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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | UNIGEL DRONABINOL + ACETAZOLAMIDA Capsule |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Unigel Dronabinol + Acetazolamide |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg and Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Capsule (Unigel) |
| Route of administration | Oral |
| Dose(s) | As determined by clinical study results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos should be opaque to maintain study blinding. Final color to be defined post clinical dose determination |
| Type of packaging material | Blister pack in a box of 28 capsules |
| Commercial presentations | Blister packs of 28 capsules |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Dronabinol |
| CAS number: | 1972-08-3 |
| Description: | Solid 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] |
| Solubility: | Essentially insoluble in water 2.63e-03 g/L 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. 2.8 mg/L at 73 °F (NTP, 1992) In water, 2.8 mg/L at 23 °C |
| 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 polymorphs 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 forms and understanding their thermodynamic stability. The melting points of different polymorphic forms can vary, impacting the drug's bioavailability and therapeutic efficacy. The presence of multiple polymorphs necessitates rigorous quality control during formulation development to ensure consistent drug performance. The influence of polymorphism on the solubility and stability of dronabinol underscores the importance of solid-state characterization in pharmaceutical development. For further details, refer to the following sources: [StatPearls - NCBI Bookshelf](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 (Δ9-THC) exhibits significant degradation pathways influenced by environmental conditions such as pH, temperature, and light exposure. Under acidic conditions, dronabinol is particularly labile, leading to rapid degradation and the formation of various degradation products. The degradation mechanisms primarily involve hydrolysis and oxidation, resulting in the formation of non-psychoactive metabolites. Studies indicate that dronabinol undergoes first-order kinetics in degradation, with temperature and light acting as critical factors in accelerating the process. The presence of excipients and packaging materials can also impact stability, necessitating careful formulation considerations. Notably, dronabinol's stability is compromised in aqueous solutions, highlighting the importance of formulation strategies to enhance its shelf life. The degradation products formed can include both synthetic byproducts and metabolites, which may have implications for pharmacological activity and safety. Understanding these degradation pathways is essential for optimizing the formulation and storage conditions of dronabinol to ensure therapeutic efficacy and safety. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol), [Kinetics and mechanisms of drug degradation](https://www.sciencedirect.com/science/article/pii/B9780443134661000325). |
| 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 alteration in appearance. The study also included forced-degradation tests under acidic conditions to validate the stability-indicating capability of the HPLC-UV method. The findings suggest that the formulation, particularly the use of high-grade sesame oil, effectively protects Δ9-THC from oxidative degradation to cannabinol. Consequently, pharmacies can store dronabinol capsules at room temperature for up to 90 days post-refrigeration without compromising stability. This data 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, with unspecified impurities typically being oxidative in nature. The structures of these unspecified impurities were proposed based on LCMS results, indicating a need for thorough identification as per FDA and ICH guidelines for pharmaceuticals. The investigation highlighted the importance of understanding the impurity profile of Dronabinol to ensure product quality and safety. The analytical methods employed provide a robust framework for impurity detection and quantification, essential for regulatory compliance and therapeutic efficacy. The findings underscore the necessity for continuous monitoring of Dronabinol samples from various sources to maintain consistency in purity levels. Further studies may be warranted to elucidate the origins and mechanisms of these impurities, enhancing the overall understanding of Dronabinol's stability and safety profile. For detailed insights, 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). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol, a synthetic form of Δ9-tetrahydrocannabinol (THC), is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, characterized by high permeability but low solubility. Its solubility is approximately 0.77 mg/mL, indicating poor aqueous solubility, which is a significant barrier to its bioavailability (Mehta et al., 2018). The drug exhibits high oral absorption (90-95%) but only 10-20% reaches systemic circulation due to extensive first-pass metabolism (O'Donnell et al., 2020). The BCS framework evaluates drugs based on solubility and permeability, crucial for predicting oral absorption (Bhor et al., 2021). Dronabinol's low solubility necessitates innovative formulation strategies to enhance its bioavailability, such as soft gelatin capsules and sublingual tablets (Papich, 2016). The drug's pharmacokinetics reveal a peak effect at 2-4 hours post-administration, with a terminal half-life of 25-36 hours (Fraguas-Sánchez Torres-Suárez, 2018). Understanding these properties is essential for optimizing therapeutic efficacy and minimizing adverse effects in clinical settings (Wallach, 2021).   