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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | THC + Melatonin Oral Solution |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) |  |
| Brand name / Generic name |  |
| API(s) |  |
| Strength(s) |  |
| Dosage form | Oral solution |
| Route of administration | Oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Type of packaging material | 60ml glass bottles |
| Commercial presentations |  |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | THC |
| CAS number: | 1972-08-3 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | No online available information. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies represent a crucial analytical approach to elucidate the scheme of degradation route for the THC active pharmaceutical ingredient. Under severe environmental and chemical conditions, including elevated temperature, diverse pH environments, oxidative stress, and intense light exposure, the molecule undergoes controlled decomposition resulting in distinct degradation products. These experiments employ advanced techniques such as HPLC with diode array detection and mass spectrometry for quantitation and structural elucidation of degradants. Regulatory guidelines suggest achieving degradation between five and twenty percent to ensure appropriate method validation. This process facilitates determination of degradation mechanisms such as hydrolysis, oxidation, and thermal decomposition, thereby supporting formulation optimization and packaging strategies. The generated degradation profiles enable early identification of reactive sites within the molecule and assist in the design of stability indicating methods. Data from forced degradation studies are essential for predicting shelf life and guiding quality control in both drug substance and product phases. Comprehensive reports documenting these studies have been published with extensive experimental details [Pharmaguidesline](https://pharmaguidesline.com/forced-degradation/), [ResearchGate](https://www.researchgate.net/profile/Mangesh-Kumare/publication/261799053\_7\_AJPR\_3\_4\_2013-libre/links/0f3175358b1b43579c000000/7-AJPR-3-4-2013-libre.pdf), [Wiley](https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/pdf/10.1002/rcm.8032), and [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0165993613001313). These forced degradation findings are essential for optimizing THC formulation robustness, ensuring compliance with regulatory demands, and mitigating long term stability risks. The study substantiates intervention in manufacturing to safeguard product integrity. |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurities in THC active pharmaceutical ingredient represent a critical quality attribute that must be thoroughly characterized to ensure both efficacy and patient safety. These impurities can originate from degradation of THC, residual solvents, synthetic side products from the manufacturing process, and leachables from packaging materials. Analytical techniques such as high-performance liquid chromatography (HPLC), ultra‐high performance liquid chromatography (UHPLC), and LC‐QTOF mass spectrometry are routinely employed to detect and quantify these impurities with high sensitivity and precision. The impurity profile not only includes degradation compounds but also synthetic artefacts that may exhibit toxicological risks at elevated concentrations. Thorough impurity profiling, including forced degradation studies, supports regulatory compliance by confirming that impurity levels remain below safety thresholds. Emphasis is placed on method validation, mass accuracy, and the detection of trace levels in the ppb to ppm range. A comprehensive understanding of impurity origins, chemical structure, and kinetic behavior is essential during product development and quality assurance testing. This systematic approach is well documented in studies and reviews on impurity significance and analytical methods [Ivory Research](https://www.ivoryresearch.com/samples/significance-impurities-active-pharmaceutical-ingredients/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/31226425/), [Simson Pharma](https://www.simsonpharma.com/blog-details/sources-of-impurities-in-pharmaceutical-substances), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27686474/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/39058576/). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Data Analysis: The biopharmaceutical classification system (BCS) categorizes active pharmaceutical ingredients based on aqueous solubility and intestinal permeability. Regarding THC, the evaluation involves experimental determinations of dissolution rates, water solubility assays, and permeability studies using in vitro models such as Caco-2 cell systems. Although specific numerical values for THC solubility and permeability were not delineated in the provided evidence, application of the BCS framework guides formulation strategies by predicting in vivo absorption profiles for immediate-release oral dosage forms. Current regulatory guidelines from the World Health Organization, US Food and Drug Administration, and European Medicines Agency allow BCS‐based biowaivers when robust in vitro data supports high solubility or permeability designations [Source Emerging Role Of Biopharmaceutical Classification And Biopharmaceutical ...](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). Detailed mechanistic studies of drug dissolution and intestinal transport offer scientific justification through in vitro–in vivo correlations [Source PDF](https://link.springer.com/content/pdf/10.1007/978-3-030-51519-5\_139-1). Additional insights from global reviews substantiate these protocols [Source ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0378517319304004) and [Source Online BCS Classification Database](https://www.pharmaspecialists.com/2021/08/online-bcs-classification-database.html). Advanced in vitro studies further clarify THC’s precise BCS classification, thereby supporting regulatory acceptance and robust streamlined development of optimized immediate-release formulations. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** THC  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 314.5  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** For THC active pharmaceutical ingredient, hygroscopicity assessment is critical due to its potential impact on physical and chemical stability. This report synthesizes methods and findings from several studies. Water vapor sorption is typically measured gravimetrically using automated sorption microbalances, enabling rapid evaluation of water uptake under controlled relative humidity conditions. One study demonstrated an efficient throughput method for hygroscopicity classification that minimizes sample consumption and time, ensuring optimal equilibration conditions [https://www.tandfonline.com/doi/full/10.3109/10837450.2011.618947]. Further, academic research from the University of Minnesota has elaborated on the thermodynamic and kinetic factors influencing water uptake in pharmaceutical crystals, especially the role of crystalline versus amorphous forms, which is crucial for predicting long-term stability [https://hdl.handle.net/11299/47878]. Additional insights from a minireview highlight that an accurate evaluation of hygroscopicity involves considering not only water vapor sorption isotherms but also the associated mechanisms that may trigger polymorphic transformation or surface solution formation [https://www.sciencedirect.com/science/article/pii/S0022354916325230]. Complementary findings published on PubMed reinforce the importance of optimizing experimental conditions to avoid future stability challenges [https://pubmed.ncbi.nlm.nih.gov/17630643/]. A classification study on hygroscopic properties further supports these strategies [https://www.researchgate.net/figure/Hygroscopicity-classification-of-inactive-pharmaceutical-ingredients-studied-by\_tbl1\_51701306].  **Chirality/Specific optical rotation:** The chirality and specific optical rotation assessment of the THC active pharmaceutical ingredient is performed using established polarimetric methodologies. A polarimeter equipped with a sodium D-line light source (589.3 nm) and a 1 dm cell is utilized to measure the rotation of plane polarized light, a fundamental parameter in chiral analysis. The measurement procedures, as described in the British Pharmacopoeia and related general chapters, involve determining the angle of rotation at controlled temperatures (20–25 °C) and calculating the specific optical rotation by correcting the observed value for concentration and path length. This method serves not only to confirm the enantiomeric composition but also to assess the chiral purity critical to THC’s pharmacological profile. Quality control laboratories such as Protheragen-ING Lab emphasize the role of optical rotation testing in regulatory compliance and routine batch analysis. In addition, recent machine learning studies have successfully predicted specific optical rotations for chiral compounds, reinforcing traditional polarimetric approaches. It should be noted that while these methods provide the framework for chiral evaluation, no THC-specific numerical rotation values were provided in the available evidence. [Pharmaguideline](https://www.pharmaguideline.com/2014/06/optical-activity-in-pharmaceutical-analysis.html), [Protheragen-ING Lab](https://labs.protheragen-ing.com/optical-rotation-test.html), [British Pharmacopoeia](https://www.drugfuture.com/Pharmacopoeia/BP2010/data/973.html), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S1386142519306791).  **Degradation temperature:**Recent investigations on the thermal degradation of Δ9‐tetrahydrocannabinol (THC) have emphasized that elevated temperatures play a critical role in catalyzing the degradation pathways of this active pharmaceutical ingredient. Studies conducted using gas chromatography have demonstrated that the temperature of the GC injector port can induce significant degradation of Δ9‐THC, leading to the formation of by-products such as cannabinol (CBN) and Δ8‐THC. Experimental observations indicate that the degradation of THC follows pseudo‐first order kinetics, highlighting that even slight increases in temperature can accelerate the breakdown of the molecule. Although explicit numerical values defining the exact degradation temperature of THC are not provided in the available literature, the cumulative data suggest that heat-induced stress, similar to conditions experienced during certain analytical and storage procedures, initiates these degradation processes. Complementary studies employing high‐performance liquid chromatography and mass spectrometry techniques reinforce the understanding that thermal degradation is a key stability indicator for cannabinoids. Further research under standardized stress conditions is necessary to precisely calibrate the degradation temperature of THC. Citations: [PMC9664148](https://pmc.ncbi.nlm.nih.gov/articles/PMC9664148/), [PMC9418372](https://pmc.ncbi.nlm.nih.gov/articles/PMC9418372/), [Springer](https://link.springer.com/article/10.1007/s13596-021-00590-7).  No online available information.  **Boiling point:** Información no disponible |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Melatonin |
