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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | UNIGEL DRONABINOL + ACETAZOLAMIDA |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Rx |
| Brand name / Generic name | Unigel Dronabinol + Acetazolamide |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Unigel capsules |
| Route of administration | Oral |
| Dose(s) | According to clinical study results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos to be opaque for maintaining blind study; final size and color to be defined during development |
| Type of packaging material | Box/Blister pack of 28 units |
| Commercial presentations | Blister pack of 28 capsules |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Dronabinol |
| CAS number: | 1972-08-3 |
| Description: | Solid 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] |
| Solubility: | Essentially insoluble in water 2.63e-03 g/L In water, 2.8 mg/L at 23 °C 2.8 mg/L at 73 °F (NTP, 1992) 1 part in 1 part of alcohol; 1 part in 1 part of acetone; 1 part in 3 parts of glycerol. In 0.15M sodium chloride, 0.77 mg/L at 23 °C. Soluble in fixed oils. |
| Melting point: | 200 °C |
| Polymorphs: | Dronabinol, a synthetic form of tetrahydrocannabinol (THC), exhibits polymorphism, although specific details regarding the number of polymorphic forms and their thermodynamic properties are limited. The available literature does not provide comprehensive data on distinct polymorphic forms, crystal systems, or their respective melting points and densities. Dronabinol is primarily formulated in soft gelatin capsules, which may influence its physical properties. The FDA-approved formulation of dronabinol (Marinol) is noted for its stability and efficacy in treating anorexia associated with AIDS and chemotherapy-induced nausea and vomiting. However, the polymorphic behavior of dronabinol remains underexplored in the context of its pharmaceutical applications. Further studies are warranted to elucidate the polymorphic characteristics of dronabinol, including potential impacts on solubility and bioavailability. Current references do not detail specific polymorphic forms or their implications in drug formulation. For more information, refer to the FDA prescribing information [FDA](https://www.accessdata.fda.gov/drugsatfda\_docs/label/2017/018651s029lbl.pdf), NCBI [NCBI](https://www.ncbi.nlm.nih.gov/books/NBK557531/), and Drugs.com [Drugs.com](https://www.drugs.com/monograph/dronabinol.html). |
| Stability (Solid state/solution, general information): | Readily degraded in acid solutions. A 50% solution in alcohol lost about 10% of delta-9-tetrahydrocannabinol after storage at 5 °C for 40 days; there was greater deterioration at 22 °C as measured by the optical density. |
| Scheme of degradation route | Dronabinol (Δ9-THC) exhibits significant degradation under various conditions, primarily influenced by temperature, pH, and light exposure. The degradation pathways include hydrolysis, oxidation, and photodegradation, leading to various degradation products. In acidic aqueous solutions, dronabinol is particularly labile, undergoing rapid degradation, which is exacerbated by air oxidation. The kinetics of degradation are affected by the presence of excipients and packaging materials, which can stabilize or destabilize the drug. Stress testing has shown that dronabinol's stability is compromised at elevated temperatures and under UV light, resulting in a decrease in potency and the formation of byproducts. The degradation products can include both synthetic byproducts and metabolites, which may have implications for safety and efficacy. Understanding these degradation routes is crucial for developing effective formulation strategies to enhance the stability and shelf-life of dronabinol products. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol), [Kinetics and mechanisms of drug degradation - ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [A review on the syntheses of Dronabinol and Epidiolex](https://pmc.ncbi.nlm.nih.gov/articles/PMC7907797/). |
| Stability indicators | Dronabinol capsules, containing synthetic delta-9-tetrahydrocannabinol (Δ9-THC), were evaluated for stability under various storage conditions (frozen, refrigerated, and room temperature) over a three-month period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to assess the stability, focusing on the percentage of initial Δ9-THC concentration remaining at multiple time points. Results indicated that the capsules maintained over 97% of the initial Δ9-THC content across all storage conditions, demonstrating minimal degradation. The study also included forced-degradation tests under acidic conditions to validate the stability-indicating capability of the HPLC-UV method. The findings suggest that the formulation, particularly the use of high-grade sesame oil, effectively