Citations: [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol), [Bhor et al.](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [Papich, 2016](https://www.sciencedirect.com/science/article/pii/B9780323244855002345), [Fraguas-Sánchez Torres-Suárez, 2018](https://www.sciencedirect.com/science/article/pii/S0753332218351412), [Wallach, 2021](https://www.sciencedirect.com/science/article/pii/B9780128200070000052). |
| 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 of dronabinol are critical, as they can affect the drug's physical properties and bioavailability. Experimental conditions for assessing hygroscopicity typically involve varying relative humidity (RH) levels, with studies indicating that the hygroscopicity of pharmaceutical materials is influenced by factors such as temperature and the specific formulation of the API. For instance, the Discovery SA Dynamic Vapor Sorption Analyzer is utilized to characterize moisture sorption properties, allowing for precise control over humidity and temperature during testing. This method provides insights into the moisture absorption behavior of dronabinol, which is essential for understanding its stability under different environmental conditions. The impact of moisture on the structural integrity of APIs, including dronabinol, underscores the importance of controlling storage conditions to maintain drug quality and efficacy. The propensity of dronabinol to adsorb moisture can lead to potential degradation pathways, necessitating careful formulation and packaging strategies to mitigate these effects. For further details, refer to the following sources: [Characterization of the Hygroscopic properties of active pharmaceutical ingredients](https://www.researchgate.net/publication/6206923\_Characterization\_of\_the\_Hygroscopic\_properties\_of\_active\_pharmaceutical\_ingredients), [Characterizing the Effects of Moisture on Pharmaceutical Materials](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 chiral properties characterized by specific optical rotation (SOR). The intrinsic specific optical rotation can be determined using advanced techniques such as cavity-enhanced polarimetry, which allows for accurate measurement of enantiomeric compositions. The specific rotation values are influenced by concentration, solvent, and temperature, with the intrinsic rotation being a constant at zero concentration. The relationship between optical purity and enantiomeric excess is critical, as demonstrated by the Horeau effect, which indicates that specific rotation does not always correlate linearly with enantiomeric excess. This phenomenon has implications for the practical use of specific rotations in determining enantiomeric purity. Theoretical models and experimental data support the understanding of these chiral properties, emphasizing the importance of precise measurement conditions. For further details, refer to the studies on optical purity and enantiomeric excess, as well as the absolute optical chiral analysis methodologies. The specific rotation values and their implications for Dronabinol's chiral nature are essential for its pharmaceutical applications. [Source 1](https://ncbi.nlm.nih.gov/pmc/articles/PMC9075150/), [Source 2](https://pubs.rsc.org/en/content/getauthorversionpdf/D0OB01497D), [Source 3](https://www.science.org/doi/10.1126/sciadv.abm3749).  **Degradation temperature:**Dronabinol, a synthetic delta-9-tetrahydrocannabinol, exhibits stability under various temperature conditions. A study assessed the stability of dronabinol capsules stored at room temperature (25°C), refrigerated, and frozen over a 90-day period using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Results indicated that the percentage of the initial Δ9-THC concentration remained above 97% across all storage conditions, suggesting minimal degradation at room temperature. The study also highlighted that exposure to high temperatures could accelerate degradation, impacting efficacy. Therefore, while dronabinol does not require refrigeration, it is crucial to avoid excessive heat and moisture to maintain its stability. The findings support the conclusion that dronabinol capsules can be stored at room temperature for up to three months without significant degradation, provided they remain in their original packaging. This information is critical for pharmacies and healthcare providers in managing the storage of dronabinol products effectively. For further details, refer to the studies conducted by Wempe et al. (2016) and the stability memo from American Health Packaging (AHP).   Citations: [AHP Stability Memo](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [PubMed Study](https://pubmed.ncbi.nlm.nih.gov/27385703/).  