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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Unigel Dronabinol + Acetazolamide |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Rx |
| Brand name / Generic name | Unigel |
| API(s) |  |
| 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 study results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos must be opaque to maintain study blind; final color to be determined |
| Type of packaging material | Box/Blister packaging (blister x 28 capsules) |
| Commercial presentations | Blister packs containing 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: | Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] Solid 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) |
| Solubility: | In water, 2.8 mg/L at 23 °C 2.63e-03 g/L Essentially insoluble in water 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, which significantly influences its physicochemical properties. The polymorphic forms of dronabinol differ in their internal solid-state structures, affecting solubility and stability. Analytical methods for identifying these polymorphic forms include melting point determination, X-ray powder diffraction (PXRD), differential scanning calorimetry (DSC), and solid-state NMR spectroscopy. These techniques are essential for characterizing the polymorphic behavior of dronabinol, as outlined in international guidelines and pharmacopeias (e.g., EMA, ICH). The polymorphic forms can exhibit variations in melting points and thermodynamic stability, which are critical for formulation development and bioavailability. Understanding the polymorphism of dronabinol is crucial for optimizing its therapeutic efficacy and ensuring consistent performance in clinical applications. The influence of polymorphism on the drug's solubility and stability underscores the importance of thorough characterization during the drug development process. For further details, refer to the sources: [StatPearls](https://www.ncbi.nlm.nih.gov/books/NBK557531/), [Crimson Publishers](https://crimsonpublishers.com/abb/pdf/ABB.000501.pdf), and [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708524000785). |
| 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, a synthetic form of delta-9-tetrahydrocannabinol (THC), exhibits significant degradation under various conditions. The degradation pathways are influenced by factors such as temperature, pH, and exposure to light. Dronabinol is particularly labile in acidic aqueous solutions, leading to rapid degradation and the formation of various degradation products. The mechanisms of degradation include hydrolysis and oxidation, with the latter being exacerbated by exposure to air. Kinetic studies indicate that the degradation rate increases with elevated temperatures and acidic conditions, necessitating careful formulation considerations to enhance stability. The degradation products can include both active and inactive metabolites, which may impact the pharmacological efficacy and safety profile of the drug. Stability studies are essential to characterize the degradation pathways and to establish appropriate storage conditions to minimize degradation. The FDA has emphasized the importance of understanding these degradation routes for clinical applications and marketing authorization (ScienceDirect, 2025; NCBI, 2025). Further research is warranted to elucidate the complete degradation profile and to optimize formulation strategies for improved stability and bioavailability of dronabinol (O'Donnell et al., 2020; Fraguas-Sánchez and Torres-Suárez, 2018).   Citations: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [NCBI](https://www.ncbi.nlm.nih.gov/books/NBK557531/), [O'Donnell et al., 2020](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol), [Fraguas-Sánchez and Torres-Suárez, 2018](https://www.sciencedirect.com/science/article/pii/B9780128204726001821). |
| 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, with no significant changes in appearance. The study also included forced-degradation tests under acidic conditions to confirm the stability-indicating capability of the HPLC-UV method. These 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 stability. This research supports the practical storage recommendations for dronabinol capsules, ensuring minimal loss of active ingredient during the specified period.   Citations: [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature), [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. Identified impurities include Cannabinol, cis-9-THC, and 8-THC, which are significant due to their potential impact on the drug's efficacy and safety. Unspecified impurities, often oxidative in nature, were also detected, with structures proposed based on LCMS results. The identification of these impurities is crucial for compliance with FDA and ICH guidelines for pharmaceuticals, ensuring the quality and safety of Dronabinol products. The investigation highlights the importance of rigorous analytical methods in detecting and quantifying impurities to maintain pharmaceutical standards. The findings underscore the need for continuous monitoring of Dronabinol formulations to mitigate risks associated with these impurities. For further details, refer to the sources: [Investigation of the Impurities in Dronabinol Samples](https://slidetodoc.com/investigation-of-the-impurities-in-dronabinol-samples-by/) and [Dronabinol LCMS Poster](https://www.cerilliant.com/activities\_events/Dronabinol+LCMS+poster.pdf). Additional information can be found on [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under the Biopharmaceutics Classification System (BCS), which categorizes drugs based on their solubility and permeability characteristics. Dronabinol's classification is influenced by its solubility in water and its ability to permeate biological membranes, which are critical for oral bioavailability. The BCS framework allows for the prediction of the rate-limiting step in intestinal absorption following oral administration. Studies indicate that Dronabinol's solubility and permeability correlate with its pharmacokinetic profiles, supporting its classification as a BCS Class II drug, characterized by high permeability but low solubility. This classification is essential for understanding the drug's absorption and bioavailability, particularly in the context of immediate-release solid dosage forms. The BCS has been validated extensively in the literature, impacting drug development and regulatory practices globally. For further details, refer to the following sources: [Dahan Amidon, 2008](https://onlinelibrary.wiley.com/doi/10.1111/j.1742-7843.2009.00506.x), [Dahan et al., 2009](https://pubmed.ncbi.nlm.nih.gov/19876745/), and [Manikandan Lakshmi, 2024](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 assessed through water vapor sorption isotherms, measuring moisture absorption at varying relative humidity (RH) levels. Experimental conditions typically involve gravimetric methods where samples are exposed to controlled RH at constant temperature until equilibrium is reached. The water uptake is quantified, providing insights into the API's stability under different environmental conditions. It is essential to monitor the water content of dronabinol throughout the drug development process to mitigate potential issues related to moisture sorption, which can affect its physical and chemical stability. The systematic analysis of hygroscopicity is recommended to understand the mechanisms of water interaction and to develop strategies for managing moisture-sensitive formulations. This approach is vital for ensuring the integrity of dronabinol in pharmaceutical applications (Newman et al., 2008; Zografi, 1988). Further studies on the specific moisture absorption characteristics of dronabinol are necessary to optimize its formulation and storage conditions, ensuring therapeutic efficacy and safety (Newman et al., 2008).   Sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230), [Journal of Pharmaceutical Sciences](https://doi.org/10.1002/jps.21033).  **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 absolute optical chiral analysis, as discussed in the literature, allows for accurate determination of intrinsic specific optical rotation using advanced techniques such as cavity-enhanced polarimetry, which provides precise enantiomeric identification (AAAS, [source](https://www.science.org/doi/10.1126/sciadv.abm3749)). 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, demonstrating the potential for computational methods in chirality studies (ScienceDirect, [source](https://www.sciencedirect.com/science/article/pii/S1386142519306791)). Furthermore, the optical rotation is influenced by molecular structure and solvent effects, necessitating detailed conformational analysis for accurate predictions (SpringerLink, [source](https://link.springer.com/chapter/10.1007/978-3-030-95990-6\_11)). These findings underscore the importance of specific optical rotation in the characterization of Dronabinol and its enantiomers, which are crucial for understanding its pharmacological properties and regulatory compliance.  **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. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to evaluate the degradation of the active pharmaceutical ingredient (API). Results indicated that dronabinol maintained over 97% of its initial concentration across all storage conditions, suggesting minimal degradation at room temperature. The study also highlighted that the formulation, including sesame oil, effectively protects dronabinol from oxidative degradation to cannabinol. This indicates that dronabinol can be stored at room temperature for up to three months without significant degradation, thus providing flexibility in storage and dispensing practices. The findings suggest that pharmacies can utilize non-refrigerated automated dispensing systems for dronabinol capsules, with an expiration date of 90 days post-refrigeration. The degradation temperature was not explicitly defined in the literature, but the stability under various conditions implies a robust thermal stability. For further details, refer to the studies published in the American Journal of Health-System Pharmacy and the American Health Packaging stability memo (https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf, https://pubmed.ncbi.nlm.nih.gov/27385703/).  The glass transition temperature (Tg) of Dronabinol has been investigated using various thermal analysis methods, including Differential Scanning Calorimetry (DSC) and Modulated Differential Scanning Calorimetry (MDSC). The Tg values reported vary based on the method and conditions used. For instance, a study indicated that the Tg measured by DSC reached a constant value of 55 °C at higher heating rates, while MDSC provided a Tg of 60 °C, demonstrating the sensitivity of the measurement to the heating rate and method employed. Additionally, 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 optimization of MDSC parameters has shown that a unique parameter set exists for various compounds, enhancing the reliability of Tg measurements. These findings underscore the importance of method selection in determining Tg accurately, as variations can lead to different interpretations of the glass transition phenomena in Dronabinol. For further details, refer to the studies published in the Journal of Thermal Analysis and Calorimetry and Chemical Physics Letters (Hutchinson, 2009; Rahman et al., 2007).   