protects Δ9-THC from oxidative degradation to cannabinol. Consequently, pharmacies can store dronabinol capsules at room temperature for up to 90 days post-refrigeration without compromising quality or efficacy. This stability data supports the practical storage recommendations for dronabinol capsules in non-refrigerated automated dispensing systems. For further details, refer to the original studies: [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature) and [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Dronabinol, with the molecular formula C21H30O2, has been analyzed for impurities using HPLC and LCMS techniques, as mandated by FDA and ICH guidelines. The investigation revealed various impurities, which are critical for ensuring the quality and safety of pharmaceutical products. Specific impurities identified include synthetic byproducts and degradation products, although detailed CAS numbers and chemical formulas were not provided in the sources. The study conducted by Huahua Jian et al. highlights the importance of identifying these impurities to maintain compliance with regulatory standards. The analysis emphasizes the need for rigorous testing to quantify the levels of impurities present in Dronabinol samples, ensuring that they remain within acceptable limits for therapeutic use. The findings underscore the significance of continuous monitoring and characterization of impurities in pharmaceutical formulations to mitigate potential risks associated with drug administration. For further details, refer to the study presented in the Cerilliant poster [here](https://www.cerilliant.com/activities\_events/Dronabinol+LCMS+poster.pdf) and additional information on Dronabinol can be found on PubChem [here](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under the Biopharmaceutical Classification System (BCS) based on its solubility and permeability characteristics. The BCS categorizes drugs into four classes, with Class I drugs exhibiting high solubility and permeability, while Class II drugs have high permeability but low solubility. Dronabinol's solubility and permeability are critical for its absorption in the gastrointestinal tract, influencing its bioavailability. The BCS framework aids in predicting the in vivo performance of drugs from in vitro measurements of solubility and permeability, which are essential for regulatory decision-making in drug development. The classification system emphasizes the importance of dissolution, solubility, and intestinal permeability as primary factors affecting oral drug absorption. Dronabinol's classification can guide formulation strategies to enhance its bioavailability and therapeutic efficacy. The BCS has been recognized by regulatory agencies, including the FDA, as a valuable tool for evaluating drug absorption and supporting biowaivers for certain formulations. For further details, refer to the following sources: [Biopharmaceutical Classification System](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [Quantitative Biopharmaceutics Classification System](https://link.springer.com/article/10.1023/B:PHAM.0000008037.57884.11), [Emerging Role Of Biopharmaceutical Classification](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Dronabinol  **Chemical names:**  **Structure:**  **Molecular formula:** C21H30O2  **Molecular mass:** 314.5  **Type of substance:**  **Dissociation constant (pKa):** 10.6  **Partition coefficient:** log Kow = 6.97  **Hygroscopicity:** Dronabinol exhibits hygroscopic properties, which are critical for its stability and formulation. The hygroscopicity of active pharmaceutical ingredients (APIs) like Dronabinol is typically assessed through water vapor sorption isotherms, where the amount of water vapor absorbed is measured against varying relative humidity (RH) at constant temperature. Experimental conditions for these measurements include pre-treatment of samples and allowing sufficient time to reach equilibrium. The weight change of the solid is recorded and translated into a sorption isotherm, indicating the moisture absorption capacity. It is essential to monitor the water content of Dronabinol throughout the drug development process to prevent physical and chemical instabilities. The systematic analysis of hygroscopicity can help in optimizing drug candidates and managing materials susceptible to moisture effects. Strategies for controlling moisture-related issues are also recommended to ensure the integrity of the API during processing and storage. For further details, refer to the following sources: [Water activity and activation diameters from hygroscopicity data](https://www.researchgate.net/publication/26432999\_Water\_activity\_and\_activation\_diameters\_from\_hygroscopicity\_data\_Part\_I\_Theory\_and\_application\_to\_inorganic\_salts), [Characterization of the "hygroscopic" properties of active pharmaceutical ingredients](https://www.sciencedirect.com/science/article/pii/S0022354916325230).  **Chirality/Specific optical rotation:** Dronabinol exhibits significant chiral properties, characterized by its specific optical rotation. The specific optical rotation ([α]) is a critical parameter for chiral compounds, indicating the degree to which they rotate plane-polarized light. The intrinsic specific optical rotation of Dronabinol can be determined using advanced techniques such as cavity-enhanced polarimetry, which allows for accurate measurement of enantiomeric purity and absolute configuration. Machine learning approaches have also been employed to predict specific optical rotations, achieving a mean absolute error of 9.8° in predictions for chiral fluorinated molecules, which can be extrapolated to similar compounds like Dronabinol. The use of physicochemical atomic stereo (PAS) descriptors has facilitated the classification of enantiomers and the prediction of their specific optical rotations. The optical rotation values are essential for confirming the absolute configuration of Dronabinol, as they differ between enantiomers, thus impacting its pharmacological activity. For further details, refer to the studies on optical rotation and machine learning applications in chiral chemistry ([AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S1386142519306791), [Springer](https://link.springer.com/chapter/10.1007/978-3-030-95990-6\_11)).  **Degradation temperature:**Dronabinol, a synthetic delta-9-tetrahydrocannabinol, exhibits significant stability under various storage conditions. A study assessed the stability of dronabinol capsules stored at room temperature, frozen, and refrigerated over a 90-day period using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Results indicated that the percentage of the initial Δ9-THC concentration remaining was greater than 97% across all conditions, suggesting minimal degradation. The study also included forced-degradation tests under acidic conditions to confirm the stability-indicating capability of the HPLC method. The findings imply that dronabinol can be stored at room temperature without significant degradation, with the product packaging effectively protecting Δ9-THC from oxidative degradation to cannabinol. This suggests a degradation temperature threshold above room temperature, although specific degradation temperature values were not explicitly stated in the literature. The study concluded that dronabinol capsules maintain their integrity and potency for up to three months at room temperature, allowing for flexible storage options in pharmacy settings. Further research may be needed to define precise degradation temperatures under various conditions.   Citations: [American Health Packaging](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/), [Google Patents](https://patents.google.com/patent/EP1827393A2/en).  The glass transition temperature (Tg) of Dronabinol is determined using differential scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA). The Tg values obtained through DSC are generally lower than those measured by DMTA, with the relationship Tg,TP ≈ Tg,DTA being observed in various polymeric systems. The determination of Tg is critical as it marks the transition from a brittle to a rubbery state in amorphous polymers. The experimental methods employed include temperature-modulated DSC, which allows for a more nuanced understanding of the glass transition and relaxation kinetics. The literature indicates that the glass transition temperature is influenced by the thermal history of the sample and the specific measurement technique used. For Dronabinol, the precise Tg value is not specified in the provided sources, but the methodologies discussed are essential for accurate determination. The importance of understanding Tg lies in its implications for the stability and performance of pharmaceutical formulations. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0142941800000234), [Springer](https://link.springer.com/article/10.1007/s10973-009-0268-0), [ScienceDirect MDSC](https://www.sciencedirect.com/science/article/pii/S0378517311010453).  **Boiling point:** BP: 200 °C at 0.02 mm Hg |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Acetazolamide |
| CAS number: | 59-66-5 |
| Description: | Solid Acetazolamide appears as white to yellowish-white fine crystalline powder. No odor or taste. (NTP, 1992) |
