and gastric fluids can provide an assessment of likely in vivo performance of oral dosage forms, particularly those made with poorly soluble drug substances.<sup>19,20,21,22</sup>

In particular, chewable tablets should be evaluated using dissolution media such as simulated fasted and fed state gastric and intestinal fluids with enzymes (biorelevant dissolution media). Hardness testing after brief exposure (30 seconds) to a small quantity (for example, 1 mL) of human simulated saliva may provide data that could be used to support the hardness specification.<sup>23</sup> 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.

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<sup>16</sup> USP-NF <701> *Disintegration*.

<sup>17</sup> See guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>18</sup> USP-NF <711> *Dissolution*.

<sup>19</sup> Dressman JB, GL Amidon, C Reppas, VP Shah, 1998, Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms, *Pharm Res*, 15:11-22.

<sup>20</sup> Klein S, 2010, The Use of Biorelevant Dissolution Media to Forecast the in vivo Performance of a drug, *AAPS J*, 12:3, 397-406.

<sup>21</sup> Markopoulos C, CJ Andreas, M Vertzoni, J Dressman, C Reppas, 2015, In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media, *Europ J Pharm and Biopharm*, 93:173-182.

<sup>22</sup> Marques MRC, R Loebenberg, and M Almukainz, 2011, Simulated Biological Fluids with Possible Application in Dissolution Testing, *Dissolution Technologies*, 15-28.

<sup>23</sup> See footnote 14.

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### **E. Use of In Vitro Bioequivalence Data 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, use of in vitro data to support bioequivalence (BE) may be considered for chewable tablets.<sup>24</sup> 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.<sup>25</sup>

## **IV. RECOMMENDATIONS**

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

### **A. Patient Acceptability and In vivo Performance**

Potential product design and development considerations should include disintegrant(s) to facilitate release of the active ingredient, and sweeteners and flavoring agents for taste-masking.<sup>26,27</sup> 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 evaluated.

For an NDA, the following information should be collected during the conduct of clinical trials and reported :

1. Was the subject's sensory experience associated with chewing the tablet acceptable (e.g., taste, mouthfeel, and aftertaste)?<sup>28,29</sup>
2. Did subjects have difficulty in thoroughly chewing the tablet (i.e., were the tablets inadvertently swallowed intact)?
3. If inadvertently swallowed intact, does the shape and size of the chewable tablet pose a choking or bowel obstruction risk?<sup>30</sup>
4. If water was used to aid swallowing, what was the volume?

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<sup>24</sup> See guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

<sup>25</sup> See guidance for industry *Immediate Release Solid Oral Dosage Forms: Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.

<sup>26</sup> The Agency recommends the use of sweeteners that do not contribute to dental decay.

<sup>27</sup> See guidance for industry *Q8(R2) Pharmaceutical Development*.

<sup>28</sup> See footnote 9.

<sup>29</sup> 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](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf).

<sup>30</sup> See footnote 9.



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For ANDA applications for which in vivo bioequivalence studies are conducted, general information such as the subject's sensory experience (acceptability of taste, mouthfeel, and aftertaste) and ease of swallowing – in the event that the tablet is not thoroughly chewed – should be collected during the conduct of bioequivalence studies and reported in the subsequent ANDA.

### **B. Buccal Absorption**

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.

### **C. Critical Quality Attributes**

Appropriate acceptance criteria for 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 technical document (CTD)-formatted submission. The information on tablet hardness, disintegration and dissolution should be provided in section 3.2.P.3.4 (Control of Critical Steps and Intermediates) or section 3.2.P.5.1 (Specifications) of a CTD-formatted application.<sup>31</sup> Sponsors/applicants are encouraged to calculate and submit the chewing difficulty index (see Appendix I) in section 3.2.P.2.

The Agency recommends that applicants of currently approved chewable tablets and sponsors of nonapplication chewable tablets reevaluate the product's critical quality attributes and ensure appropriate specifications are in place considering the recommendations above.<sup>32</sup> If the Agency identifies that a marketed chewable tablet poses a particular risk to public health because it is difficult to chew (e.g., causes damage to teeth or dentures, or GI obstruction), the Agency will communicate with the sponsor/applicant or manufacturer and consider appropriate action to alleviate the risk to public health.

