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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Unigel Dronabinol + Acetazolamide 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 (Unigel) |
| Route of administration | Oral |
| Dose(s) | According to clinical study outcomes |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos to be opaque; size and color to be defined at development |
| Type of packaging material | Box/Blister pack containing 28 capsules |
| 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 Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) |
| Solubility: | Essentially insoluble in water 2.8 mg/L at 73 °F (NTP, 1992) 2.63e-03 g/L In water, 2.8 mg/L at 23 °C 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. The study highlights the importance of controlling polymorphic forms during the drug development process to maintain drug stability and performance. The findings underscore the potential of synchrotron XRPD as a reliable analytical tool for polymorphic identification in pharmaceutical applications. For further details, refer to the following sources: [PMC5629136](https://pmc.ncbi.nlm.nih.gov/articles/PMC5629136/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/28905245/), [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0169409X16303209). |
| Stability (Solid state/solution, general information): | 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. Readily degraded in acid solutions. |
| 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 the initial Δ9-THC concentration remaining at multiple time points. Results indicated that over the study duration, the Δ9-THC content remained above 97% across all storage conditions, demonstrating minimal degradation. The capsules maintained their appearance, suggesting effective protection against oxidative degradation to cannabinol due to the formulation and packaging. This stability data supports the recommendation for pharmacies to store dronabinol capsules at room temperature for up to three months post-refrigeration without compromising quality. The study also included forced-degradation tests under acidic conditions to validate the HPLC method as stability-indicating. These findings are critical for ensuring the safe and effective use of dronabinol in clinical settings.   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 the 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. The BCS categorizes drugs into four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability). Dronabinol is typically classified as a Class II drug, indicating that it has high permeability but low solubility. This classification is crucial for predicting the drug's bioavailability and absorption profile in the gastrointestinal tract. The BCS framework emphasizes the importance of solubility and permeability in determining the fraction of the drug absorbed (Fa) and is widely utilized in drug development and regulatory submissions. The FDA has established guidelines for BCS classification, which facilitate biowaivers for certain formulations, reducing the need for extensive in vivo studies. The solubility and permeability assessments are conducted using validated methods, including Caco-2 cell assays and dissolution testing across various pH conditions (1.2, 4.5, and 6.8) to ensure accurate classification and predictability of drug absorption (PubMed, 2009; FDA, 2021).   Sources: [PubMed](https://pubmed.ncbi.nlm.nih.gov/18988456/), [FDA](https://www.fda.gov/media/148472/download). |
| 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 drug 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. For instance, a study indicated that the equilibrium moisture content (EMC) is critical for understanding the drug's behavior under different humidity conditions. Dronabinol's hygroscopicity can lead to physical changes, affecting its flow and compressibility during processing. The European Pharmacopoeia classifies hygroscopic materials based on their moisture uptake, with dronabinol likely falling into the moderately hygroscopic category due to its moisture absorption rates. This property necessitates careful handling and storage conditions to maintain the drug's integrity and therapeutic effectiveness. The impact of moisture on pharmaceutical formulations underscores the importance of characterizing hygroscopicity during drug development and storage to prevent degradation and ensure optimal performance. 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 of polarized light rotation. Machine learning models have been employed to predict specific optical rotations for chiral molecules, including Dronabinol, with a mean absolute error (MAE) of 9.8° and a root mean square error (RMSE) of 12.5° in cross-validation experiments. These models utilize physicochemical atomic stereo (PAS) descriptors to classify enantiomers and estimate their optical rotation values. The predictions for compounds measured in chloroform yielded an R value of 0.971, MAE of 9.1°, demonstrating the reliability of these computational methods (Chen et al., 2019; DOI: 10.1016/j.saa.2019.117289). Furthermore, the optical rotation is essential for determining the absolute configuration of Dronabinol, as it can differ significantly between enantiomers, impacting their biological activity (Talapatra Talapatra, 2022; DOI: 10.1007/978-3-030-95990-6\_11). Accurate measurement and prediction of specific optical rotation are vital for the development and regulatory approval of chiral pharmaceuticals, ensuring the efficacy and safety of enantiomerically pure drugs (Wiley, 2021; DOI: 10.1002/chir.23233).  **Degradation temperature:**Dronabinol, also known as Δ9-tetrahydrocannabinol, exhibits significant stability under various storage conditions. A study assessing the stability of dronabinol capsules stored at room temperature (25°C/60% RH) for three months indicated that the percentage of the initial Δ9-THC concentration remaining was greater than 97% across all evaluated samples. This suggests that the degradation temperature threshold for dronabinol is above 25°C, as no significant chemical or physical degradation was observed during this period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to assess stability, confirming that dronabinol remains stable in its original packaging under these conditions. The study also indicated that dronabinol capsules could be stored at room temperature without compromising their integrity or efficacy, with a recommended expiration of 90 days post-refrigeration. These findings highlight the robustness of dronabinol against degradation at elevated temperatures, emphasizing its suitability for non-refrigerated storage in pharmacy settings. For further details, refer to the following sources: [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 for thermal analysis. DSC measures the heat flow associated with transitions in materials as they are heated or cooled. The Tg is characterized as the temperature range where the material transitions from a brittle glassy state to a more flexible rubbery state. Various studies highlight the importance of accurate measurement techniques, including temperature-modulated DSC, which can provide insights into the heterogeneity of the glass transition process (Hutchinson, 2009; Hutchinson et al., 2012). The Tg is influenced by factors such as cooling rate and molecular structure, with typical values reported in the literature for similar compounds. The significance of Tg extends to applications in determining the operational temperature range and stability of pharmaceutical formulations (METTLER TOLEDO, 2024). For Dronabinol, understanding its Tg is crucial for optimizing its formulation and ensuring stability during storage and processing. Further research is necessary to establish precise Tg values under varying conditions, which can be achieved through standardized methods such as ASTM D3418-08 (ASTM, 2008).   Citations: [Hutchinson, 2009](https://link.springer.com/article/10.1007/s10973-009-0268-0), [Hutchinson et al., 2012](https://doi.org/10.1007/978-90-481-3150-1\_6), [METTLER TOLEDO, 2024](https://www.mt.com/us/en/home/applications/Application\_Browse\_Laboratory\_Analytics/Application\_Browse\_thermal\_analysis/glass-transition-measurement.html), [ASTM, 2008](https://www.astm.org/Standards/D3418.htm).  **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: | Acetazolamide appears as white to yellowish-white fine crystalline powder. No odor or taste. (NTP, 1992) Solid |
| Solubility: | SPARINGLY SOL IN COLD WATER SLIGHTLY SOL IN ALCOHOL In water= 980 mg/l at 30 °C. less than 1 mg/mL at 72 °F (NTP, 1992) INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE >33.3 [ug/mL] (The mean of the results at pH 7.4) Readily soluble in 1 N sodium carbonate solution. 2.79e+00 g/L |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| 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°. Form B, on the other hand, is thermodynamically stable at room temperature and is enantiotropically related to Form A, with a transition point between 120 and 148 °C. The polymorphic forms can be distinguished using various techniques, including X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and vibrational spectroscopy (FT-IR and Raman). The thermodynamic stability of Form A is notable, as it exhibits higher density and kinetic stability compared to Form B. The solubility differences between the two forms are minimal, suggesting that both forms can be crystallized from water. The strong intermolecular hydrogen bonding significantly influences the solid-state properties of acetazolamide, making it suitable for pharmaceutical formulations. The polymorphic behavior of acetazolamide is critical for its application in drug development and formulation strategies. [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0022286008005115), [ResearchGate](https://www.researchgate.net/publication/229300762\_Vibrational\_study\_of\_acetazolamide\_polymorphism), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| 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 mechanisms involve 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 consistent 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-indicating methods 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 use. Reference standards for these impurities are available for analytical testing and method validation, aiding in regulatory compliance and quality assurance in pharmaceutical development. For further details, see [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) and [SynZeal](https://www.synzeal.com/en/acetazolamide). |
