USP Dietary Supplements Stakeholder Forum
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USP Chewable Gels Monographs

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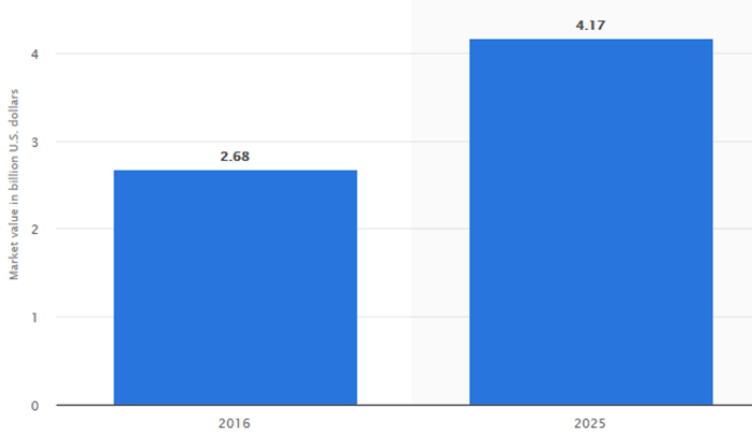
DS Gummies Market

- Value of the gummy vitamins market in the United States in 2016 and 2025 (in billion U.S. dollars)



https://www.statista.com

- Single vitamins and multivitamins are the two main types of gummy vitamins sold in the market

Gummies composition

- Gummies major ingredients
  - Gelatin or Pectin or Agar (5-8 %), water (15-20%), sucrose (28-50%), and corn syrup solids (40-55 %)
- The formulations of gummy vitamin products pose additional challenges with respect to a tablet or capsule preparation due to vitamins stability issue in a gummy delivery system
- Due to stability issue, manufacturers add an excessive amount of the nutrients during manufacture to compensate for loss during storage and achieve the declared shelf-life

Presentation Outline

- Monographs components
  - Nomenclature
  - Overage
  - Sample preparation
  - Performance Tests
    - GC <2040> & GC <2091>
  - Specific Tests
- Comments received
- How the comments were addressed by DS EC
- Current status of the monographs
- USP recommendations

Monographs Components

- USP Nomenclature EC agreed to introduce the name “Chewable gels“ for monographs covering dietary supplements commonly called "gummies”

- GC <1151> Pharmaceutical Dosage Forms had been revised to include information on chewable gels – a new dosage form for oral delivery of dietary supplements and over-the-counter medicines.





Chewable Gels Definition

GC <1151>

“Chewable gels are used to deliver drug substances and dietary supplements via the oral route. Chewable gels can consist of all or some of the following components—gelling agent(s), sugars, water, sweeteners, and flavoring agents. The sweeteners and flavoring are intended to enhance patient acceptance and mask the taste of the delivered labeled drug substance. Chewable gels maintain their molded shape, are elastic, and yield to mastication. They are intended to be chewed before swallowing. Chewable gels are also known as "gummies" in the confectionary and dietary supplement industries but that term is not used in official article titles.”

Chewable Gels Monographs

- Ascorbic Acid Chewable Gels
  - Submitted to PF 43(3) [May-Jun, 2017]
- Cholecalciferol Chewable Gels
  - Submitted to PF 43(3) [May-Jun, 2017]
- Cyanocobalamin Chewable Gels
  - Submitted to PF 44(3) [May-Jun, 2018]
- Oil-and Water-Soluble Vitamins with Minerals Chewable Gels
  - Under development, target PF 44(6) [Nov.-Dec. 2018]

Monographs Components

DEFINITION

- DS are expected to meet 100% label claim through the declared shelf-life under recommended storage conditions
- Shelf life acceptance criteria should be derived from consideration of the available stability information
  - Ascorbic Acid Chewable Gels: NLT 90.0% and NMT 150.0% or NLT 100.0% and NMT 160.0%
    - Vs. Tablets - NLT 90.0% and NMT 110.0% or NLT 100.0% and NMT 120.0%
  - Cholecalciferol Chewable Gels: NLT 90.0% and NMT 140.0% or NLT 100.0% and NMT 150.0%
    - Vs. Capsules - NLT 90.0% and NMT 110.0% or NLT 100.0% and NMT 120.0%
  - Cyanocobalamin Chewable Gels: NLT 90.0% and NMT 150.0% or NLT 100.0% and NMT 160.0%
    - Vs. Tablets - NLT 90.0% and NMT 110.0% or NLT 100.0% and NMT 120.0%
  - Oil-and Water-Soluble Vitamins with Minerals Chewable Gels: under development

USP Recommended Limits

- DS with a wide range of doses are on the market and overage could be a safety concern
- Science Division at USP had special meeting to discuss the issue of USP being asked by sponsors to excessively increase upper limits to compensate for stability losses
- The outcome of that discussion was that USP would avoid for new monographs overages above those already existing in similar monographs currently official at USP, except in very well substantiated instances

Monographs Components

STRENGTH

- ***Sample solution***: Immerse 25–30 Chewable Gels in liquid nitrogen in a cryogenic vessel for 10 min. Cool a blender jar by swirling liquid nitrogen for about 1 min and discard the contents. Add frozen Chewable Gels to the cooled blender jar and grind to a fine powder. Transfer a portion of the powder, nominally equivalent …..