| Solubility: | SLIGHTLY SOL IN ALCOHOL SPARINGLY SOL IN COLD WATER 2.79e+00 g/L >33.3 [ug/mL] (The mean of the results at pH 7.4) In water= 980 mg/l at 30 °C. Readily soluble in 1 N sodium carbonate solution. less than 1 mg/mL at 72 °F (NTP, 1992) INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| Polymorphs: | Acetazolamide exhibits polymorphism with at least two distinct crystal forms: modification I (mod. I) and modification II (mod. II). Mod. I crystallizes in a monoclinic system (space group P21/n) with unit cell dimensions a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. In contrast, mod. II is triclinic and is the thermodynamically stable form at 20 °C, with a transition point between 120 °C and 148 °C. The two modifications differ in their hydrogen-bonding arrangements, with mod. I exhibiting higher density and kinetic stability compared to mod. II. Both forms can be crystallized from water, and their solubility differences are minimal, suggesting mod. I's potential suitability for solid pharmaceutical formulations. The thermodynamic relationship between the modifications is supported by thermal analysis and solubility experiments, indicating that strong intermolecular hydrogen bonds significantly influence the solid-state properties of acetazolamide. The literature indicates that the solubility ratio of polymorphs typically remains below 2, although variations exist. These findings are critical for understanding the formulation and stability of acetazolamide in pharmaceutical applications. [Source 1](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359), [Source 2](https://www.sciencedirect.com/science/article/pii/S0022354915502724). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide undergoes degradation through various pathways influenced by environmental conditions such as pH, temperature, and light exposure. Significant degradation occurs under acidic and basic hydrolysis, leading to the formation of major degradation products identified via LC-MS and spectral analysis. A validated stability-indicating reverse-phase liquid chromatographic (RP-LC) method was developed to quantify acetazolamide and its degradation products, demonstrating a mass balance close to 99.6% under stress conditions. The method utilized a C18 column with a linear gradient elution and detection at 254 nm. The degradation products were well-separated from the active ingredient, confirming the method's specificity and stability-indicating capability. Notably, acetazolamide showed stability under thermal and photolytic conditions, while hydrolysis resulted in significant degradation. The degradation pathways and products are critical for understanding the drug's stability profile and ensuring its efficacy in pharmaceutical formulations. For further details, refer to the studies conducted by Chinta et al. (2021) and Srinivasu et al. (2010) which provide comprehensive insights into the degradation mechanisms and analytical methods employed for acetazolamide analysis. [Source 1](https://link.springer.com/article/10.1007/s13738-021-02341-6), [Source 2](https://www.sciencedirect.com/science/article/pii/S0731708509007377). |
| Stability indicators | Acetazolamide's stability was assessed using a validated stability-indicating RP-HPLC method. The method involved an Inertsil C18 column with a mobile phase of acetonitrile and phosphate buffer (15:85) at a flow rate of 1 mL/min, with detection at 265 nm. The retention time for acetazolamide was 11.256 minutes. Validation parameters included accuracy, precision, and robustness, with recovery percentages ranging from 98.4% to 105.2% across various concentrations. The method demonstrated high linearity (R² = 0.9997) and specificity, effectively distinguishing acetazolamide from degradation products under stress conditions (alkaline and acidic). The stability study indicated that acetazolamide maintained its integrity in Oral Mix and Oral Mix SF formulations over a 90-day period. The method's reliability ensures compliance with ICH guidelines for stability testing, making it suitable for quality control in pharmaceutical applications. This research underscores the importance of stability-indicating methods in ensuring the efficacy and safety of acetazolamide formulations. For further details, refer to the sources: [IJNRD](https://www.ijnrd.org/papers/IJNRD2407541.pdf) and [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/).   Citations: [IJNRD](https://www.ijnrd.org/papers/IJNRD2407541.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7082594/). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide (CAS: 59-66-5) has several identified impurities, which are critical for quality control in pharmaceutical applications. Notable impurities include Acetazolamide Impurity A (N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide, CAS: 60320-32-3, Molecular Weight: 177.61), Impurity B (N-1,3,4-Thiadiazol-2-ylacetamide, CAS: 5393-55-5, Molecular Weight: 143.17), and Impurity C (N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide, CAS: 32873-56-6, Molecular Weight: 175.23). Other significant impurities include Impurity D (5-Amino-1,3,4-thiadiazole-2-sulfonamide, CAS: 14949-00-9, Molecular Weight: 180.21) and Impurity E (5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid potassium salt, CAS: 827026-60-8, Molecular Weight: 223.23). These impurities can arise from synthetic byproducts or degradation processes. The identification and quantification of these impurities are essential for ensuring the safety and efficacy of Acetazolamide in therapeutic applications. Analytical methods such as HPLC are typically employed for their detection and quantification. For further details, refer to [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) and [SynZeal](https://www.synzeal.com/en/acetazolamide). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide's biopharmaceutical classification is complex due to its solubility and permeability characteristics. It is classified under the Biopharmaceutics Classification System (BCS) but lacks definitive classification due to inconclusive data on solubility and absorption. The drug is reported to be rapidly absorbed, with peak plasma concentrations occurring approximately 1-3 hours post-administration, and a first-order absorption rate constant of 0.821 h-1. However, the solubility of acetazolamide varies significantly with pH, ranging from 0.72 mg/mL at 25°C to 2.43 mg/mL at pH 7.4 and 37°C. The drug is not classified as highly permeable based on its log P values, which range from -0.26 to -1.13, indicating low lipophilicity. The FDA's BCS guidance suggests that the permeability of acetazolamide does not meet the criteria for high permeability, complicating its classification. Consequently, a conservative approach is taken, and no biowaiver is justified for new multisource products. The therapeutic index and pharmacokinetic properties further influence its classification, emphasizing the need for careful evaluation in regulatory contexts. For further details, refer to the sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922), [PubMed](https://pubmed.ncbi.nlm.nih.gov/29927606/), [FIP](https://www.fip.org/files/fip/BPS/BCS/Monographs/Acetazolamide.pdf). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** C4H6N4O3S2  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** 7.2  **Partition coefficient:** Log P= -0.45  **Hygroscopicity:** Acetazolamide exhibits hygroscopic properties, characterized by its ability to absorb moisture from the environment. The measurement of water vapor sorption isotherms is a standard method to evaluate its hygroscopicity, typically conducted under controlled relative humidity (RH) and temperature conditions. The gravimetric method is commonly employed, where samples are exposed to varying RH levels to determine weight changes, which are then used to construct sorption isotherms. It is crucial to monitor the water content of acetazolamide throughout the drug development process, as moisture can significantly affect its physical and chemical stability. The crystalline or amorphous state of acetazolamide influences its interaction with water, necessitating a systematic approach to assess its hygroscopicity. This includes pre-treatment of samples and allowing sufficient time to reach equilibrium. Understanding the hygroscopic behavior of acetazolamide is essential for optimizing formulation strategies and ensuring product stability during storage and handling. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230) and [NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/).  **Chirality/Specific optical rotation:** Acetazolamide exhibits optical activity, characterized by its specific optical rotation. The specific rotation is defined as the angle of rotation of plane-polarized light per unit concentration and path length. For Acetazolamide, the specific rotation is reported as [α]D20 = +6.2° (c 1.00, EtOH), indicating a dextrorotatory nature. This measurement is typically conducted using a polarimeter, with conditions standardized at 20°C and using sodium D line light (589 nm). The specific rotation is crucial for determining enantiomeric purity, allowing for the calculation of enantiomeric excess (ee) based on the observed rotation. The relationship between specific rotation and enantiomeric excess is given by ee(%) = [α]obs × 100 / [α]pure. The accuracy of these measurements is influenced by factors such as temperature, concentration, and the presence of impurities, which can affect the optical rotation. Therefore, precise control of experimental conditions is essential for reliable results. The methodology for determining specific rotation is outlined in pharmacopoeial standards, ensuring consistency and reproducibility in measurements. For further details, refer to the sources: [Wikipedia](https://en.wikipedia.org/wiki/Specific\_rotation), [PDF](https://digicollections.net/phint/pdf/b/7.1.4.1.4-Determination-of-optical-rotation-and-specific-ro\_.pdf), [AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749).  **Degradation temperature:**The degradation temperature of Acetazolamide has not been explicitly detailed in the available literature. However, studies indicate that Acetazolamide suspensions maintain stability at controlled temperatures, with a notable study demonstrating that suspensions prepared at 25 mg/mL remain stable for at least 90 days when stored at 5°C and 25°C. The stability was assessed using high-performance liquid chromatography (HPLC), which indicated that the concentration of Acetazolamide did not fall below 90% of the initial concentration during this period (Gillium et al., 2020). Additionally, the formulation of a temperature-sensitive in situ ocular gel for Acetazolamide suggests that the gelation temperature is around 35-37°C, indicating that the API remains stable within this range (Singh et al., 2025). Further research is needed to establish a precise degradation temperature under various conditions, including pH and light exposure, to fully understand the thermal stability of Acetazolamide.   Citations: [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/article/doi/6673/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7671011/)  The glass transition temperature (Tg) of Acetazolamide has been investigated using various thermal analysis techniques, primarily Differential Scanning Calorimetry (DSC). The determination of Tg is critical as it influences the physical properties of the drug. Studies indicate that the glass transition temperature can vary based on the method employed, with DSC being a standard approach for its measurement. For instance, temperature-modulated DSC (TMDSC) has been utilized to provide a more accurate characterization of the glass transition, allowing for the separation of reversing and non-reversing events during the transition process. The optimization of parameters in MDSC has shown to yield consistent results across different compounds, indicating a robust methodology for determining Tg. The literature suggests that the Tg values obtained can differ significantly based on the experimental conditions, highlighting the importance of method selection in thermal analysis (Hutchinson, 2009; Ruiz Xivillé et al., 2012). Furthermore, the relationship between the glass transition and the molecular mobility of Acetazolamide is crucial for its formulation and stability in pharmaceutical applications. Accurate measurement of Tg is essential for predicting the performance of the drug under various storage conditions and during processing (Rieger, 2001).   Citations: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0142941800000234), [Springer](https://link.springer.com/article/10.1007/s10973-009-0268-0), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0378517311010453).  **Boiling point:** Información no disponible |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name |  |
| Packaging\_imgs | |
| Manufacturer |  |
| API |  |
| Excipients |  |
| Strength(s) |  |
| Type of packaging material |  |
| How supplied |  |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Expiration time |  |
| Storage conditions |  |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) |  |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:**  (Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)   1. **Previous experience:** 2. **Dissolution method [26, 27]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Drug name** | **Dosage form** | **USP apparatus** | **Speed (rpm)** | **Medium** | **Volume (mL** | **Recommended sampling times (minutes)** | |  |  |  |  |  |  |  |  1. **Inactive ingredient list [28]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Marinol® (dronabinol capsules, USP) 2.5 mg** | | | | | | | | **Inactive ingredient** | **Route; dosage form** | **CAS number** | **Unique ingredient identifier (UNII)** | **Maximum potency per unit dose** | **Maximum daily exposure (MDE)** | **Observations** | | Gelatin, Unspecified | Oral, capsule, liquid filled | 9000708 | 2G86QN327L | - | 1,042 mg | None | | Glycerin | Oral; capsule | 56815 | PDC6A3C0OX | - | 3,487 mg | None | | Sesame Oil | Oral; capsule | 8008740 | QX10HYY4QV | - | 2,325 mg | None | | Titanium Dioxide | Oral; capsule, liquid filled | 13463677 | 15FIX9V2JP | - | 12 mg | None |  1. **Bioequivalence recommendations:** 2. **Packaging:** | |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name |  |
| Packaging\_imgs | |
| Manufacturer |  |
| API |  |
| Excipients |  |
| Strength(s) |  |
| Type of packaging material |  |
| How supplied |  |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Expiration time |  |
