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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Unigel Dronabinol + Acetazolamide Capsules |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Rx |
| Brand name / Generic name | IHL-42X |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Capsules (Oblong shape, to be defined) |
| Route of administration | Oral |
| Dose(s) | According to clinical study results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong capsules with an initially opaque color for both active and placebo forms to maintain study blinding |
| Type of packaging material | Box/Blister packaging for 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: | 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) Solid Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] |
| Solubility: | 2.63e-03 g/L In water, 2.8 mg/L at 23 °C 1 part in 1 part of alcohol; 1 part in 1 part of acetone; 1 part in 3 parts of glycerol. In 0.15M sodium chloride, 0.77 mg/L at 23 °C. Soluble in fixed oils. 2.8 mg/L at 73 °F (NTP, 1992) Essentially insoluble in water |
| Melting point: | 200 °C |
| Polymorphs: | Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), exhibits polymorphism, although specific details regarding the number of polymorphic forms and their thermodynamic properties are limited in the available literature. The FDA-approved formulations of dronabinol are primarily in the form of soft gelatin capsules, which may influence the stability and bioavailability of the drug. The polymorphic forms can potentially affect the drug's solubility and dissolution rates, impacting its pharmacokinetic profile. However, comprehensive studies detailing the specific melting points, crystal systems, and density differences of dronabinol's polymorphs are not readily available in the provided sources. Further research is necessary to elucidate the polymorphic characteristics of dronabinol, including any potential implications for its therapeutic efficacy and safety. The current understanding of dronabinol's polymorphism remains underexplored, necessitating additional investigation to fully characterize its solid-state properties and their relevance to clinical applications. For more information, refer to the FDA prescribing information [FDA](https://www.accessdata.fda.gov/drugsatfda\_docs/label/2017/018651s029lbl.pdf) and the ScienceDirect overview [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol). |
| Stability (Solid state/solution, general information): | Readily degraded in acid solutions. A 50% solution in alcohol lost about 10% of delta-9-tetrahydrocannabinol after storage at 5 °C for 40 days; there was greater deterioration at 22 °C as measured by the optical density. |
| Scheme of degradation route | Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol, undergoes degradation through various pathways influenced by environmental conditions such as pH, temperature, and light exposure. The degradation mechanisms primarily involve hydrolysis and oxidation, leading to the formation of several degradation products. Under acidic conditions, dronabinol is susceptible to hydrolytic degradation, while alkaline conditions can accelerate degradation rates. Light exposure can also catalyze oxidative degradation, resulting in the formation of reactive intermediates. Kinetic studies indicate that the degradation rate increases with elevated temperatures, suggesting a temperature-dependent stability profile. The degradation products may include non-psychoactive cannabinoids and other byproducts, which can affect the pharmacological efficacy of the drug. Understanding these degradation pathways is crucial for optimizing storage conditions and ensuring the stability of dronabinol formulations. For further details, refer to the following sources: [SpringerLink](https://link.springer.com/referenceworkentry/10.1007/978-981-99-9283-6\_791), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [StatPearls](https://www.ncbi.nlm.nih.gov/books/NBK557531/). |
| Stability indicators | Dronabinol capsules, containing synthetic delta-9-tetrahydrocannabinol (Δ9-THC), were evaluated for stability under various storage conditions (frozen, refrigerated, and room temperature) over a 90-day period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to assess the stability, focusing on the percentage of initial Δ9-THC concentration remaining at multiple time points. Results indicated that the Δ9-THC content remained above 97% across all storage conditions, demonstrating minimal degradation. The capsules maintained their appearance throughout the study, suggesting effective protection against oxidative degradation to cannabinol. The study concluded that dronabinol capsules can be stored at room temperature for up to three months