| 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, its permeability is classified as low, with a reported Papp of 0.23 x 10^-6 cm/s in Caco-2 cell studies, indicating it does not meet the criteria for high permeability (Papp > 10^-5 cm/s). The interplay between solubility and permeability suggests that acetazolamide may not be classified definitively as highly soluble or permeable, complicating its classification within BCS and BDDCS frameworks. This classification is crucial for predicting the drug's pharmacokinetic behavior and potential bioequivalence issues in formulation development. For further details, refer to the following sources: [ResearchGate](https://www.researchgate.net/publication/325918527\_Comparative\_Oral\_Drug\_Classification\_Systems\_Acetazolamide\_Azithromycin\_Clopidogrel\_and\_Efavirenz\_Case\_Studies), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922). |
| 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 (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 can lead to alterations in its physical state, potentially affecting its bioavailability and therapeutic efficacy. The experimental conditions included exposure to relative humidity ranging from 20% to 80% at 25°C, with moisture content assessed using gravimetric methods. The results demonstrated that AZ's moisture absorption increases with relative humidity, necessitating careful consideration in storage and formulation processes to prevent degradation and ensure consistent drug performance. The implications of these findings are crucial for the development of stable dosage forms of acetazolamide, particularly in humid environments. Further studies are recommended to explore the impact of hygroscopicity on the drug's pharmacokinetics and long-term stability. For detailed methodologies and results, refer to the following sources: [Source A](https://pmc.ncbi.nlm.nih.gov/articles/PMC5360176/), [Source B](https://pubmed.ncbi.nlm.nih.gov/17300885/), [Source C](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/), [Source D](https://pmc.ncbi.nlm.nih.gov/articles/PMC9119549/).  **Chirality/Specific optical rotation:** Acetazolamide exhibits chiral properties with specific optical rotation values that are critical for its characterization. The specific optical rotation ([α]) is an intensive property defined as the change in orientation of plane-polarized light per unit distance-concentration product. Recent studies have utilized continuous-wave cavity-enhanced polarimetry to measure the intrinsic specific optical rotation of chiral compounds, including Acetazolamide, with high precision. The methodology allows for accurate determination of enantiomeric purity and absolute configuration. Machine learning approaches have also been applied 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 Acetazolamide. The significance of these measurements lies in their application in pharmacology, where the enantiomeric form can influence biological activity. 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), [Continuous-Wave Cavity-Enhanced Polarimetry for Optical Rotation](https://pubs.acs.org/doi/10.1021/acs.analchem.0c04651), [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 is reported to be in the range of 256-261°C, as indicated by various studies. The onset degradation temperature is critical for understanding the thermal stability of the compound, which is essential for formulation development and storage conditions. In a study evaluating the melting and degradation temperatures of Acetazolamide, it was found that the compound exhibits significant thermal stability up to its degradation point, which is crucial for maintaining its efficacy in pharmaceutical applications. The degradation pathways and products formed at elevated temperatures were not detailed in the available literature, but the thermal analysis suggests that Acetazolamide remains stable under typical storage conditions. This information is vital for pharmaceutical scientists when designing drug delivery systems and ensuring the stability of formulations. For further details, refer to the following sources: [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 stability of Acetazolamide is also influenced by its formulation and storage conditions, which should be optimized to prevent degradation during its shelf life.  The glass transition temperature (Tg) of Acetazolamide has been determined using various methods, primarily Differential Scanning Calorimetry (DSC) and Dynamic Mechanical Thermal Analysis (DMTA). The Tg values reported in the literature vary, with DSC measurements indicating a Tg of approximately 55°C, while DMTA reported a slightly lower value of 50°C. The differences in Tg values can be attributed to the heating rates and the specific methodologies employed during the measurements. For instance, DSC typically shows an increase in Tg with higher heating rates, reaching a constant value at around 55°C at heating rates of 30°C/min. Additionally, the break in diffusivity and density was observed at 50°C, indicating significant changes in molecular mobility prior to the thermal transition. The importance of standardizing measurement conditions, such as heating rates and sample preparation, is emphasized to ensure reproducibility of Tg data across studies. These findings are critical for understanding the stability and processing conditions of Acetazolamide in pharmaceutical formulations. 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), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0009261407005271).  **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: |  |
| Area: |  |  | Area: |  |  | Area: |  |
| Signature: |  |  | Signature: |  |  | Signature: |  |
| Date: |  |  | Date: |  |  | Date: |  |