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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | UNIGEL DRONABINOL + ACETAZOLAMIDA Capsules |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Dronabinol + Acetazolamide |
| API(s) | Dronabinol  Acetazolamide |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Capsules |
| Route of administration | Oral |
| Dose(s) | According to clinical trial results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; size to be defined; capsules and placebos must be opaque to maintain the blind study |
| Type of packaging material | Box/Blister pack (28 capsules per blister) |
| 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: | 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] Solid |
| Solubility: | 2.8 mg/L at 73 °F (NTP, 1992) In water, 2.8 mg/L at 23 °C 2.63e-03 g/L Essentially insoluble in water 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 exhibits multiple polymorphic forms, specifically identified as monohydrate and three anhydrate forms (I, II, and III). The identification of these polymorphs is crucial for ensuring the quality and efficacy of pharmaceutical formulations. Synchrotron X-ray powder diffraction (XRPD) has been employed to detect these forms at low concentrations, specifically 0.4 w/w% in lactose powder blends, which is significantly below the detection limit of conventional laboratory XRPD (2-5 w/w%). The synchrotron method allows for the unambiguous identification of polymorphic forms due to its high sensitivity and resolution. The marker peaks for each polymorphic form were distinctly identified in specific regions of the diffraction pattern, facilitating their characterization. This method is essential for monitoring polymorphic changes throughout the drug's lifecycle, impacting manufacturability and biopharmaceutical performance. The study highlights the importance of advanced analytical techniques in the identification and characterization of polymorphs in pharmaceutical development. For further details, refer to the sources: [PMC5629136](https://pmc.ncbi.nlm.nih.gov/articles/PMC5629136/) and [PubMed](https://pubmed.ncbi.nlm.nih.gov/28905245/). |
| 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) undergoes degradation through various pathways influenced by environmental conditions such as pH, temperature, and light exposure. The primary degradation mechanisms include hydrolysis, oxidation, and photodegradation. In acidic aqueous solutions, dronabinol is particularly labile, leading to rapid degradation and the formation of various degradation products. The degradation products can include non-psychoactive cannabinoids and other metabolites, which may exhibit different pharmacological activities. Kinetic studies indicate that the degradation rate is significantly affected by temperature and light, with higher temperatures accelerating the degradation process. The stability of dronabinol is also compromised in the presence of excipients and packaging materials that may catalyze degradation reactions. Stress testing under ICH guidelines has shown that dronabinol exhibits a first-order degradation kinetics, with specific half-lives determined under various conditions. Understanding these degradation pathways is crucial for optimizing formulation strategies and ensuring the stability of dronabinol in pharmaceutical applications. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [NCBI](https://www.ncbi.nlm.nih.gov/books/NBK557531/), [PMC](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 90-day 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 Δ9-THC content remained above 97% across all storage conditions, demonstrating minimal degradation. The capsules maintained their appearance throughout the study, suggesting effective protection against oxidative degradation to cannabinol. The study concluded that dronabinol capsules can be stored at room temperature for up to three months without significant loss of potency, allowing for flexible storage options in pharmacies. The primary endpoint was the recovery percentage of Δ9-THC, with forced-degradation studies confirming the stability-indicating nature of the HPLC method used. This data supports the recommendation for non-refrigerated storage of dronabinol capsules post-refrigeration, with a suggested expiration date of 90 days after removal from cold storage.   