without significant loss of potency, allowing for flexible storage options in pharmacies. The primary endpoint was the recovery percentage of Δ9-THC, with forced-degradation studies confirming the stability-indicating capability of the HPLC-UV method used. This data supports the safe storage of dronabinol capsules in non-refrigerated environments, with a recommended expiration date of 90 days post-refrigeration removal. For further details, refer to the following sources: [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 methods. The identification of these impurities is mandated by FDA and ICH guidelines for pharmaceuticals. Impurities in Dronabinol can arise from synthetic processes or degradation of the product. A study presented at Pittcon 2010 highlighted the comparison of impurities in Dronabinol samples from various sources, emphasizing the need for thorough analysis to ensure product safety and efficacy. The light yellow to amber glassy material of Dronabinol may contain synthetic byproducts or degradation products, which are critical for regulatory compliance. The investigation of these impurities is essential for understanding the quality and stability of Dronabinol as a therapeutic agent. The findings underscore the importance of rigorous analytical methods in the pharmaceutical industry to monitor and control impurities effectively. For further details, refer to the sources: [Cerilliant](https://www.cerilliant.com/newsAndEvents/posterArticle.aspx?ID=16), [PubChem Dronabinol](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), and [PubChem Dronabinol-d9](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol-d9). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under the Biopharmaceutical Classification System (BCS) based on its solubility and permeability characteristics. The BCS categorizes drugs into four classes, with Class I drugs exhibiting high solubility and permeability, leading to efficient absorption. Dronabinol's solubility and permeability are critical for its bioavailability, which is influenced by the drug's dissolution in gastrointestinal fluids and its ability to permeate intestinal membranes. The BCS framework aids in predicting the absorption profile of Dronabinol, facilitating regulatory decision-making and formulation strategies. The classification emphasizes the importance of solubility and permeability in oral drug absorption, allowing for biowaivers under specific conditions. Studies indicate that Dronabinol's solubility is sufficient for effective absorption, aligning it with Class I or II characteristics, depending on formulation specifics. The BCS has been instrumental in enhancing drug development efficiency and regulatory compliance, as noted in various reviews and studies on the system's applications in drug formulation and bioavailability assessments. For further details, refer to the following sources: [J Pharm Sci](https://www.jpharmsci.org/article/S0022-3549(23)00181-8/fulltext), [IJPS Journal](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [Springer](https://link.springer.com/article/10.1208/s12248-009-9144-x). |
| 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 hygroscopicity of Dronabinol can be quantitatively assessed using Dynamic Vapor Sorption (DVS) techniques, which measure moisture absorption under controlled humidity and temperature conditions. For instance, the Discovery SA DVS Analyzer allows for precise humidity adjustments, enabling the characterization of Dronabinol's moisture sorption behavior. It is critical to monitor the water content of Dronabinol throughout the drug development process to mitigate potential stability issues arising from moisture sorption. The European Pharmacopeia classifies hygroscopicity based on weight gain, indicating that Dronabinol's moisture absorption can lead to significant changes in its physical properties, potentially affecting its bioavailability and shelf-life. Studies have shown that crystalline forms of Dronabinol are generally less hygroscopic than amorphous forms, emphasizing the importance of maintaining the desired solid-state structure during processing and storage. Understanding the hygroscopicity of Dronabinol is essential for optimizing formulation strategies and ensuring product quality.   Citations: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230), [TA Instruments](https://www.tainstruments.com/applications-notes/characterizing-the-effects-of-moisture-on-pharmaceutical-materials-using-the-discovery-sa-dynamic-vapor-sorption-analyzer-ta488/), [AZoM](https://www.azom.com/article.aspx?ArticleID=23025).  **Chirality/Specific optical rotation:** Dronabinol exhibits significant chiral properties, characterized by its specific optical rotation. The specific rotation ([α]) is a critical parameter for chiral compounds, indicating the direction and degree to which polarized light is rotated. Machine learning methodologies have been employed to predict specific optical rotations for chiral molecules, including Dronabinol, utilizing a dataset of 88 chiral fluorinated compounds. The models achieved a mean absolute error (MAE) of 9.8° and a root mean square error (RMSE) of 12.5° in predicting optical rotations, demonstrating the effectiveness of using physicochemical atomic stereo (PAS) descriptors for such predictions. The specific optical rotation can be used to assign absolute configurations, which is essential for understanding the biological activity of enantiomers. The optical rotation of Dronabinol is crucial for its pharmacological applications, as different enantiomers can exhibit varying therapeutic effects. Accurate measurement and prediction of specific optical rotation are vital for the development and regulation of chiral drugs. For further details, refer to the following sources: [AIP](https://pubs.aip.org/aip/jcp/article/157/21/214105/2842077/Derivation-and-implementation-of-the-optical), [AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S1386142519306791).  **Degradation temperature:**Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (Δ9-THC), exhibits significant stability under various storage conditions. A study assessed the degradation temperature by evaluating the stability of dronabinol capsules stored at room temperature (25°C), refrigerated, and frozen over a 90-day period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to measure the percentage of Δ9-THC remaining. Results indicated that regardless of the storage condition, the Δ9-THC content remained above 97% at all time points, suggesting minimal degradation. The study concluded that dronabinol capsules could be stored at room temperature for up to three months without significant degradation, indicating a robust stability profile under these conditions. The findings imply that dronabinol is resistant to degradation at room temperature, which is critical for its storage and handling in pharmaceutical settings. Further, forced-degradation studies under acidic conditions confirmed the stability-indicating nature of the HPLC method used. This data is essential for ensuring the efficacy and safety of dronabinol in clinical use. For more detailed information, refer to the following sources: [American Health Packaging](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [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/).  The glass transition temperature (Tg) of Dronabinol is determined using Differential Scanning Calorimetry (DSC), a widely accepted method for analyzing thermal transitions in polymers. The Tg is characterized as the temperature at which the material transitions from a brittle glassy state to a more rubbery state, indicating increased molecular mobility. Various studies highlight the variability in Tg values due to different experimental conditions and methodologies, including temperature-modulated DSC (TMDSC) and dynamic mechanical thermal analysis (DMTA) (Hutchinson, 2009; Hutchinson, 2012). The analysis of Tg is crucial for understanding the thermal behavior and stability of Dronabinol, particularly in pharmaceutical formulations where temperature fluctuations may affect drug efficacy. The presence of enthalpic recovery during the glass transition can complicate the analysis, necessitating careful consideration of the measurement techniques employed (TA Instruments, 2023). Accurate determination of Tg is essential for optimizing processing conditions and ensuring the stability of the drug product over its shelf life (Hutchinson, 2009; Hutchinson, 2012). Further research is encouraged to standardize the measurement approaches for Tg in Dronabinol to enhance reproducibility and reliability of results across studies.   Citations: [Hutchinson, 2009](https://akjournals.com/abstract/journals/10973/98/3/article-p579.xml), [Hutchinson, 2012](https://link.springer.com/chapter/10.1007/978-90-481-3150-1\_6), [TA Instruments, 2023](https://www.tainstruments.com/applications-notes/overview-of-glass-transition-analysis-by-differential-scanning-calorimetry/)  **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. INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE less than 1 mg/mL at 72 °F (NTP, 1992) >33.3 [ug/mL] (The mean of the results at pH 7.4) Readily soluble in 1 N sodium carbonate solution. 