Overview of USP Monographs for Chewable Gels (Marketed as Gummies)

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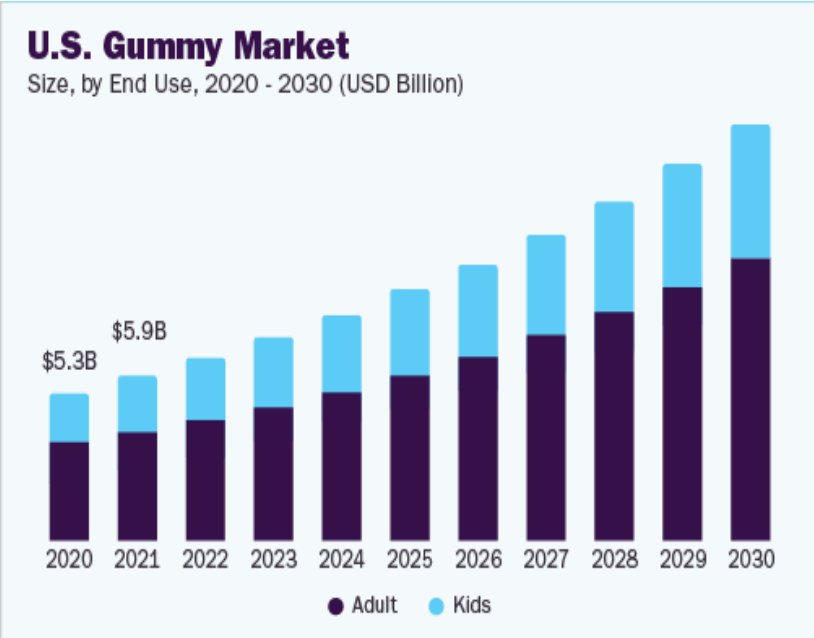
Dietary supplement chewable gels



The US gummy market is expected to grow at a compound annual growth rate (CAGR) of 10.8% from 2022 to 2030.

Source: www.grandviewresearch.com

- Dietary supplement chewable gels continue to gain popularity in the market among a wide range of the population, from children to the elderly, due to their pleasant taste, attractive appearance and ease of intake.
- It is important that manufacturers of dietary supplement chewable gel products produce high quality chewable gels that are safe and effective to deliver the intended nutritional benefits indicated on the product label.
- This presentation provides information on USP Quality Attributes for this dosage form.

Presentation Outline

- Chewable Gels Monographs
- Monographs components
  - Title (Nomenclature)
  - Definition (Overage)
  - Strength (Sample preparation)
  - Performance Tests
    - GC <2040>; GC <2091>
  - Specific Tests
    - Water Activity; pH
- Potential safety issue
- Recommendations for consideration

USP Chewable Gels Monographs

- Currently Official
  - Ascorbic Acid Chewable Gels
  - Cholecalciferol Chewable Gels
  - Cyanocobalamin Chewable Gels
  - Oil-and Water-Soluble Vitamins with Minerals Chewable Gels

- Published in PF 49(4) – comment due date was September 30, 2023
  - Ubidecarenone Chewable Gels
  - No comments were received

Chewable Gels Monographs

- Under development and documents review
  - Calcium with Vitamin D Chewable Gels
  - Water-Soluble Vitamins Chewable Gels
  - Plant-Based DHA Chewable Gels*
  - Melatonin Chewable Gels

* *Working title. The title will be defined by the USP Nomenclature Expert Committee*

Monographs Components

- **Title**
  - Gummies major ingredients: Gelatin or Pectin or Agar (5-8%), water (15-20%), sucrose (28-50%), and corn syrup solids (40-55%)
  - 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 drug substances

Nomenclature

GC <1151>: Chewable Gels Definition

“Chewable gels are used to deliver drug substances or dietary supplements via the oral route. In addition to drug substances(s) or dietary supplements, 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 or dietary supplement. 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”