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<sup>31</sup> ICH Harmonised Tripartite Guideline, 2002, The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1).

<sup>32</sup> Reevaluation of critical quality attributes can be accomplished through review of historical data from development and validation studies, adverse event reporting, customer complaint trends, or through collection of new data.

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- **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).<sup>33</sup>
- A higher hardness value (e.g.,  $\geq 12$  kp) may be considered if justified. An example of such justification could be demonstrating significant disintegration and/or reduction in hardness of such tablets following brief (approximately 30 seconds) exposure to saliva before chewing. An in vivo study may be performed using human volunteers, or an in vitro study may be conducted in which the tablet is exposed to a small quantity (e.g., 1 mL) of simulated salivary fluid (see Appendix II) for 30 seconds.
- In all other cases, the sponsor/applicant should provide justification for the proposed hardness, including studies demonstrating that the tablet can be readily chewed by the intended population without GI obstruction, damage to teeth or dentures, or other adverse events related to chewing these tablets.
- In addition to evaluating the hardness of chewable tablets, the sponsor/applicant 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 currently no reported validated method for this process. 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, additional dissolution assessments may be needed on a case-by-case basis 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.

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<sup>33</sup> In general, adverse events were not associated with the hardness value of < 12 kp in approved products. The Agency recognizes that tablet size and shape are important in determining acceptable tablet hardness. For example, for a very small tablet, a hardness value of 12 kp may be quite high.

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- **Other Critical Quality Attributes**

- If other critical quality attributes are applicable to a particular chewable tablet, they should be evaluated using Agency-recommended methods or using methods that are demonstrated to be equivalent or superior to the existing approaches. For example, if the chewable tablet consists of functionally-coated particles, it is important to ensure the functional coating continues to perform after the tablet is chewed.

### **D. 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.<sup>34</sup> These two types of chewable tablets are differentiated by the way they are named and labeled.<sup>35,36</sup>

- The text “[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 text “[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 principal 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 on the principle display panel 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 DOSAGE AND ADMINISTRATION and PATIENT COUNSELING INFORMATION sections of the prescribing information as well as other sections when appropriate, and any

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<sup>34</sup> See footnote 6.

<sup>35</sup> See guidance for industry *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products-Content and Format*.

<sup>36</sup> The format of the dosage form may differ in the prescribing information, FDA-approved patient labeling, and carton/container labeling.

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accompanying patient labeling (e.g., Medication Guide, Patient Package Insert, Instructions for Use) if applicable.

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### **APPENDIX I: CHEWING DIFFICULTY INDEX FOR FLAT-FACED ROUND TABLETS**

One of the critical quality attributes for tablets, tablet hardness,<sup>37</sup> also referred to as breaking force or crushing force, is the force required to cause the tablets to break in a specific plane. Tablet hardness is a useful parameter for in-process control and quality assurance.

For chewable tablets, tablet hardness is also an important indicator for its suitability for use by the targeted patient population.

Early publications have shown that the variations in fracture strength were due to inaccuracies of the instrumental scales of the various hardness testers as well as variations in the method of application of the load, physical dimensions, and shape of the tablet.<sup>38,39,40,41</sup> Of the several approaches applied to measure tablet breaking strength, tensile strength measurement is indicated as a more reliable approach where variations due to the method are minimized. Tensile strength measurement is applied as a more fundamental measure of the tablet's ability to withstand breaking force due to the inherent strength of the compacted material.<sup>42</sup>

Two methods used for measuring tablet strength are: diametral compression (diametrical tensile strength) and flexural bending (flexure tensile strength test). The relationship between the two methods is explored to calculate a value which is described here as a chewing difficulty index.<sup>43</sup>

A diametral tensile strength measurement is carried out for a flat disc-like tablet, taking into account its shape (round) and size (adjustment for its thickness), and can be described by Equation 1. While modified tensile strength equations for tablets with different shapes and sizes are available, the approach described here is for flat-faced round tablets.<sup>44,45,46</sup>

The diametral tensile strength ( $\sigma_h$ ) is calculated using the following equation:<sup>47</sup>

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<sup>37</sup> See footnote 8.

<sup>38</sup> Jarosz PJ and EL Parrott, 1982, Tensile Strength and Hardness of Tablets, *J Pharm Sci*, 71(6), 705-707.