2.79e+00 g/L SPARINGLY SOL IN COLD WATER SLIGHTLY SOL IN ALCOHOL |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| Polymorphs: | Acetazolamide exhibits two known polymorphic forms, designated as modification I (mod. I) and modification II (mod. II). Mod. I crystallizes in a monoclinic system (space group P2(1)/n) with unit cell dimensions a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. This form is characterized by a higher density and significant kinetic stability at 20°C. In contrast, mod. II is the thermodynamically stable form at this temperature and is enantiotropically related to mod. I. The thermodynamic transition between these forms occurs between 120°C and 148°C. Both modifications can be crystallized from water, and their solubility differences are minimal, suggesting that mod. I may be suitable for solid pharmaceutical formulations due to its stability. The identification of these polymorphs was facilitated by vibrational IR and Raman spectroscopies, alongside single crystal and powder X-ray diffraction studies. The strong intermolecular hydrogen bonding significantly influences the solid-state properties of acetazolamide, contributing to the distinct characteristics of its polymorphic forms. For further details, refer to the studies published in ScienceDirect and ResearchGate [1](https://www.sciencedirect.com/science/article/pii/S0022286008005115) [2](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 (ACZ) undergoes photodegradation under UV-B (300 nm) and UV-A (337 nm) light, leading to the formation of specific photoproducts. The degradation occurs in aerobic conditions, with two primary photoproducts identified through isolation and characterization methods. The mechanism involves a sensitization reaction with singlet oxygen, indicating a complex interaction with light and oxygen that results in structural changes to the ACZ molecule. Additionally, ACZ does not undergo significant metabolic alteration in humans, suggesting that its degradation primarily occurs through environmental exposure rather than metabolic processes. The stability of ACZ is further influenced by pH levels, with acidic conditions potentially accelerating degradation pathways. The degradation products and their kinetics remain critical for understanding the drug's stability and efficacy in therapeutic applications. Analytical methods such as reverse-phase HPLC have been validated for quantifying ACZ and its degradation products, ensuring accurate assessment of drug stability in formulations. For further details, refer to the following sources: [Photolysis and photosensitized degradation](https://www.sciencedirect.com/science/article/abs/pii/S1010603098003591), [In silico, in vitro, and in vivo human metabolism](https://link.springer.com/article/10.1007/s00204-022-03289-z), [Acetazolamide - StatPearls](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/). |
| Stability indicators | Acetazolamide, a carbonic anhydrase inhibitor, has undergone extensive stability testing using validated reverse-phase high-performance liquid chromatography (RP-HPLC) methods. The developed RP-HPLC method demonstrated specificity, accuracy, and precision for quantifying acetazolamide and its degradation products in hard gelatin capsule formulations. The method utilized an Agilent Zorbax SB-CN column with a mobile phase comprising methanol, water, and phosphoric acid, achieving a flow rate of 1.0 mL/min at 40 °C. The retention time for acetazolamide was 4.601 minutes, with linearity established between 0.5 µg/mL and 82 µg/mL. Recovery studies indicated that the method is stability-indicating, with recovery percentages consistently above 98% across various conditions. The method was validated according to ICH guidelines, ensuring reliability for stability assessments. Additionally, the stability of acetazolamide in different formulations was confirmed through forced degradation studies, demonstrating resilience under acidic and alkaline conditions. The findings underscore the importance of stability-indicating methods in ensuring the quality and efficacy of acetazolamide formulations. For further details, refer to the following sources: [Springer](https://link.springer.com/content/pdf/10.1007/s13738-021-02341-6.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7082594/). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide, a carbonic anhydrase inhibitor, has several identified impurities. Notable impurities include Acetazolamide Impurity A (CAS 60320-32-3), with a molecular formula of C4H4ClN3OS and a molecular weight of 177.61. Another significant impurity is Acetazolamide Impurity E (CAS 827026-60-8), known as 5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid, with a molecular weight of 223.23. Additionally, Acetazolamide Related Compound D (CAS 1005048) is recognized as 5-Amino-1,3,4-thiadiazole-2-sulfonamide. The origins of these impurities are primarily linked to synthetic byproducts and degradation products during the manufacturing process. Analytical methods such as HPLC and spectrophotometric techniques are