Monographs Components

- **Definition** – limit for overages
  - In the US, DS are expected to meet 100% label claim through the declared shelf-life under recommended storage conditions
  - The formulations of these products pose additional challenges compared to a tablet or capsule preparation due to dietary ingredients stability issue in a chewable gel delivery system
  - Due to stability issues and manufacturing process, manufacturers regularly add an extra amount of the nutrients during manufacturing to compensate for loss during storage and achieve the declared shelf-life
  - Establishing specifications for the upper limits of dietary ingredients in chewable gels is challenging

USP Recommended Limits

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

Supplement Facts

Serving Size 2 Gummies
Servings Per Container 75

Amount Per Serving	% Daily Value
Vitamin A (as Retinyl Acetate) 1200 mcg	133%
Vitamin C (as Ascorbic Acid) 60 mg	67%
Vitamin D3 (as Cholecalciferol) 25 mcg (1000 IU)	125%
Vitamin E (as dl-Alpha Tocopheryl Acetate) 13.5 mg	90%
Niacin (as Niacinamide) 13 mg	81%
Vitamin B6 (as Pyridoxine Hydrochloride) 5 mg	294%
Folate 400 mcg DFE (240 mcg Folic Acid)	100%
Vitamin B12 (as Cyanocobalamin) 12 mcg	500%
Biotin 100 mcg	333%

Supplement Facts

Serving Size: 2 Gummies
Servings Per Container: 150

Amount Per Serving		% Daily Value
Vitamin A (as Retinyl Acetate)	290 mcg	32%
Vitamin C (as Ascorbic Acid)	30 mg	33%
Vitamin D (as Cholecalciferol)	20 mcg	100%
Vitamin E (as DL-Alpha Tocopheryl Acetate)	6.8 mg	45%
Vitamin B6 (as Pyridoxine Hydrochloride)	2 mg	118%
Folate (as Folic Acid)	665 mcg DFE (400 mcg Folic Acid)	166%
Vitamin B12 (as Cyanocobalamin)	9 mcg	375%
Biotin	1000 mcg	3333%

Chewable Gels vs. Tablets/Capsules

Definition

Chewable Gels

Ascorbic Acid
- NLT 90% and NMT 150% (100-160%)*

Cholecalciferol
- NLT 90% and NMT 140% (100-150%)*

Cyanocobalamin
- NLT 90% and NMT 150% (100-160%)*

Tablets/Capsules

Ascorbic Acid
- NLT 90% and NMT 110% (100-120%)*

Cholecalciferol
- NLT 90% and NMT 110% (100-120%)*

Cyanocobalamin
- NLT 90% and NMT 110% (100-120%)*

* General Notice 4.10.20 "… Where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, the upper acceptance criterion contained in the monograph may be increased by a corresponding amount…".

Chewable Gels vs. Tablets/Capsules

- **Definition:** Oil- and Water- Soluble Vitamins with Minerals

Ingredients	Tablets/Capsules	Chewable Gels
	%	%
Vitamin A	90 – 165 (100-175)	90 – 170 (100-180)
Vitamin D	90 – 165 (100-175)	90 – 170 (100-180)
Vitamin E	90 – 165 (100-175)	90 -170 (100-180)
Vitamin C	90 – 150 (100-160)	90 – 250 (100-260)
Vitamin B3	90 – 150 (100-160)	90 – 150 (100-160)
Pantothenic acid	90 – 150 (100-160)	Removed from the definition due to instability
Vitamin B6	90 – 150 (100-160)	90 – 150 (100-160)
Vitamin B12	90 – 150 (100-160)	90 – 170 (100-180)
Biotin	90 – 150 (100-160)	90 – 170 (100-180)
Folic Acid	90 – 150 (100-160)	90 – 245 (100-255) (Any overage should not exceed the tolerable upper intake level)
Iodine	90 – 125 (100-135)	90 – 160 (100-170)
Zinc	90 – 125 (100-135)	90 – 130 (100-140)
Magnesium	90 – 125 (100-135)	90 – 130 (100-140)
Calcium	90 – 125 (100-135)	90 – 130 (100-140)
Chromium	90 – 125 (100-135)	90 – 160 (100-170)

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.]