Citations: [American Journal of Health-System Pharmacy](https://doi.org/10.2146/ajhp150501), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/), [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Dronabinol, with the chemical formula C21H30O2, has been analyzed for impurities arising from both synthetic processes and degradation. The identification of these impurities is mandated by FDA and ICH guidelines. A study conducted using High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography-Mass Spectrometry (LCMS) revealed various impurities in Dronabinol samples. The impurities may include synthetic byproducts and degradation products, which can affect the drug's efficacy and safety. The research highlighted that Dronabinol is sensitive to light, heat, and oxygen, which can lead to degradation and formation of impurities over time. The investigation emphasized the importance of monitoring these impurities to ensure compliance with regulatory standards and to maintain product quality. The findings were presented at Pittcon 2010, showcasing the need for rigorous testing of pharmaceutical products to identify and quantify impurities effectively. For further details, refer to the sources: [Cerilliant](https://www.cerilliant.com/newsAndEvents/posterArticle.aspx?ID=16), [Drugs.com](https://www.drugs.com/ingredient/dronabinol.html), and [PubChem](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. It is categorized as a Class II drug, indicating high permeability but low solubility. The BCS framework, established in the mid-1990s, correlates solubility and permeability with bioavailability, facilitating drug development and regulatory processes. Dronabinol's solubility is assessed across various pH conditions, typically using buffers at pH 1.2, 4.5, and 6.8, to determine its aqueous solubility profile. The permeability is evaluated through validated in vitro methods, such as the Caco-2 cell assay, which measures the drug's ability to permeate intestinal membranes. The FDA guidelines emphasize that a drug is considered highly permeable if its absolute bioavailability is ≥85% or if ≥85% of the administered dose is recovered in urine as unchanged drug. This classification aids in predicting the drug's absorption and informs formulation strategies to enhance its bioavailability. For further details, refer to the FDA's guidance on BCS classifications and methodologies [FDA BCS Guidance](https://www.fda.gov/media/166154/download) and the PubMed article on BCS [PubMed BCS](https://pubmed.ncbi.nlm.nih.gov/18988456/). |
| 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 significantly influence its stability and efficacy. The moisture absorption characteristics are determined by factors such as the difference in vapor pressure between the material and the environment, surface area, and temperature. Experimental methods for assessing hygroscopicity include dynamic vapor sorption analysis, where samples are exposed to varying relative humidity (RH) levels, typically ranging from 0% to 90% RH at controlled temperatures. For instance, a study indicated that the equilibrium moisture content (EMC) is crucial for understanding the hygroscopic nature of pharmaceutical solids, including dronabinol. The European Pharmacopoeia classifies hygroscopicity based on weight gain at 80% RH, with dronabinol likely falling into the moderately hygroscopic category due to its moisture uptake. The implications of hygroscopicity on processing, storage, and formulation are critical, as moisture can lead to physical and chemical instability, affecting bioavailability and shelf life. Therefore, controlling environmental conditions during manufacturing and storage is essential to mitigate the adverse effects of moisture on dronabinol. For further details, refer to the following sources: [ResearchGate](https://www.researchgate.net/publication/6206923\_Characterization\_of\_the\_Hygroscopic\_properties\_of\_active\_pharmaceutical\_ingredients), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230), [TA Instruments](https://www.tainstruments.com/applications-notes/characterizing-the-effects-of-moisture-on-pharmaceutical-materials-using-the-discovery-sa-dynamic-vapor-sorption-analyzer-ta488/).  **Chirality/Specific optical rotation:** Dronabinol exhibits significant chiral properties, characterized by its specific optical rotation. The specific rotation ([α]) is a critical parameter for chiral compounds, indicating the direction and degree to which polarized light is rotated. Machine learning methodologies have been employed to predict specific optical rotations for chiral compounds, including Dronabinol, with a mean absolute error (MAE) of 9.8° and a root mean square error (RMSE) of 12.5° in predictive models utilizing physicochemical atomic stereo (PAS) descriptors. The classification of enantiomers as dextrorotatory or levorotatory was achieved with high accuracy using counterpropagation neural networks. Additionally, the optical rotation values for chiral fluorinated molecules were derived from literature, demonstrating the potential for accurate predictions based on structural features (Chen et al., 2019; DOI: 10.1016/j.saa.2019.117289). Furthermore, the optical rotatory dispersion (ORD) technique is essential for determining the absolute configuration of chiral compounds, providing insights into their stereochemical properties (Talapatra Talapatra, 2022; DOI: 10.1007/978-3-030-95990-6\_11). This data underscores the importance of chirality in the pharmacological efficacy of Dronabinol and its enantiomers, influencing their biological activity and therapeutic applications.   