  [Note— Proceed to this step immediately or keep the powdered Chewable Gels frozen until use.]

Monographs Components

PERFORMANCE TESTS

- Dissolution testing is recommended
  - Some vitamins are quite unstable in the chewable gel matrix (high water content and low pH)
  - The majority of finished vitamins products contain stabilized forms of vitamins including a protective coating, which could affect the release of vitamins
  - Gelatin aging may impair the release of nutrients from the matrix
  - A dissolution test would be useful to assess performance characteristics of marketed chewable gels containing vitamins and ensure that nutrients will be released from the dosage form

- GC <2040> was revised to include chewable gels dosage forms – *PF* 43(3)
  - Vitamin-Mineral chewable gels should meet dissolution requirements for folic acid, vitamin A, index water-soluble vitamins and index minerals, similar to tablets and capsules to ensure vitamins are released from matrix

Comparison of the results obtained from the dissolution samples with the Assay results

Product	Label Claim (µg)	Dissolution (% Release)	Assay (% label)
A	687.5 (1250 IU)	153	153.04
B	385 (700 IU)	76	140.07
C	687.5 (1250 IU)	54	96.07

Monographs Components

PERFORMANCE TESTS

- GC <2091> WEIGHT VARIATION OF DIETARY SUPPLEMENTS
  - Revision submitted to PF 44(4) [Jul.- Aug. 2018] where a new test procedure and acceptance criteria for Chewable Gels dosage forms were added.
  - The proposed acceptance criteria for weight variation are based on the results from different lots of chewable gel products currently on the market from several manufacturers.

CHEWABLE GELS

Weigh an equal number of units from each color and shape individually to obtain a total of NLT 20 individual weights, and calculate the average weight. The requirements are met if no individual weight differs from the average weight by more than 7.5%.

If 1 unit falls outside of the limits, repeat the procedure with an additional set of NLT 20 chewable gels. The requirements are met if none of the units tested differ from the average weight by more than 10%.

Monographs Components

SPECIFIC TESTS

- pH <791>
- Water Activity
  - Measure the water activity using the AOAC's Official Methods of Analysis, No. 978.18.
  - New GC is under development

Comments received

- Increase or eliminate the acceptance criteria for the upper limit in the *Definition*. It was proposed that product manufacturers could establish a suitable upper limit based on safety and stability studies conducted for the particular formulation.
  - Comment not incorporated. The Expert Committee agreed that there is no adequate justification to consider additional changes to the proposed upper limit of NMT 150% of the labeled amount of ascorbic acid and NMT 140% of the labeled amount of cholecalciferol

Comments received (cont.)

- Increase the acceptance criteria for the pH value since product pH is highly dependent on the formulation and may be above the recommended value of NMT 3.7.
  - Comment incorporated. The Expert Committee agreed to set the pH value at NMT 4.5.
- Remove the Water Activity acceptance criteria from the monographs. Although Water Activity is used to control product microbial contamination, specific microbial testing and microbial specifications are also listed in the monograph.
  - Comment not incorporated. Water Activity is an important parameter for the quality of chewable gel products

Current status of the monographs

- Ascorbic Acid Chewable Gels
  - USP 41–NF 36, First Supplement, Official August 1, 2018
- Cholecalciferol Chewable Gels
  - USP 41–NF 36, First Supplement, Official August 1, 2018
- Cyanocobalamin Chewable Gels
  - Published in PF 44(3) [May-Jun, 2018]. Comment deadline: July 31, 2018
- Oil-and Water-Soluble Vitamins with Minerals Chewable Gels
  - Under development, target PF 44(6) [Nov.-Dec. 2018]

Chewable Gels – Safety Issue

- Chewable gels are not recommended as pharmaceutical dosage forms yet because of the risk of accidental overdose due to its attractive candy appearance and pleasant taste.
- Chewable gel DS can be also dangerous if eat them like candy – common problem
  - The American Association of Poison Control Centers reported more than 50,000 cases of adverse effects from vitamins in 2014
  - Most reported issues from Fe overdose in kids and fat-soluble vitamins such as vitamin A, D, and K overdose in adults
  - Even very educated customer (having knowledge about upper tolerable level) can be overdosed due to high (not reported) nutrients overage

DS Chewable Gels

- USP Recommendations for consideration
  - Manufacturers may consider shortening the shelf-lives given to chewable gels in comparison to tablets and capsules instead of adding overages
  - Work on stabilization strategies may be needed to achieve longer shelf-lives.

Questions

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Thank You

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