- This sample preparation procedure has been shown to be suitable for reproducible results.

Monographs Components

Performance tests

- Dissolution testing is recommended
  - The absorption of dietary ingredients from a DS product after oral administration depends on the ability of the dosage forms to release the dietary ingredients.
  - Most chewable gel products contain stabilized forms of dietary ingredients, including a coating to protect some dietary ingredients from degradation or interaction with other components in the chewable gel matrix (high water content and low pH). Protective coating can affect the release of nutrients
  - Gelatin aging may impair the release of nutrients from the matrix
  - A dissolution test is useful to assess performance characteristics of marketed chewable gels and ensure that nutrients will be released from the dosage form.

Dissolution and Assay results of vitamin A palmitate in multivitamin chewable gels as % of label claim

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

- GC <2040>
  - 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.

Monographs Components

Performance tests

- Meet the requirements of GC <2091> Weight Variation of Dietary Supplements

Individually weigh an equal number of units of each color and shape to obtain a total of NLT 20 and NMT 30 individual weights and calculate the average weight.

The requirements are met if no individual weight deviates from the average weight by more than 7.5%. If more than 1 unit exceeds the specified limit, the test fails.

If 1 unit falls outside of the limits, repeat the procedure with an additional set of NLT 20 and NMT 30 individual chewable gels. The requirements are met if none of the units tested in the second set differ from their average weight by more than 10%.

Monographs Components

Specific Tests

- Water Activity
  - Chewable gels are formulated with one or more gelling agents (e.g., gelatin, pectin or starch), nutritive sweeteners (e.g., sucrose, fructose, or corn syrup), flavoring agents, non-nutritive sweeteners, colorants, and water.
  - Determination of Water activity is a critical to the quality attribute required to ensure product stability during shelf life.
  - Water activity can be used to predict and resolve problems with moisture migration, can identify whether microbial growth will be a concern (i.e., surface mold grown), and may be a predictor of shelf stability.
  - General chapter <922> Water Activity outlines the recommended methods to qualify, calibrate, and use water activity meters to accurately measure the water activity.
  - Monographs recommend a water activity value of NMT 0.75 (may not be appropriate without a controlled pH value of NMT 4.5)

Monographs Components

Specific Tests

- pH <791>
  - pH is important factor that determines if a chewable gel product will support the growth of a pathogenic microorganism.
  - Monographs recommend a pH value of NMT 4.5.
- The effects of Water activity and pH should be combined to control microorganisms more effectively.

Chewable Gels – Potential Safety Issue

- The chewable gel finished dosage form may have potential safety concerns because of the risk of accidental overdose due to its attractive candy appearance and pleasant taste.

- Eating DS chewable gels like candy is a common problem
  - Nearly 50,000 instances of vitamin toxicity from dietary supplements are reported annually to The American Association of Poison Control Centers.
  - Most reported issues from Fe overdose in kids and fat-soluble vitamins such as vitamin A, D, and K overdose in adults
  - Nutrient overage not reported on the product label can mislead consumers about the amount of nutrient consumed.

DS Chewable Gels

Recommendations for consideration

- Manufacturers should consider the risk of adverse effects from unknown degradation products, as well as the uncertainty associated with the presence of a huge amounts of degraded vitamins or botanicals.
- A stabilization process used should not compromise the ability of the chewable gel dosage form to release dietary ingredients
- Consider the established safe tolerable level for each ingredient. Do not exceed these levels, even if overages are used.
- Make sure that the manufactured product maintains its safety and ability to deliver the labeled nutritional ingredients for potential absorption throughout its expected shelf life.

Questions

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Thank You

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