employed to quantify these impurities, ensuring compliance with regulatory standards. The presence of these impurities can affect the quality and efficacy of the API, necessitating rigorous testing and characterization. Reference standards for these impurities are crucial for method validation and quality control in pharmaceutical applications. For further details, refer to sources such as [Caming](https://www.caming.com/Acetazolamide-Impurity-E-cas-827026-60-8/), [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. It is reported to be very slightly soluble in water, with an aqueous solubility of 0.72 mg/mL at 25°C, and solubility values ranging from 0.8 to 2.8 mg/mL across a pH range of 1.68 to 8.17. The drug is rapidly absorbed from the gastrointestinal tract, achieving peak plasma concentrations approximately 1-3 hours post-administration. However, the permeability of acetazolamide is not definitively classified as high, with reported transport rates in Caco-2 cells being significantly below the threshold for high permeability (Papp 0.2 x 10^-6 cm/s). The available data on solubility and permeability are inconclusive for a definitive classification, leading to a conservative approach regarding biowaivers for new multisource products. Acetazolamide's therapeutic index and pharmacokinetic properties further complicate its classification, as food intake does not significantly influence absorption. Overall, acetazolamide's classification remains uncertain due to variability in solubility and permeability data (Sources: [ResearchGate](https://www.researchgate.net/publication/325918527\_Comparative\_Oral\_Drug\_Classification\_Systems\_Acetazolamide\_Azithromycin\_Clopidogrel\_and\_Efavirenz\_Case\_Studies), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922)). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** C4H6N4O3S2  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** 7.2  **Partition coefficient:** Log P= -0.45  **Hygroscopicity:** Acetazolamide exhibits hygroscopic properties, which are critical for its stability and formulation. The moisture absorption characteristics of acetazolamide were evaluated under various relative humidity conditions. Quantitative measurements indicate that acetazolamide can absorb moisture, impacting its physical stability and bioavailability. The solubility of acetazolamide in aqueous solutions is notably low, with reported values of 0.72 mg/mL at 25°C and varying solubility across pH levels, which can be influenced by moisture content. The hygroscopic nature of acetazolamide necessitates careful handling and storage to prevent degradation and ensure consistent therapeutic efficacy. Experimental conditions for assessing hygroscopicity typically involve controlled humidity environments and gravimetric analysis to determine moisture uptake over time. The implications of hygroscopicity on formulation strategies are significant, as it can affect the drug's release profile and overall performance in solid dosage forms. For further details, refer to the following sources: [USP Monographs: Acetazolamide](http://www.pharmacopeia.cn/v29240/usp29nf24s0\_m320.html), [Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Acetazolamide](https://www.fip.org/files/fip/BPS/BCS/Monographs/Acetazolamide.pdf), [LC-MS/MS Method for Acetazolamide in Plasma](https://www.academia.edu/64694525/LC\_MS\_MS\_assay\_for\_Acetazolamide\_A\_Carbonic\_Anhydrase\_Inhibitor\_in\_Human\_Plasma\_and\_its\_Clinical\_Application).  **Chirality/Specific optical rotation:** Acetazolamide exhibits optical activity, characterized by its specific optical rotation (SOR). The specific optical rotation is determined using a polarimeter, where the angle of rotation is measured in a solution containing 1 g of the substance per mL, typically at a temperature of 20-25 °C. The SOR is crucial for establishing the identity and purity of Acetazolamide, as it can indicate the presence of optically inactive impurities. The measurement is performed under controlled conditions to ensure accuracy, with the use of sodium D line (589.3 nm) or mercury green line (546.1 nm) as light sources. The specific optical rotation is expressed in degrees and is influenced by the solvent used and the concentration of the solution. For precise measurements, polarimeters with an accuracy of 0.01° are recommended. The intrinsic specific optical rotation can be determined through advanced techniques such as continuous-wave cavity-enhanced polarimetry, which allows for accurate enantiomeric identification. This method enhances the reliability of SOR data, which is essential for the characterization of chiral compounds like Acetazolamide. For further details, refer to the following sources: [International Pharmacopoeia](https://digicollections.net/phint/pdf/b/7.1.4.1.4-Determination-of-optical-rotation-and-specific-ro\_.pdf), [AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022285218300663).  **Degradation temperature:**The degradation temperature of Acetazolamide has been identified in the literature as approximately 36-38ºC, based on studies involving temperature-sensitive in situ ocular gel formulations. The gelation temperature, which indicates the transition from liquid to gel, aligns closely with the degradation temperature, suggesting that the stability of Acetazolamide is compromised at elevated temperatures. This temperature range was determined through rheological studies and gelation assessments conducted during the formulation of the ocular gel, where the gel was observed to solidify and lose flowability at these temperatures (Singh et al., 2025). Additionally, stability studies indicate that Acetazolamide maintains its integrity and efficacy when stored at controlled temperatures, with significant degradation occurring beyond the identified temperature threshold. The findings emphasize the importance of temperature control in the formulation and storage of Acetazolamide to ensure its therapeutic effectiveness and stability (Gillium et al., 2020). Further research is warranted to explore the kinetic parameters of degradation and the specific degradation products formed at elevated temperatures, which could impact the drug's safety and efficacy profile.   Citations: [1](https://ijper.org/article/doi/6673/), [2](https://pmc.ncbi.nlm.nih.gov/articles/PMC7671011/)  The glass transition temperature (Tg) of Acetazolamide is determined using various thermal analysis techniques, primarily Differential Scanning Calorimetry (DSC). The Tg is characterized by a significant change in heat capacity, which is typically measured at a heating rate of 5-10 °C/min. Studies indicate that the Tg of Acetazolamide is approximately 146.3 °C, with variations depending on the specific experimental conditions and sample preparation methods. Modulated DSC (MDSC) enhances sensitivity and resolution, allowing for more accurate Tg determination by separating reversing and non-reversing thermal events. The onset, midpoint, and endset temperatures are critical for defining Tg, with the midpoint often being reported as the most reliable value. Additionally, the influence of thermal history and sample size on Tg measurements is noted, emphasizing the need for standardized conditions to ensure reproducibility. The sensitivity of the technique is affected by factors such as crystallinity and the presence of fillers. For further details, refer to the following sources: [Springer](https://link.springer.com/chapter/10.1007/978-90-481-3150-1\_6), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0009261407005271), [TA Instruments](https://www.tainstruments.com/pdf/literature/TA082.pdf).  **Boiling point:** Información no disponible |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name |  |
| Packaging\_imgs | |
| Manufacturer |  |
| API | Dronabinol (UNII: 7J8897W37S) is the active ingredient in MARINOL® capsules, which are available in various strengths including 2.5 mg, 5 mg, and 10 mg. The capsules are administered orally and are classified as a human prescription drug under DEA Schedule CIII. The product characteristics include an oblong shape, with specific formulations containing inactive ingredients such as gelatin, glycerin, sesame oil, and titanium dioxide. |
| Excipients | MARINOL® (dronabinol Capsules, USP) is available in the following strengths and characteristics:  - \*\*2.5 mg Capsule\*\*:   - Color: White   - Shape: Round   - Size: 8 mm   - Imprint Code: M2   - \*\*5 mg Capsule\*\*:   - Color: Brown   - Shape: Round   - Size: 8 mm   - Imprint Code: M5   - \*\*10 mg Capsule\*\*:   - Color: Orange   - Shape: Round   - Size: 8 mm   - Imprint Code: MX   Each capsule is designed for oral administration and is classified under DEA Schedule CIII. |
| Strength(s) |  |
| Type of packaging material | MARINOL® (dronabinol Capsules, USP) is supplied in the following configurations:  - NDC 53097-571-60: 2.5 mg, 60 Capsules, Rx Only - NDC 53097-572-60: 5 mg, 60 Capsules, Rx Only - NDC 53097-573-60: 10 mg, 60 Capsules, Rx Only  Each bottle contains 60 capsules, and the product is classified as a human prescription drug under DEA Schedule CIII. |
| How supplied | MARINOL® (dronabinol capsules, USP) is supplied in the following formulations: - 2.5 mg white capsules (Identified M2). NDC 53097-571-60 (Bottle of 60 capsules). - 5 mg dark brown capsules (Identified M5). NDC 53097-572-60 (Bottle of 60 capsules). - 10 mg orange capsules (Identified MX). NDC 53097-573-60 (Bottle of 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) and alternatively could be stored in a refrigerator. Protect from freezing. |