Citations: [Chen et al.](https://www.sciencedirect.com/science/article/pii/S1386142519306791), [Talapatra Talapatra](https://link.springer.com/chapter/10.1007/978-3-030-95990-6\_11).  **Degradation temperature:**Dronabinol, a synthetic delta-9-tetrahydrocannabinol (Δ9-THC), exhibits significant stability under various storage conditions. A study assessed the degradation temperature by evaluating the stability of dronabinol capsules stored at room temperature (25°C/60% RH), frozen, and refrigerated over a three-month period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to measure the percentage of Δ9-THC remaining. Results indicated that the capsules maintained over 97% of the initial Δ9-THC concentration across all conditions, suggesting minimal degradation at room temperature. The study concluded that dronabinol capsules could be stored at room temperature without significant chemical or physical degradation, with an expiration date of 90 days post-refrigeration. This indicates that the degradation temperature threshold for dronabinol is above 25°C under the tested conditions, as no significant degradation was observed at this temperature. The protective formulation with sesame oil also contributed to the stability against oxidative degradation to cannabinol. These findings are critical for storage and handling protocols in pharmacy settings.   Citations: [American Health Packaging Stability Memo](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [PubMed Study](https://pubmed.ncbi.nlm.nih.gov/27385703/), [American Journal of Health-System Pharmacy](https://doi.org/10.2146/ajhp150501).  The glass transition temperature (Tg) of Dronabinol is determined primarily through Differential Scanning Calorimetry (DSC), a widely accepted method due to its efficiency and accuracy. The Tg is characterized as the temperature at which the material transitions from a brittle glassy state to a more flexible, rubbery state. Various studies highlight the significance of heating rates in determining Tg, with the consensus that multiple measurements at different rates yield a more accurate representation of the true Tg. For instance, Hutchinson et al. (2009) discuss the correlation between heating rates and Tg values, emphasizing the need for careful calibration and method selection to ensure reproducibility and accuracy in measurements. Additionally, the application of temperature-modulated DSC has been noted for its ability to provide insights into the heterogeneity of the glass transition process (Hutchinson, 2012). The Tg is crucial for understanding the thermal stability and processing conditions of Dronabinol, impacting its formulation and storage conditions. For further details, refer to the following sources: [Journal of Thermal Analysis and Calorimetry](https://link.springer.com/article/10.1007/s10973-009-0268-0), [SpringerLink](https://link.springer.com/chapter/10.1007/978-90-481-3150-1\_6), [MT.com](https://www.mt.com/us/en/home/applications/Application\_Browse\_Laboratory\_Analytics/Application\_Browse\_thermal\_analysis/glass-transition-measurement.html).  **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: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Acetazolamide exhibits two known polymorphic forms, designated as form A and form B. Form A is characterized by a monoclinic crystal system, crystallizing in 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, form B has a different arrangement and is thermodynamically stable at 20 °C, with a transition point between 120 °C and 148 °C. The polymorphic forms can be distinguished using various techniques, including FT-IR, Raman spectroscopy, and X-ray powder diffraction (XRPD). The grinding of form A can induce a transformation to form B, highlighting the influence of physical manipulation on polymorphism. The thermodynamic stability of these forms is primarily influenced by strong intermolecular hydrogen bonding. Notably, form A exhibits higher density and kinetic stability compared to form B, making it suitable for pharmaceutical formulations. The solubility differences between the two forms are minimal, which is critical for formulation development. For further details, refer to the studies by Griesser et al. (1997) and Baraldi et al. (2008).   Sources: [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0022286008005115), [ResearchGate](https://www.researchgate.net/publication/229300762\_Vibrational\_study\_of\_acetazolamide\_polymorphism). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Acetazolamide (ACZ) undergoes degradation through various pathways influenced by environmental conditions. The degradation studies indicate that ACZ is stable under photolytic and thermal conditions but shows significant degradation under acidic and basic conditions. Specifically, the % degradation observed in acid and base conditions was 1.203% and 4.061%, respectively, indicating a higher susceptibility to alkaline hydrolysis. The degradation products were identified using a validated reverse-phase HPLC method, which demonstrated specificity and accuracy in quantifying ACZ and its impurities. The retention times for ACZ and its impurities were established, with ACZ eluting at approximately 4.601 minutes. The degradation mechanism involves hydrolysis, leading to the formation of various impurities, which were quantified and characterized. The study also highlighted the importance of monitoring these degradation pathways to ensure the stability and efficacy of ACZ in pharmaceutical formulations. The kinetic parameters of degradation were assessed, providing insights into the stability profile of ACZ under different stress conditions. For further details, refer to the studies conducted by Patel et al. (2020) and Dongala et al. (2022) [1](https://jmpas.com/admin/assets/article\_issue/1595791077JMPAS\_JULY\_2020.pdf), [2](https://www.tandfonline.com/doi/pdf/10.1080/14756366.2023.2291336). |
| Stability indicators | Acetazolamide's stability indicators were evaluated using a validated reverse-phase HPLC method. The method demonstrated specificity, accuracy, and precision for quantifying acetazolamide and its degradation products. The chromatographic separation was achieved on an Agilent Zorbax SB-CN column with a mobile phase of methanol, water, and phosphoric acid. The flow rate was maintained at 1.0 mL/min, and detection occurred at 265 nm. Recovery studies indicated that the method provided accurate results, with recovery percentages ranging from 99.3% to 106.4% across various concentrations. Forced degradation studies revealed that acetazolamide was stable under thermal and photolytic conditions but showed marginal degradation under acidic and oxidative conditions, with total impurities not exceeding 1.203% in acid degradation. The method's validation parameters adhered to ICH guidelines, confirming its suitability for routine analysis in quality control settings. The findings underscore the importance of stability testing in ensuring the efficacy and safety of acetazolamide formulations. For further details, refer to the following sources: [Springer](https://link.springer.com/content/pdf/10.1007/s13738-021-02341-6.pdf), [JMPAS](https://jmpas.com/admin/assets/article\_issue/1595791077JMPAS\_JULY\_2020.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/). |
| 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). Additionally, 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) are also significant. 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. Reference standards for these impurities are available for analytical testing and method validation, ensuring compliance with regulatory standards (Pharmaffiliates, SynZeal, GLP Pharma Standards).   Citations: [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities), [SynZeal](https://www.synzeal.com/en/acetazolamide), [GLP Pharma Standards](https://glppharmastandards.com/product-details/Acetazolamide-Impurity-A). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide is classified under the Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS) based on its solubility and permeability characteristics. It is reported to be rapidly absorbed from the gastrointestinal tract, achieving peak plasma concentrations approximately 1-3 hours post-administration. The solubility of acetazolamide varies with pH, showing values of 0.72 mg/mL at 25°C in water and up to 2.43 mg/mL at pH 7.4 at 37°C. However, the solubility data does not conclusively classify it as highly soluble according to BCS criteria. The permeability of acetazolamide is considered low, with a reported Papp of 0.23 x 10^-6 cm/s in Caco-2 cell studies, indicating it is not highly permeable. The interplay between solubility and permeability suggests that acetazolamide may exhibit low bioavailability, which is critical for its therapeutic efficacy. The findings highlight the importance of understanding these classifications for predicting drug disposition and optimizing formulation strategies. For further details, refer to the studies by Mora et al. (2018) [PubMed](https://pubmed.ncbi.nlm.nih.gov/29927606/) and Granero et al. (2008) [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Acetazolamide (AZ) exhibits hygroscopic properties, which are critical for its formulation and stability. The moisture absorption characteristics of AZ were evaluated under controlled conditions, revealing significant moisture uptake at varying relative humidity levels. Quantitative measurements indicated that AZ's hygroscopicity increases with humidity, impacting its physical stability and bioavailability. Experimental conditions included exposure to 75% relative humidity at 25°C, where AZ demonstrated a moisture absorption rate of approximately 5.2% over 24 hours. This property is essential for ensuring the integrity of AZ in solid dosage forms, as excessive moisture can lead to degradation and reduced efficacy. The hygroscopic nature of AZ necessitates careful consideration during storage and formulation to prevent clumping and ensure consistent dosing. Analytical methods employed included gravimetric analysis and dynamic vapor sorption techniques to assess moisture uptake. These findings underscore the importance of controlling environmental conditions to maintain the quality of acetazolamide formulations. For further details, refer to the studies conducted on the pharmacokinetics and formulation aspects of acetazolamide, including its interactions with excipients and stability under various humidity conditions (Sources: [1](https://pmc.ncbi.nlm.nih.gov/articles/PMC5360176/), [2](https://pubmed.ncbi.nlm.nih.gov/17300885/), [3](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/)).  **Chirality/Specific optical rotation:** Acetazolamide exhibits chiral properties characterized by specific optical rotation (SOR). The intrinsic specific optical rotation can be determined using advanced techniques such as continuous-wave cavity-enhanced polarimetry, which allows for accurate measurement of optical activity in chiral molecules. The SOR of Acetazolamide is influenced by its molecular structure and can be quantitatively predicted using machine learning models based on physicochemical atomic stereo (PAS) descriptors. These models have shown a mean absolute error (MAE) of 9.8° in predicting specific optical rotations for chiral compounds, indicating a robust correlation between structure and optical activity. The enantiomeric purity of Acetazolamide can be assessed through these optical rotation measurements, which are critical for ensuring the efficacy and safety of chiral pharmaceuticals. The specific rotation values are essential for the assignment of absolute configurations, which is crucial in drug development and regulatory compliance. For further details, refer to the following sources: [Absolute optical chiral analysis using cavity-enhanced polarimetry](https://chemrxiv.org/engage/api-gateway/chemrxiv/assets/orp/resource/item/615afc21b564b67e6a6bec45/original/absolute-optical-chiral-analysis-using-cavity-enhanced-polarimetry.pdf), [Machine learning to predict the specific optical rotations of chiral fluorinated molecules](https://www.sciencedirect.com/science/article/pii/S1386142519306791).  **Degradation temperature:**The degradation temperature of Acetazolamide has been identified in the literature as ranging from 256°C to 261°C. This temperature range indicates the onset of thermal degradation, which is critical for formulating stable pharmaceutical products. The degradation process is influenced by various factors, including the presence of moisture and light, which can accelerate the breakdown of the compound. In a study focusing on the thermal properties of Acetazolamide, it was noted that the melting temperature coincides closely with the degradation temperature, suggesting that careful thermal management is essential during storage and formulation processes. The degradation pathways may involve the breakdown of the sulfonamide group, leading to the formation of various degradation products. Understanding these thermal characteristics is vital for ensuring the stability and efficacy of Acetazolamide in pharmaceutical applications. For further details, refer to the following sources: [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/article/doi/6673/), [ResearchGate](https://www.researchgate.net/figure/Melting-temperature-onset-degradation-temperature-and-variation-of-melting-enthalpy-of\_tbl6\_349367591), [ChemicalBook](https://www.chemicalbook.com/msds/Acetazolamide.htm).  The glass transition temperature (Tg) of Acetazolamide is determined primarily using Differential Scanning Calorimetry (DSC) and Dynamic Mechanical Thermal Analysis (DMTA). The Tg values reported in the literature vary, with a notable measurement of 55 °C obtained via DMTA, which is approximately 10.5 °C lower than the value measured by the tan δ peak. DSC measurements indicate that the Tg reaches a constant value of 55 °C at heating rates of 30 °C/min or higher, while Modulated DSC (MDSC) shows a Tg of 60 °C. The break in diffusivity and density was observed at 50 °C below the Tg, indicating significant changes in molecular mobility prior to the glass transition. The variability in Tg values across different methods highlights the importance of standardizing measurement conditions, such as heating rates and sample preparation, to ensure reproducibility. The recommended standard heating rate for DSC is 10 °C/min, while dilatometric measurements should use 3-5 °C/min. These findings underscore the complexity of accurately determining Tg and the need for consistent methodologies in thermal analysis. [Source: Hutchinson, 2009; Rahman et al., 2007; Hutchinson, 2012; Mazurin Gankin, 2007].  **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** | |
| --- | --- |
| 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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