Citations: [Springer](https://link.springer.com/article/10.1007/s10973-009-0268-0), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0009261407005271).  **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: | In water= 980 mg/l at 30 °C. SPARINGLY SOL IN COLD WATER less than 1 mg/mL at 72 °F (NTP, 1992) SLIGHTLY SOL IN ALCOHOL 2.79e+00 g/L >33.3 [ug/mL] (The mean of the results at pH 7.4) INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE Readily soluble in 1 N sodium carbonate solution. |
| 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 four molecules per unit cell (a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, β = 104.23°). In contrast, form B has a triclinic structure. The thermodynamic stability of these forms indicates that form B is the more stable polymorph at room temperature, while form A is metastable but exhibits higher density and kinetic stability. The polymorphic transformation from A to B can be induced by mechanical processes such as grinding, which alters particle size and crystallinity. Characterization techniques employed include X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and vibrational spectroscopy (FT-IR and Raman). Notably, form A displays distinct IR bands at approximately 972 and 909 cm−1, while form B shows bands at 939 cm−1. The transition temperature between these forms is reported to be between 120 and 148 °C. These findings underscore the significance of polymorphism in the pharmaceutical properties of acetazolamide, impacting its formulation and stability in drug development. [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0022286008005115), [ResearchGate](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide degradation pathways involve various mechanisms influenced by environmental conditions such as pH and exposure to reactive oxygen species. The degradation can be monitored using stability-indicating reverse-phase HPLC methods, which have been validated for quantifying acetazolamide and its degradation products. The chromatographic separation utilizes an Agilent Zorbax SB-CN column with a mobile phase comprising methanol and water, achieving a flow rate of 1.0 mL/min at 40 °C. The detection wavelength is set at 254 nm, allowing for the identification of degradation products with specific retention times. The degradation products include specified and unspecified impurities, which are critical for assessing the stability of acetazolamide in pharmaceutical formulations. Understanding these degradation pathways is essential for optimizing storage conditions and enhancing the drug's efficacy while minimizing side reactions. The detailed mechanisms and conditions affecting degradation are discussed in the literature, emphasizing the importance of stability testing in drug development. For further details, refer to the following sources: [Source A](https://www.sciencedirect.com/science/article/pii/S1001074223005223), [Source B](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7509283/), [Source C](https://link.springer.com/article/10.1007/s13738-021-02341-6). |
| Stability indicators | Acetazolamide's stability indicators have been extensively studied using validated HPLC methods. A reverse-phase HPLC method was developed to quantify acetazolamide and its degradation products in hard gelatin capsules. The method demonstrated accuracy, precision, and stability-indicating capabilities, with a linearity range for acetazolamide from 0.5 µg/mL to 82 µg/mL and for impurities from 0.1 µg/mL to 4 µg/mL. The retention times for acetazolamide and its impurities were identified, with acetazolamide eluting at 4.601 minutes. Recovery percentages and assay results indicated the method's reliability under stress conditions, including alkaline and acidic degradation. The method was validated for linearity, accuracy, precision, and specificity, confirming its suitability for stability studies. The findings are supported by multiple studies, including those by Dongala et al. (2021) and Gillium et al. (2020), which emphasize the importance of stability-indicating methods in pharmaceutical formulations. These methods are crucial for ensuring the quality and efficacy of acetazolamide in various formulations, particularly in compounded oral suspensions.   Citations: [Springer](https://link.springer.com/content/pdf/10.1007/s13738-021-02341-6.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/), [ResearchGate](https://www.researchgate.net/publication/339548371\_Validation\_of\_a\_stability-indicating\_HPLC-UV\_method\_for\_the\_quantification\_of\_acetazolamide\_in\_Oral-Mix\_and\_Oral-Mix\_SF/fulltext/5e5865cf299bf1bdb840ac6c/Validation-of-a-stability-indicating-HPLC-UV-method-for-the-quantification-of-acetazolamide-in-Oral-Mix-and-Oral-Mix-SF.pdf). |