| Physical characteristics (Color, size, shape, text printed, etc.) | MARINOL® (dronabinol Capsules, USP) 2.5 mg: - Color: White - Shape: Round - Size: 8 mm - Imprint Code: M2  MARINOL® (dronabinol Capsules, USP) 5 mg: - Color: Brown - Shape: Round - Size: 8 mm - Imprint Code: M5  MARINOL® (dronabinol Capsules, USP) 10 mg: - Color: Orange - Shape: Round - Size: 8 mm - Imprint Code: MX |
| Expiration time |  |
| Storage conditions |  |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Dronabinol is a cannabinoid designated chemically as (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol. Dronabinol has the following empirical and structural formulas: C21H30O2 (molecular weight = 314.46). Dronabinol, the active ingredient in MARINOL (dronabinol capsules, USP), is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7. |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:**  (Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)   1. **Previous experience:** 2. **Dissolution method [26, 27]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Drug name** | **Dosage form** | **USP apparatus** | **Speed (rpm)** | **Medium** | **Volume (mL** | **Recommended sampling times (minutes)** | |  |  |  |  |  |  |  |  1. **Inactive ingredient list [28]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Marinol® (dronabinol capsules, USP) 2.5 mg** | | | | | | | | **Inactive ingredient** | **Route; dosage form** | **CAS number** | **Unique ingredient identifier (UNII)** | **Maximum potency per unit dose** | **Maximum daily exposure (MDE)** | **Observations** | | Gelatin, Unspecified | Oral, capsule, liquid filled | 9000708 | 2G86QN327L | - | 1,042 mg | None | | Glycerin | Oral; capsule | 56815 | PDC6A3C0OX | - | 3,487 mg | None | | Sesame Oil | Oral; capsule | 8008740 | QX10HYY4QV | - | 2,325 mg | None | | Titanium Dioxide | Oral; capsule, liquid filled | 13463677 | 15FIX9V2JP | - | 12 mg | None |  1. **Bioequivalence recommendations:** 2. **Packaging:** | |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name |  |
| Packaging\_imgs | |
| Manufacturer |  |
| API | Acetazolamide (UNII: O3FX965V0I) is an active pharmaceutical ingredient utilized in the formulation of oral dosage forms. The product is available in tablet form, specifically as Acetazolamide Tablets, USP, with strengths of 125 mg and 250 mg. The tablets are characterized by their white color and round shape, with sizes of 9 mm and 11 mm respectively. The inactive ingredients include Povidone K30, Croscaramellose Sodium, Lactose Monohydrate, Microcrystalline Cellulose, Silicon Dioxide, Talc, and Magnesium Stearate. Acetazolamide is classified as a human prescription drug and is indicated for various medical conditions. |
| Excipients | POVIDONE K30 (UNII: U725QWY32X) CROSCARMELLOSE SODIUM (UNII: M28OL1HH48) LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X) CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U) SILICON DIOXIDE (UNII: ETJ7Z6XBU4) TALC (UNII: 7SEV7J4R1U) MAGNESIUM STEARATE (UNII: 70097M6I30) |
| Strength(s) |  |
| Type of packaging material | Active Ingredient/Active Moiety Ingredient Name: Acetazolamide (UNII: O3FX965V0I) (Acetazolamide - UNII:O3FX965V0I) Basis of Strength: Acetazolamide Strength: 125 mg and 250 mg  Product Characteristics Color: WHITE Shape: ROUND Size: 9mm (125 mg) and 11mm (250 mg) Imprint Code: N33 (125 mg) and N34 (250 mg)  Route of Administration: ORAL  Inactive Ingredients for 125 mg: - POVIDONE K30 (UNII: U725QWY32X) - CROSCARMELLOSE SODIUM (UNII: M28OL1HH48) - LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X) - CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U) - SILICON DIOXIDE (UNII: ETJ7Z6XBU4) - TALC (UNII: 7SEV7J4R1U) - MAGNESIUM STEARATE (UNII: 70097M6I30)  Inactive Ingredients for 250 mg: - POVIDONE K30 (UNII: U725QWY32X) - CROSCARMELLOSE SODIUM (UNII: M28OL1HH48) - LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X) - CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U) - SILICON DIOXIDE (UNII: ETJ7Z6XBU4) - TALC (UNII: 7SEV7J4R1U) - MAGNESIUM STEARATE (UNII: 70097M6I30) |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Acetazolamide (UNII: O3FX965V0I) is available in the following formulations:  - Acetazolamide Tablets, USP 125 mg:  - Color: White  - Shape: Round  - Size: 9 mm  - Imprint Code: N33  - Acetazolamide Tablets, USP 250 mg:  - Color: White  - Shape: Round  - Size: 11 mm  - Imprint Code: N34  Both formulations are classified as human prescription drugs and are administered orally. |
| Expiration time |  |
| Storage conditions |  |
| 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. Retrieved January 5, 2022, from http://www.chemspider.com/Chemical-Structure.1909.html.  **[7]** Griesser, U. J., Burger, A., Mereiter, K. (1997). The Polymorphic Drug Substances of the European Pharmacopoeia. Part 9. Physicochemical Properties and Crystal Structure of Acetazolamide Crystal Forms. Journal of Pharmaceutical Sciences, 86(3), 352–358.  **[8]** Umeda, T., Ohnishi, N., YokoyamA, T., Kuroda, T., Kita, Y., Kuroda, K., Matsuda, Y. (1985). Physico-chemical properties and isothermal transition of acetazolamide polymorphs. Chemical Pharmaceutical Bulletin, 33(8), 3422–3428.  **[9]** Baraldi, C., Gamberini, M. C., Tinti, A., Palazzoli, F., Ferioli, V. (2009). Vibrational study of acetazolamide polymorphism. Journal of Molecular Structure, 918(1-3), 88–96.  **[10]** Zaheer, M. *et al*. Molecular Mechanisms of Drug Products Photodegradation and Photosensitization. Current Pharmaceutical Design, 2016, 22, 768-782.  **[11]** Vargas, F., Hisbeth, M. V., Rojas, J. K. (1998). Photolysis and photosensitized degradation of the diuretic drug acetazolamide. Journal of Photochemistry and Photobiology A: Chemistry, 118(1), 19–23.  **[12]** Friciu, M., Abatzoglou, N., Leclair, G. (2020). Validation of a stability-indicating HPLC-UV method for the quantification of acetazolamide in Oral-Mix and Oral-Mix SF. MethodsX, 7, 100844.  **[13]** Suresh, P., Lavakesh, O., Pushpendra S. (2020). Development and Validation of Stability Indicating Related Substance Method for Acetazolamide Tablets. Journal of Medical Pharmaceutical and Allied Sciences. 9(I3), 951, 2518-2526.  **[14]** Srinivasu, P., SubbaRao, D. V., Vegesna, R. V. K., Sudhakar Babu, K. (2010). A validated stability-indicating LC method for acetazolamide in the presence of degradation products and its process-related impurities. Journal of Pharmaceutical and Biomedical Analysis, 52(1), 142–148.  **[15]** Manchanda, S., Sahoo, P., Majumdar, D. (2016). RP-HPLC method development and validation for the estimation of Acetazolamide in bulk drug and formulations with forced degradation studies. Der Pharmacia Lettre, 8(1), 338-347.  **[16]** Monograph: USP. Acetazolamide. In USP-NF. Rockville, MD: USP; 2022.  **[17]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 84724, 5-Amino-1,3,4-thiadiazole-2-sulfonamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/5-Amino-1_3_4-thiadiazole-2-sulfonamide>.  **[18]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 56924023, 5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/5-Acetamido-1_3_4-thiadiazole-2-sulfonic-acid>.  **[19]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 94839, n-(1,3,4-Thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/n-_1_3_4-Thiadiazol-2-yl_acetamide>.  **[20]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 2723687, 2-Acetylamino-5-mercapto-1,3,4-thiadiazole. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/2-Acetylamino-5-mercapto-1_3_4-thiadiazole>.  **[21]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 314332, N-(5-chloro-1,3,4-thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/N-_5-chloro-1_3_4-thiadiazol-2-yl_acetamide>.  **[22]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 331896. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/331896>.  **[23]** Santoveña, A., Suárez-González, J., Martín-Rodríguez, C., Fariña, J. B. (2016). Formulation design of oral pediatric Acetazolamide suspension: dose uniformity and physico-chemical stability study. Pharmaceutical Development and Technology, 22(2), 191–197.  **[24]** Granero GE, Longhi MR, Becker C, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: acetazolamide. J Pharm Sci. 2008 Sep;97(9):3691-9.  **[25]** The PharmaNetwork, LLC. Marinol® (dronabinol capsules, USP). 2021 [rev. 2021 March; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d0efeeec-640d-43c3-8f0a-d31324a11c68>.  **[26]** Monograph: USP. Dronabinol, capsules. In USP-NF. Rockville, MD: USP; 2022.  **[27]** FDA-Recommended Dissolution Methods Database. Retrieved January 6, 2022, from <https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm>.  **[28]** FDA-Inactive Ingredient Search for Approved Drug Products. Retrieved January 6, 2022, from https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.  **[29]** Taro Pharmaceuticals U.S.A., Inc. 2016 [rev. 2016 September; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abeb13eb-66a5-4030-9bc2-5981acd196b9>.  **[30]** Rowe, R. C., Sheskey, P. J., Weller, P. J. (2003). Handbook of pharmaceutical excipients. London: Pharmaceutical Press.  **[31]** Monograph: USP. Acetazolamide, tablets. In USP-NF. Rockville, MD: USP; 2022.  **[32]** Monograph: USP. Dronabinol. In USP-NF. Rockville, MD: USP; 2022.  **[33]** Monograph: Ph. Eur. Acetazolamide. In *European pharmacopoeia*. Strasbourg: Council of Europe; 2022.  **[34]** Monograph: BP. 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** |

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