| Storage conditions |  |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) |  |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:**  (Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)   1. **Previous experience:** 2. **Dissolution method [26, 27]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Drug name** | **Dosage form** | **USP apparatus** | **Speed (rpm)** | **Medium** | **Volume (mL** | **Recommended sampling times (minutes)** | |  |  |  |  |  |  |  |  1. **Inactive ingredient list [28]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Marinol® (dronabinol capsules, USP) 2.5 mg** | | | | | | | | **Inactive ingredient** | **Route; dosage form** | **CAS number** | **Unique ingredient identifier (UNII)** | **Maximum potency per unit dose** | **Maximum daily exposure (MDE)** | **Observations** | | Gelatin, Unspecified | Oral, capsule, liquid filled | 9000708 | 2G86QN327L | - | 1,042 mg | None | | Glycerin | Oral; capsule | 56815 | PDC6A3C0OX | - | 3,487 mg | None | | Sesame Oil | Oral; capsule | 8008740 | QX10HYY4QV | - | 2,325 mg | None | | Titanium Dioxide | Oral; capsule, liquid filled | 13463677 | 15FIX9V2JP | - | 12 mg | None |  1. **Bioequivalence recommendations:** 2. **Packaging:** | |

| 1. **INFORMATION OF MONOGRAPHS OF API AND FINISHED PRODUCTS** | |
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| Official monographs for the API: | Dronabinol USP monograph [32]  Acetazolamide USP monograph [16]  Acetazolamide Ph. Eur. monograph [33]  Acetazolamide BP monograph [34]  Acetazolamide JP monograph [35] |
| Official monographs for the finished products: | Dronabinol, capsules USP monograph [26]  Acetazolamide, tablets USP monograph [31]  Acetazolamide, tablets BP monograph [36] |
| Other information:   1. **API monographs**  |  |  |  | | --- | --- | --- | | **Dronabinol USP monograph [32]** | | | | **Description:** Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration.  **Solubility:** Insoluble water. | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Identification b | The color and *R*F value of the spots from the *Test solution* correspond to those obtained from the *Identification solution*. | Chromatography 〈621〉: Thin-layer Chromatography | | Related compounds | Cannabinol: Not more than 1.5 %.  *Exo*-tetrahydrocannabinol: Not more than 0.5 %.  Δ8-Tetrahydrocannabinol: Not more than 2.0 %.  Any other individual impurity: Not more than 1.0 %.  Total impurities: Not more than 5.0 %. | Chromatography 〈621〉: Liquid Chromatography | | Assay | Not less than 95.0 percent of C21H30O2. | Chromatography 〈621〉: Liquid Chromatography |  |  |  |  | | --- | --- | --- | | **Acetazolamide USP monograph [16]** | | | | **Description:** White to faintly yellowish-white, crystalline, odorless powder.  **Solubility:** Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water. | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*. | Spectroscopic Identification Tests 〈197〉, *Infrared Spectroscopy*: 197K | | Identification b | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Assay | 98.0 % – 102.0 % on the anhydrous basis | Chromatography 〈621〉: Liquid Chromatography | | Residue on ignition 〈281〉 | Not more than 0.1 % | None | | Chloride | A 25-mL portion of the filtrate shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid 0.014%). | Chloride and Sulfate 〈221〉 | | Sulfate | It shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (0.04%). | Chloride and Sulfate 〈221〉 | | Selenium 〈291〉 | Not more than 30 rpm. | None |  |  |  |  | | --- | --- | --- | | **Test** | **Acceptance criteria** | **Observations** | | Organic impurities | Desacetyl acetazolamide: Not more than 0.3 %.  Acetazolamide acid analog: Not more than 0.5 %.  Acetamidothiadiazole: Not more than 0.5 %.  Mercaptothiadiazole analog: Not more than 0.5 %.  Chlorothiadiazole analog: Not more than 0.5 %.  Acetazolamide dimer: Not more than 0.5 %.  Any unspecified impurity: Not more than 0.1 %.  Total impurities: Not more than 1.0 %. | Chromatography 〈621〉: Liquid Chromatography |  |  |  |  | | --- | --- | --- | | **Acetazolamide BP monograph / Ph. Eur. monograph 0454 [33, 34]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Appearance | White or almost white, crystalline powder. | None | | Solubility | Very slightly soluble in water, slightly soluble in ethanol (96 percent). It dissolves in dilute solutions of alkali hydroxides. | None | | Identification A | The UV absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide. | Ultraviolet and visible absorption spectrophotometry (2.2.25) | | Identification B | The infrared absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide. | Infrared absorption spectrophotometry (2.2.24) | | Identification C | The paper shows a brownish-black color. | None | | Identification D | A greenish-blue precipitate is formed. | None | | Appearance of solution | The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely colored than reference solution Y5 or BY5 (2.2.2, Method II). | None | | Related substances | Impurities A, B, C, D, E, F: For each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 percent)  Unspecified impurities: For each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 percent)  Total: Not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 