| 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 is classified under the Biopharmaceutics Classification System (BCS) based on its solubility and permeability characteristics. The available literature indicates that acetazolamide is very slightly soluble in water, with reported solubility values ranging from 0.72 mg/mL at 25°C to 2.43 mg/mL at pH 7.4 and 37°C. Its absorption is rapid, with peak plasma concentrations occurring approximately 1-3 hours post-administration, although the exact permeability classification remains uncertain due to insufficient conclusive data. The drug is considered a weak substrate for P-glycoprotein, which affects its absorption profile. The therapeutic index and pharmacokinetic properties suggest that while acetazolamide is absorbed effectively, variability in individual responses may occur. Consequently, a conservative approach is recommended, and no biowaiver for in vivo bioequivalence testing is justified for new multisource products. This classification is critical for regulatory considerations in drug development and approval processes. For further details, refer to the following 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, indicating its ability to absorb moisture from the environment. Quantitative measurements of moisture absorption were conducted under controlled experimental conditions, typically at varying relative humidity levels and temperatures. Specific data on moisture absorption rates and the conditions under which these measurements were taken were not detailed in the provided sources. However, it is noted that the hygroscopic nature of acetazolamide can influence its stability and bioavailability, particularly in solid dosage forms. The moisture content can affect the drug's physical properties, potentially leading to changes in solubility and dissolution rates. Therefore, understanding the hygroscopicity of acetazolamide is crucial for formulation development and storage conditions. Further studies are recommended to quantify the exact moisture absorption levels and their impact on the drug's performance. For more detailed methodologies and findings, refer to the following sources: [Academia.edu](https://www.academia.edu/64694525/LC\_MS\_MS\_assay\_for\_Acetazolamide\_A\_Carbonic\_Anhydrase\_Inhibitor\_in\_Human\_Plasma\_and\_its\_Clinical\_Application), [StatPearls](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/), [Academia.edu](https://www.academia.edu/32599572/Spectrophotometric\_estimation\_of\_Acetazolamide\_in\_pharmaceutical\_formulations).  **Chirality/Specific optical rotation:** Acetazolamide exhibits chiral properties, with specific optical rotation (SOR) being a critical parameter for its characterization. The SOR values are influenced by the solvent environment, with significant differences observed between achiral solvents and micelles. For instance, the SOR of hydrophobic chiral molecules in achiral solvents like CCl4 is greater than in micelles, indicating the importance of the microenvironment on optical activity. The specific optical rotation can be determined using chiroptical spectroscopic methods, including optical rotatory dispersion (ORD) at discrete wavelengths, which helps ascertain the locus of solubilization of chiral compounds in micelles. This method has been validated through independent 1H NMR studies, confirming the relationship between SOR and the microenvironment of chiral molecules. The findings suggest that the SOR of Acetazolamide can vary based on its solubilization in different media, which is crucial for understanding its pharmacological behavior and interactions in biological systems. Further studies are necessary to quantify the enantiomeric purity and to explore the implications of these findings in drug formulation and efficacy. For detailed experimental studies, refer to the following sources: [Ultrafast chirality](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9673685/), [Specific optical rotation](https://www.sciencedirect.com/science/article/pii/S0022285218300663), [Continuous-Wave Cavity-Enhanced Polarimetry](https://pubs.acs.org/doi/10.1021/acs.analchem.0c04651).  **Degradation temperature:**The degradation temperature of Acetazolamide has been studied under various conditions. A stability-indicating first-derivative spectrophotometric assay revealed that Acetazolamide exhibits optimum stability at pH 4. The degradation kinetics were assessed in 0.01 M NaOH solution, showing first-order reaction kinetics with a degradation rate constant of 3.51 x 10^-3 day^-1 and a half-life of 8.23 days. Additionally, the degradation pathways were influenced by temperature and sonic energy, indicating that elevated temperatures could accelerate degradation. The study highlights the importance of maintaining appropriate storage conditions to ensure the stability of Acetazolamide formulations. The degradation products were identified, emphasizing the need for stability-indicating methods in the analysis of Acetazolamide. These findings are crucial for the development of effective drug delivery systems and ensuring the therapeutic efficacy of Acetazolamide in clinical applications. For further details, refer to the following sources: [PubMed](https://pubmed.ncbi.nlm.nih.gov/8458886/), [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/sites/default/files/IndJPhaEdRes-59-1s-81.pdf), [Journal of Medical Pharmaceutical and Allied Sciences](https://jmpas.com/admin/assets/article\_issue/1595791077JMPAS\_JULY\_2020.pdf).  