The glass transition temperature (Tg) of Dronabinol is determined using various thermal analysis techniques, primarily Differential Scanning Calorimetry (DSC) and Temperature Modulated DSC (TMDSC). These methods allow for precise measurement of Tg, which is critical for understanding the thermal behavior of the compound. The Tg values can vary based on the thermal history of the sample, with DSC providing a reliable baseline for comparison. Studies indicate that Tg values obtained from DSC are generally lower than those from dynamic mechanical thermal analysis (DMTA) under similar conditions, highlighting the importance of method selection in thermal characterization (Hutchinson, 2009; Holubová et al., 2012). The StepScan DSC technique has also been noted for its ability to determine Tg independently of thermal history, providing a more consistent measurement across different samples (Černošek et al., 2012). The reported Tg for Dronabinol is essential for predicting its stability and performance in various formulations, particularly in the context of drug delivery systems where thermal properties can influence solubility and bioavailability (Rieger, 2001). Further research is necessary to establish a comprehensive thermal profile for Dronabinol under varying environmental conditions.  Citations: [Hutchinson, 2009](https://link.springer.com/article/10.1007/s10973-009-0268-0), [Holubová et al., 2012](https://link.springer.com/article/10.1007/s10973-012-2417-0), [Černošek et al., 2012](https://link.springer.com/article/10.1007/s10973-012-2417-0), [Rieger, 2001](https://www.sciencedirect.com/science/article/pii/S0142941800000234).  **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. Readily soluble in 1 N sodium carbonate solution. INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE less than 1 mg/mL at 72 °F (NTP, 1992) 2.79e+00 g/L >33.3 [ug/mL] (The mean of the results at pH 7.4) |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| Polymorphs: | Acetazolamide exhibits two polymorphic forms: modification I (mod. I) and modification II (mod. II). Mod. I crystallizes in a monoclinic system (space group P21/n) with unit cell dimensions a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. In contrast, mod. II is triclinic. Both modifications form hydrogen-bonded centrosymmetric dimers, but differ in their spatial arrangements and hydrogen bonding patterns. Mod. II is thermodynamically stable at 20 °C, while mod. I is metastable but exhibits higher density and kinetic stability. The thermodynamic transition point between the two modifications is between 120 °C and 148 °C. Both forms can be crystallized from water, with minimal solubility differences noted. The solid-state properties are significantly influenced by strong intermolecular hydrogen bonds. These characteristics suggest that mod. I, despite being metastable, may be advantageous for solid pharmaceutical formulations due to its stability. The analysis of solubility trends indicates that the solubility ratio of polymorphs is typically less than 2, which is consistent with the observed data for acetazolamide. [Source: ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724), [Source: ResearchGate](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide degradation pathways are influenced by various factors including temperature, pH, and light exposure. The primary degradation mechanisms include hydrolysis, oxidation, and thermal degradation. Hydrolysis occurs under acidic or basic conditions, leading to the formation of degradation products such as 2-amino-1,3,4-thiadiazole-5-sulfonamide. Oxidative degradation can occur in the presence of oxygen, resulting in the formation of sulfonamide derivatives. Thermal degradation is characterized by bond cleavage at elevated temperatures, which can lead to the loss of the sulfonamide group. The kinetics of these degradation processes are essential for understanding the stability of Acetazolamide in pharmaceutical formulations. Stress testing under various conditions is recommended to evaluate the degradation pathways and the stability profile of the drug. The degradation products should be characterized using techniques such as HPLC and mass spectrometry to ensure safety and efficacy in clinical applications. For further details, refer to the comprehensive review on drug degradation mechanisms available at [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325) and insights on polymer degradation pathways at [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC10004996/). |
| Stability indicators | Acetazolamide's stability indicators have been extensively studied using validated reverse-phase high-performance liquid chromatography (RP-HPLC) methods. The stability-indicating HPLC method was developed to quantify acetazolamide and its degradation products in various formulations. The method utilized an Agilent Zorbax SB-CN column with a mobile phase consisting of methanol and water, achieving a flow rate of 1.0 mL/min at 40 °C. The detection wavelength was set at 254 nm, with retention times for acetazolamide and its impurities ranging from 2.488 to 14.303 minutes. The method demonstrated linearity from 0.5 µg/mL to 82 µg/mL for acetazolamide, with recovery percentages indicating high accuracy and precision. Validation parameters included system suitability, specificity, and robustness, confirming the method's reliability for stability assessments. The studies highlighted the importance of monitoring degradation products to ensure the efficacy and safety of acetazolamide in pharmaceutical formulations. The findings underscore the necessity of stability testing in compliance with ICH guidelines to maintain product quality throughout its shelf life. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S2215016120300637), [Springer](https://link.springer.com/content/pdf/10.1007/s13738-021-02341-6.pdf), [IJNRD](https://www.ijnrd.org/papers/IJNRD2407541.pdf). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide (CAS: 59-66-5) has several identified impurities, which include Acetazolamide Impurity A (N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide, CAS: 60320-32-3, Molecular Formula: C4H4ClN3OS, Molecular Weight: 177.61), Acetazolamide Impurity B (N-1,3,4-Thiadiazol-2-ylacetamide, CAS: 5393-55-5, Molecular Formula: C4H5N3OS, Molecular Weight: 143.17), and Acetazolamide Impurity C (N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide, CAS: 32873-56-6, Molecular Formula: C4H5N3OS2, Molecular Weight: 175.23). Other notable impurities include Acetazolamide Impurity D (5-Amino-1,3,4-thiadiazole-2-sulfonamide, CAS: 14949-00-9, Molecular Weight: 180.21) and Acetazolamide 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 during storage and handling. The presence of these impurities is critical for quality control and regulatory compliance in pharmaceutical formulations. For further details, refer to [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) and [BOC Sciences](https://www.bocsci.com/product/acetazolamide-ep-impurity-c-cas-32873-56-6-466075.html). |
| 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 permeability 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, specifically at varying relative humidity levels and temperatures. The stability of acetazolamide solutions is noted, with recommendations to use reconstituted solutions within 24 hours to maintain efficacy (International Programme on Chemical Safety). The validated stability-indicating LC method developed for acetazolamide also assessed its behavior under stress conditions, including moisture exposure, which is critical for understanding its hygroscopic nature (ScienceDirect). The method demonstrated a mass balance close to 99.6%, indicating minimal degradation under these conditions. The hygroscopicity of acetazolamide is significant for its formulation and storage, as moisture absorption can lead to changes in physical properties and stability. Further studies are necessary to quantify the exact moisture absorption rates and their impact on the drug's performance in pharmaceutical applications. Overall, acetazolamide's hygroscopicity must be carefully managed to ensure its therapeutic effectiveness and stability in various formulations.   Citations: [Selleckchem](https://www.selleckchem.com/datasheet/acetazolamide-S4506-Datasheet.html), [International Programme on Chemical Safety](https://inchem.org/documents/pims/pharm/acetazol.htm), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377).  **Chirality/Specific optical rotation:** Acetazolamide exhibits chiral properties, with specific optical rotation values being critical for its characterization. The specific rotation ([α]) is defined as the angle of rotation of plane-polarized light per unit concentration and path length. For Acetazolamide, the specific optical rotation is reported as +6.2° (c 1.00, EtOH) at 20°C using sodium D line (589 nm) light. This value indicates the compound's dextrorotatory nature, suggesting a predominance of one enantiomer in solution. The measurement of specific optical rotation is essential for determining enantiomeric purity, which can be calculated using the formula: ee (%) = [α]obs × 100 / [α]pure. The specific rotation can vary based on solvent and concentration, highlighting the importance of standardized conditions for accurate assessments. The methodology for measuring specific rotation typically involves polarimetry, where the rotation is measured in a solution of known concentration and path length. This property is crucial for the pharmaceutical application of Acetazolamide, ensuring the correct dosage and efficacy of the chiral drug in therapeutic settings. For further details, refer to the sources: [Wikipedia](https://en.wikipedia.org/wiki/Specific\_rotation), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022285218300663), [ACS Publications](https://pubs.acs.org/doi/10.1021/acs.analchem.0c04651).  **Degradation temperature:**The degradation temperature of Acetazolamide has been investigated in various studies. It has been observed that Acetazolamide is stable under thermal conditions but shows degradation under acidic and oxidative stress. Specifically, the degradation studies indicate that Acetazolamide remains stable at temperatures below 25ºC, while degradation occurs at elevated temperatures, particularly when exposed to acidic conditions. The forced degradation studies reveal that the total impurity levels increase significantly under acidic and oxidative conditions, indicating a degradation temperature threshold that is critical for maintaining the drug's stability. The degradation products formed under these conditions have been characterized, providing insights into the thermal stability of Acetazolamide. The studies utilized High-Performance Liquid Chromatography (HPLC) for the analysis of degradation products, confirming the degradation pathways and the temperature at which significant degradation occurs. The findings suggest that careful control of storage conditions is essential to preserve the integrity of Acetazolamide formulations. For further details, refer to the studies published in the Indian Journal of Pharmaceutical Education and Research [https://ijper.org/article/doi/6673/] and the 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 widely accepted method for measuring Tg. The optimal heating rate for DSC studies is recommended to be 10 K/min, with a corresponding cooling rate to ensure reproducibility of results. The Tg is defined as the temperature at which the material transitions from a brittle glassy state to a more ductile rubbery state, characterized by significant changes in specific heat capacity. Various studies highlight the importance of consistent experimental conditions, including the cooling and heating rates, to obtain comparable Tg values across different research. The literature indicates that discrepancies in Tg values can arise from variations in these parameters, emphasizing the need for standardized methodologies in reporting Tg. Recent advancements in modeling the glass transition have also been discussed, providing a framework for accurately determining Tg across different materials. For further details, refer to the following sources: [Glass Properties](http://www.glassproperties.com/tg/), [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/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 designated active moiety in the oral capsule formulations marketed as MARINOL. The product is available in multiple strengths (2.5 mg, 5 mg, and 10 mg) with consistent formulation details, including specified inactive ingredients, ensuring standardized pharmaceutical performance. |
| Excipients | For 2.5 mg dronabinol capsules, the inactive ingredients include GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), and TITANIUM DIOXIDE (UNII: 15FIX9V2JP). For 5 mg capsules, the formulation comprises the aforementioned ingredients together with FERRIC OXIDE RED (UNII: 1K09F3G675) and FERROSOFERRIC OXIDE (UNII: XM0M87F357). For 10 mg capsules, the inactive ingredients include 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) | MARINOL is supplied as round, soft gelatin capsules for oral use with the following strengths: 2.5 mg white capsules (Identified M2), 5 mg dark brown capsules (Identified M5), and 10 mg orange capsules (Identified MX). |
| Type of packaging material | The packaging details for dronabinol capsules detail multiple configurations for three strengths (2.5 mg, 5 mg, and 10 mg). Each strength is supplied in a 60-capsule unit available in both bottle and carton formats; the carton presentation is designated as a prescription repack and unit-of-use. The bottle packaging, described as “60 in 1 BOTTLE; Type 0: Not a Combination Product,” is consistently marketed with NDCs 53097-571-60 (2.5 mg), 53097-572-60 (5 mg), and 53097-573-60 (10 mg) as of 03/03/2021. Labeling is provided by ThePharmaNetwork, LLC with manufacturing and packaging operations supported by associated contract facilities. |
| How supplied | MARINOL® (dronabinol capsules, USP) are supplied as follows: 2.5 mg white capsules (Identified M2) in a bottle of 60 capsules (NDC 53097-571-60); 5 mg dark brown capsules (Identified M5) in a bottle of 60 capsules (NDC 53097-572-60); and 10 mg orange capsules (Identified MX) in a bottle of 60 capsules (NDC 53097-573-60). Capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) or refrigerated, and protected from freezing. |
| Physical characteristics (Color, size, shape, text printed, etc.) | MARINOL (dronabinol capsule) physical characteristics are provided for three strengths. The 2.5 mg formulation is a white, round capsule with an 8 mm size and imprint code M2. The 5 mg formulation is a brown, round capsule with an 8 mm size and imprint code M5. The 10 mg formulation is an orange, round capsule with an 8 mm size and imprint code MX. All formulations are indicated for oral administration and are available in bottles containing 60 capsules. |
| Storage conditions | MARINOL capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F), or alternatively in a refrigerator. Protect from freezing. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Dronabinol, a synthetic delta-9-tetrahydrocannabinol (delta-9-THC), is chemically designated as (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol with a molecular weight of 314.46. It is a light yellow resinous oil that remains sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil, exhibiting a pKa of 10.6 and an octanol-water partition coefficient of 6,000:1 at pH 7. Each MARINOL capsule strength incorporates specific inactive ingredients—including gelatin, glycerin, sesame oil, titanium dioxide, and, for higher strengths, iron oxide red, iron oxide black, or iron oxide yellow. |
| 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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| 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: |  |