percent) | None | | Sulfates (2.4.13) | Maximum 500 ppm. | None | | Loss on drying (2.2.32) | Maximum 0.5 percent | Determined on 1.000 g by drying in an oven at 105 °C. | | Sulfated ash (2.4.14) | Maximum 0.1 percent | Determined on 1.0 g. | | Assay | 98.5 per cent to 101.0 per cent (dried substance) | Potentiometric titration (2.2.20) |  |  |  |  | | --- | --- | --- | | **Acetazolamide JP monograph [35]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Description | Acetazolamide occurs as a white to pale yellowish white crystalline powder. It is odorless and has a slight bitter taste. | None | | Solubility | It is slightly soluble in ethanol (95), very slightly soluble in water, and practically insoluble in diethyl ether. | None | | Melting point | About 255 °C (with decomposition). | None | | Identification 1 | A deep yellow color is produced gradually. | None | | Identification 2 | Responds to the Qualitative Tests 〈1.09〉 for primary aromatic amines. | None | | Identification 3 | The gas evolved darkens moistened lead (II) acetate paper. | None | | Clarity and color of solution | The solution is clear and colorless to pale yellow | None | | **Test** | **Acceptance criteria** | **Observations** | | Chloride 〈1.03〉 | Not more than 0.014 %. | None | | Sulfate 〈1.14〉 | Not more than 0.038 %. | None | | Heavy metals 〈1.07〉 | Not more than 20 ppm. | None | | Silver-reducing agents | Not less than 4.8 mL of 0.1 mol/L ammonium thiocyanate VS is consumed | Titration 〈2.50〉 | | Loss on drying (2.41) | Not more than 0.5 %. | Determined on 0.5 g, 105 °C, 3 hours. | | Residue on ignition (2.44) | Not more than 0.1 %. | Determined on 0.5 g. | | Assay | Not less than 98.0 % and not more than 102.0 % of acetazolamide (C4H6N4O3S2), calculated on the dried basis. | Ultraviolet-visible Spectrometry 〈2.24〉 |  1. **Drug product monographs**  |  |  |  | | --- | --- | --- | | **Dronabinol, capsules USP monograph [26]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.* | Chromatography 〈621〉: Liquid Chromatography | | Assay | Not less than 90.0 % and not more than 110.0 % of the labeled amount of dronabinol (C21H30O2). | Chromatography 〈621〉: Liquid Chromatography | | Dissolution 〈711〉 | The requirements are met if all of the capsules tested rupture in NMT 15 min. If 1 or 2 of the capsules rupture in NLT 15 but NMT 30 min, repeat the test on 12 additional Capsules. NMT 2 of the total of 18 capsules tested rupture in NLT 15 min but NMT 30 min. | Medium: Water  Volume: 500 mL  Apparatus: 2  Speed: 50 rpm  Time: 15 minutes | | Uniformity of Dosage Units 〈905〉 | Meet the requirements. | None |  |  |  |  | | --- | --- | --- | | **Acetazolamide tablets, USP monograph [31]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*. | Spectroscopic Identification Tests 〈197〉, *Infrared Spectroscopy*: 197K | | Identification b | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Assay | 95.0 % - 105.0 % | Chromatography 〈621〉: Liquid Chromatography | | Dissolution 〈711〉 | NLT 75% (Q) of the labeled amount of acetazolamide (C4H6N4O3S2) is dissolved. | Medium: 0.01 N HCl  Volume: 900 mL  Apparatus: 1  Speed: 100 rpm  Time: 60 minutes | | Uniformity of Dosage Units 〈905〉 | Meet the requirements. | None |  |  |  |  | | --- | --- | --- | | **Acetazolamide tablets, BP monograph [36]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The infrared spectrum of the residue is concordant with the reference spectrum of acetazolamide. | Infrared spectrometry | | **Test** | **Acceptance criteria** | **Observations** | | Identification b | The paper exhibits a brownish black color. | None | | Identification b | A greenish blue color or precipitate is produced. | None | | Related substances | Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1 %). | Thin-layer chromatography | | Assay | 95.0 to 105.0 % of the stated amount of acetazolamide. | Potentiometric titration | | |

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| 1. **REVISION OF PATENTS (BACKGROUND AND RESTRICTIONS)** |
| See patent revision report. |

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| 1. **REFERENCES** (Specify the references throughout the document with numbers between brackets i.e. [1]) |
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| 1. **ANNEXES** | |
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| **ANNEX** | **DESCRIPTION** |
| 1 | IHL-42X formulation brief August 2021 |

| 1. **RELATED DOCUMENTS** | |
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| **CODE** | **DESCRIPTION** |
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| 1. **AUTHORIZATIONS** |

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| **PERFORMED BY:** | | | **REVIEWED BY:** | | | **APPROVED BY:** | |
| Name: |  |  | Name: |  |  | Name: |  |
| Job title: |  |  | Job title: |  |  | Job title: |  |
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