<sup>39</sup> Podczek F, 2012, Methods for the practical determination of the mechanical strength of tablets-From empiricism to science, *Int J Pharm*, 436, 214-232.

<sup>40</sup> Shang C, IC Sinka, B Jayaraman, J Pan, 2013, Break force and tensile strength relationship for curved faced tablets subject to diametrical compression, *Int J Pharm*, 442, 57-74.

<sup>41</sup> See footnote 10.

<sup>42</sup> David ST and LL Augsburg, 1974, Flexure Test for Determination of Tablet Tensile Strength, *J Pharm Sci*, 63(6) 933-936.

<sup>43</sup> See footnote 14.

<sup>44</sup> See footnote 8.

<sup>45</sup> See footnote 10.

<sup>46</sup> Davies PN, HEC Worthington, F Podczek, JM Newton, 2007, The determination of the mechanical strength of tablets of different shapes, *Europ J Pharm Biopharm*, 67, 268-276.

<sup>47</sup> Fell JT and JM Newton, 1970, Determination of tablet strength by the diametral-compression test, *J Pharm Sci*, 59:688-691.

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

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 where the tablet is placed on its side).

Equation 2 provides an alternate approach to calculate diametral tensile strength by flexural bending. Tablet breaking force ( $F_f$ ) using this tablet loading method for determining strength is also referred to as a three-point bending test and is measured by applying the breaking force by means of a straight edge to an unsupported midpoint of the top face of a tablet which is supported at the lower face of the tablet with two lower supports.<sup>42</sup> The tensile strength ( $\sigma_f$ ) in this case may be calculated as:<sup>48</sup>

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

where “ $L$ ” is the constant distance between the two lower supports and the other terms are as defined earlier (see Figure B). For the three-point flexural tensile strength test, it is recommended that  $L=(2/3)D$ .<sup>42,49,50</sup>

Several publications have shown that depending on test conditions, the tensile strength values determined from the two test methods (diametral and flexural methods) have been shown to be proportional to each other.

Thus,

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

where “ $k$ ” is the proportionality constant.

Substituting equations 1 and 2 in equation 3, gives

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

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

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

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 parameters and their relationship as indicators of the Chewing Difficulty Index.

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<sup>48</sup> 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.

<sup>49</sup> Moser MA, M Krumme, PC Schmidt, 1998, Flexure Test of Tablets, Pharmazie, 53, 46-51.

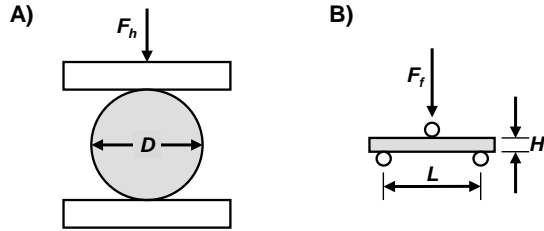
<sup>50</sup> Stanley P, 2001, Mechanical strength of compacted powders, Int J Pharm, 227, 27-38.

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If the diametral compression test is used for tensile strength measurement, the product of the load required to break the tablet (i.e., at failure) ( $F_h$ ) and tablet thickness ( $H$ ) provide a measure of the difficulty of breaking/chewing the chewable tablets, as

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

**FIGURES**



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### **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.<sup>51</sup> An example of simulated salivary fluid (pH 6.8) is presented below.<sup>52</sup>

Ingredient	Concentration (mg/L)
Magnesium chloride, anhydrous (MgCl <sub>2</sub> )	100
Calcium chloride, dihydrate (CaCl <sub>2</sub> ·2H <sub>2</sub> O)	220
Sodium phosphate dibasic, heptahydrate (Na <sub>2</sub> HPO <sub>4</sub> ·7H <sub>2</sub> O)	1350
Potassium phosphate monobasic (KH <sub>2</sub> PO <sub>4</sub> )	680
Potassium chloride (KCl)	750
Urea (CO(NH) <sub>2</sub> )	600
Sodium chloride (NaCl)	600
De-ionized water	<i>q.s.</i>

<sup>51</sup> Gal JY, Y Fovet, M Adib-Yadzi, 2001, About a synthetic saliva for in vitro studies, *Talanta*, 53:1103-1115.

<sup>52</sup> See footnote 14.