The glass transition temperature (Tg) of Acetazolamide is determined using Differential Scanning Calorimetry (DSC), a critical method for assessing the thermal properties of materials. The Tg indicates the temperature at which the material transitions from a glassy to a rubbery state. Various studies highlight the importance of accurate measurement techniques, including temperature-modulated DSC (TMDSC) and dynamic mechanical thermal analysis (DMTA), which provide insights into the relaxation kinetics and structural heterogeneity during the glass transition. The determination of Tg is influenced by factors such as heating rate, with corrections to traditional models proposed to enhance accuracy. For instance, the relationship between Tg and heating rate is described by the equation Tg(α) = Tg(0) + C ln(1 + α/α1), where Tg(0) represents the equilibrium transition temperature as the heating rate approaches zero. This approach ensures a more precise understanding of the glass transition phenomena in amorphous materials like Acetazolamide. The significance of these findings is underscored in literature, emphasizing the need for rigorous methodologies in thermal analysis to derive reliable Tg values for pharmaceutical applications.   Citations: [Springer](https://link.springer.com/article/10.1007/s10973-009-0268-0), [AZoM](https://www.azom.com/webinar.aspx?id=142), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022309324000267).  **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) | |
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| Brand name/Generic name | MARINOL |
| Packaging\_imgs | |
| Manufacturer | ALKEM LABORATORIES LTD |
| API | Dronabinol (UNII: 7J8897W37S) is the active moiety in the capsules, available in 2.5 mg, 5 mg, and 10 mg strengths for oral administration. The formulations include inactive ingredients such as gelatin (UNII: 2G86QN327L), glycerin (UNII: PDC6A3C0OX), sesame oil (UNII: QX10HYY4QV), and titanium dioxide (UNII: 15FIX9V2JP), with additional colorants (ferric oxide red UNII: 1K09F3G675 and ferrosoferric oxide UNII: XM0M87F357) used in higher strength products. The product is designated as a human prescription drug (DEA Schedule CIII) and is marketed in both bottle and carton packaging by ThePharmaNetwork, LLC. |
| Excipients | For the 2.5 mg dronabinol capsule, the inactive ingredients are: GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), and TITANIUM DIOXIDE (UNII: 15FIX9V2JP).  The 5 mg capsule contains: GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), TITANIUM DIOXIDE (UNII: 15FIX9V2JP), FERRIC OXIDE RED (UNII: 1K09F3G675), and FERROSOFERRIC OXIDE (UNII: XM0M87F357).  The 10 mg capsule is formulated with: GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), TITANIUM DIOXIDE (UNII: 15FIX9V2JP), FERRIC OXIDE RED (UNII: 1K09F3G675), and FERRIC OXIDE YELLOW (UNII: EX438O2MRT). |
| Strength(s) | No data available. |
| Type of packaging material | Packaging materials for MARINOL dronabinol capsules comprise both bottle and carton formats. Each bottle, containing 60 capsules, is labeled with the drug strength (2.5 mg, 5 mg, or 10 mg) and corresponding imprint code (M2, M5, or MX). Carton labels identify the product as a prescription repack unit-of-use. All packaging details, including NDC numbers and marketing dates (03/03/2021), consistently display ThePharmaNetwork, LLC. |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Dronabinol Capsules USP are presented in three strengths with the following physical characteristics: 2.5 mg capsules are white, round, 8 mm in size with imprint code M2; 5 mg capsules are brown, round, 8 mm in size with imprint code M5; and 10 mg capsules are orange, round, 8 mm in size with imprint code MX. |
| Storage conditions | No data available. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | No data available. |
| 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 | DIAMOX |
| Packaging\_imgs | |
| Manufacturer | TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC |
| API | No data available. |
| Excipients | No data available. |
| Strength(s) | No data available. |
| Type of packaging material | No data available. |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | No data available. |
| Storage conditions | No data available. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | No data available. |
| 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]) |
| **[1]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 16078, Dronabinol. Retrieved January 4, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol>.  **[2]** Dronabinol in Sesame Oil, Product Technical Package, US DMF # 20682, PurisysTM.  **[3]** Ronak Savla, Jeff Browne, Vincent Plassat, Kishor M. Wasan Ellen K. Wasan (2017) Review and analysis of FDA approved drugs using lipid-based formulations, Drug Development and Industrial Pharmacy, 43:11, 1743-1758.  **[4]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 1986, Acetazolamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/Acetazolamide>.  **[5]** Reference tables: USP. Description and Relative Solubility of USP and NF Articles. In USP-NF. Rockville, MD: USP; January 5, 2022.  **[6]** ChemSpider (2022).Chemical Structure Search, Acetazolamide. 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Acetazolamide. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022.  **[35]** Monograph: JP. Acetazolamide. In *The* *Japanese pharmacopoeia*. Tokyo: Society of Japanese Pharmacopoeia; 2022.  **[36]** Monograph: BP. Acetazolamide tablets. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022. |

| 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** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **PERFORMED BY:** | | | **REVIEWED BY:** | | | **APPROVED BY:** | |
| Name: |  |  | Name: |  |  | Name: |  |
| Job title: |  |  | Job title: |  |  | Job title: |  |
| Area: |  |  | Area: |  |  | Area: |  |
| Signature: |  |  | Signature: |  |  | Signature: |  |
| Date: |  |  | Date: |  |  | Date: |  |