| CAS number: | 73-31-4 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | No online available information. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies of melatonin have been extensively employed to elucidate the degradation routes under controlled stress conditions. Detailed investigations using validated stability‐indicating HPTLC methods have demonstrated that melatonin undergoes degradation in acidic, alkaline, and oxidative environments. Specifically, degradation in 1N HCl and 1N NaOH conditions follows first order kinetics, indicating a rapid decrease in drug concentration under severe pH stress. The experimental approach incorporated accelerated conditions with controlled temperature and light exposure to simulate potential in vivo and in-process degradation, thus ensuring the identification of degradation products and impurities. Kinetic parameters derived from these studies further confirmed the susceptibility of melatonin to chemical degradation, which is critical for the design of stability indicating methods in compliance with ICH guidelines. In addition, chemometrics applications have been integrated to predict degradation pathways and quantify the formation of degradants under various stress conditions. This systematic approach not only guides formulation strategies but also aids in regulatory submissions by providing robust degradation profiles. Relevant data and methodologies can be cross-referenced from studies available at [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0169409X06002730), [PubMed](https://pubmed.ncbi.nlm.nih.gov/31652589/), [RJPT](https://rjptonline.org/AbstractView.aspx?PID=2020-13-2-2), and [ResearchGate](https://www.researchgate.net/publication/340863188\_Current\_Trends\_in\_Performance\_of\_Forced\_Degradation\_Studies\_and\_Stability\_Indicating\_Studies\_of\_Drugs) and [ResearchGate](https://www.researchgate.net/publication/340533101\_Degradation\_Kinetic\_Study\_of\_Melatonin\_in\_Alkaline\_and\_Acidic\_Medium\_by\_Validated\_Stability\_Indicating\_HPTLC\_Method). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The impurity profile of melatonin as an active pharmaceutical ingredient has been rigorously characterized using validated analytical techniques. Key impurities include pharmacopeial compounds such as Melatonin Impurity C (2-(5-Methoxy-1H-indol-3-yl)ethan-1-amine, CAS 608-07-1, Molecular Weight 190.24) and Melatonin EP Impurity A (C10H12N2O·HCl, CAS 50-67-9). Additional impurities comprise deuterated analogues, nitroso derivatives, and related compounds synthesized as reference standards. These compounds are generated either as byproducts of the synthetic route or via degradation pathways during storage. Advanced methodologies including High Performance Liquid Chromatography, Mass Spectrometry, and Nuclear Magnetic Resonance spectroscopy have been employed for their identification and quantification. Structured impurity profiling not only ensures compliance with pharmacopeial standards but also mitigates risks associated with adverse effects such as eosinophilia-myalgia syndrome reported in literature. Optimized industrial manufacturing processes have been developed to control the level of these impurities, thus assuring high purity of the final melatonin product. Detailed impurity reference standards and analytical data are available from multiple sources, supporting regulatory filings and quality control measures [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities), [SynZeal](https://www.synzeal.com/en/melantonin), [PubMed](https://pubmed.ncbi.nlm.nih.gov/10085477/). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Melatonin’s biopharmaceutical classification is assessed within the framework of the Biopharmaceutics Classification System (BCS), which categorizes active pharmaceutical ingredients based on aqueous solubility and intestinal permeability. Although specific experimental BCS data for melatonin are not explicitly provided in the available evidence, general principles indicate that melatonin likely exhibits low aqueous solubility with high intestinal permeability. Such characteristics are typically aligned with BCS Class II compounds. Determination of this classification relies on experimental methods including dissolution testing and permeability assays, as outlined by the World Health Organization, US Food and Drug Administration, and European Medicines Agency. The systematic review by Manikandan and Lakshmi highlights the relevance of BCS in formulation design and biowaiver guidelines (https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). Supplementary methodological details are provided in additional sources such as the Springer PDF (https://link.springer.com/content/pdf/10.1007/978-3-030-51519-5\_139-1) and ScienceDirect publications (https://www.sciencedirect.com/science/article/pii/S0378517319304004). These robust findings underscore the necessity for comprehensive in vitro and in vivo assessments to validate dissolution and permeability models. A designation will clearly optimize formulation strategies. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Melatonin  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 232.28  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Melatonin’s hygroscopicity was characterized using gravimetric analysis under controlled relative humidity conditions. Studies utilize water vapor sorption isotherms to quantitatively measure moisture uptake, with samples exposed to various RH levels at constant temperature, facilitating the evaluation of sorption kinetics and equilibrium states. Automated sorption microbalance (ASM) techniques have been employed to accelerate measurements, although caution is advised when water vapor diffusion and heat transfer are not rate limiting. Data indicate that moisture uptake is critically influenced by the crystalline or amorphous state of Melatonin, with potential for polymorphic transitions when exposed to elevated humidity. Pre-treatment of samples and extended equilibration periods are essential for accurate assessment. The reported methodologies aid in predicting long-term stability and potential physical or chemical degradation, thus guiding drug candidate selection and formulation strategy. Observations include cases where absorbed water initiates metastable transitions, affecting the overall water content and performance of the API. Comprehensive reviews of these approaches, as found in data from the Wiley Journal of Pharmaceutical Sciences [https://onlinelibrary.wiley.com/doi/10.1002/jps.21033], ScienceDirect [https://www.sciencedirect.com/science/article/abs/pii/S0022354916325230], and the University Digital Conservancy [https://hdl.handle.net/11299/47878], underscore the importance of hygroscopicity profiling during drug development. These insights are indispensable in optimizing manufacturing processes, packaging conditions, and ensuring efficacy and stability of the Melatonin API.  **Chirality/Specific optical rotation:** Investigations into the chirality and specific optical rotation of the melatonin active pharmaceutical ingredient indicate that the natural form of melatonin, N-Acetyl-5-methoxytryptamine, is intrinsically achiral due to the absence of stereogenic centers. However, recent studies exploring melatonin receptor ligands have successfully introduced chirality through structural modifications. For instance, beta-methyl derivatives of melatonin analogues were synthesized and examined using advanced NMR spectroscopy, molecular dynamics simulations, and receptor docking approaches. These investigations revealed that the beta-methyl group alters the conformational equilibrium of the ethylamide chain, thereby generating stereoselectivity. In these studies, the (S)-enantiomer was observed to function as the eutomer and exhibited superior receptor binding characteristics compared to its (R)-counterpart. Although precise specific optical rotation values were not reported in these experiments, the chiral recognition processes clearly demonstrated that introducing a stereocenter can significantly impact receptor interactions. The integration of chiral derivatization and conformational analysis provides valuable insight into the structure–activity relationship for melatonin receptor engagement. Key references include data from PubChem [https://pubchem.ncbi.nlm.nih.gov/compound/Melatonin], MDPI Molecules [https://mdpi-res.com/d\_attachment/molecules/molecules-25-04057/article\_deploy/molecules-25-04057-v2.pdf?version=1599813272], and PMC [https://pmc.ncbi.nlm.nih.gov/articles/PMC6308847/].  **Degradation temperature:**A comprehensive review of the available literature on melatonin indicates that the molecule is sensitive to high temperatures, with degradation pathways studied under diverse stress conditions. However, explicit numerical values for the degradation temperature of melatonin have not been clearly established in the current body of research. For example, a degradation kinetic study using a stability indicating HPTLC method demonstrated that melatonin undergoes degradation in acidic, alkaline, and oxidative environments following first order kinetics, yet it did not specify an exact temperature threshold for degradation [RJPT](https://rjptonline.org/AbstractView.aspx?PID=2020-13-2-2). In related work, investigations on the stability of melatonin in eutectic systems highlighted the role of temperature, alongside light exposure, in affecting its stability; nevertheless, these studies emphasize the qualitative impact of the thermal environment rather than pinpointing a distinct degradation temperature [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S2772422024000351). Additional research on thermal degradation in aqueous media supports the concept that increased temperatures accelerate degradation, but a definitive degradation temperature under standardized conditions remains undetermined [PubMed](https://pubmed.ncbi.nlm.nih.gov/32258489/). Further targeted analytical investigations are required for precise determination of the degradation temperature of melatonin.  Data Analysis: The glass transition temperature (Tg) is a critical parameter for evaluating the stability and performance of amorphous active pharmaceutical ingredients such as melatonin. Although a specific numerical value for melatonin’s Tg is not provided in the current literature, the available evidence emphasizes the methodologies necessary for obtaining precise measurements. Differential scanning calorimetry (DSC), including both conventional DSC and modulated DSC, is highlighted as the primary analytical technique to assess Tg. Conventional DSC offers an approximate temperature range and transition width that aids in establishing initial guidelines, whereas modulated DSC provides enhanced sensitivity and accurate heat capacity data, thereby refining the evaluation of the amorphous state. Experimental conditions, including sample preparation, instrumental parameters, and moisture environment, are critical in determining the observed Tg and ensuring reproducibility. In addition, studies using molecular dynamics simulations illustrate the impact of polymer molecular mass, free volume, hydrogen bonding, and steric shielding on the Tg of pharmaceutical dispersions. Although specific Tg values for melatonin remain to be reported, these analytical approaches underscore the importance of optimizing experimental protocols in future research. Citations: [Springer](https://link.springer.com/article/10.1208/s12249-019-1562-1), [PubMed](https://pubmed.ncbi.nlm.nih.gov/21324354/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC8400648/), [ACS](https://pubs.acs.org/doi/10.1021/acs.jpcb.7b10105).  **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 | Melatonin |
| Packaging\_imgs | |
| Manufacturer |  |
| API | Melatonin (UNII: JL5DK93RCL). |
| Excipients | The melatonin solution/drops formulation contains the following inactive ingredients: Glycerin (UNII: PDC6A3C0OX) and Water (UNII: 059QF0KO0R). |
| Strength(s) | No data available. |
| Type of packaging material | The product is supplied as a dietary supplement in a single carton. The packaging consists of a 30 mL bottle with a dropper, as indicated by Item Code NHRIC:71399-0128-1 and associated marketing details. Labeler: Akron Pharma (067878881). |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | The MAX SLEEP JUNIOR CHILDRENS SLEEP AID is a melatonin solution/drops formulated as a dietary supplement for oral use. It contains melatonin at a concentration of 1 mg per mL and is supplied in a 30 mL bottle with a dropper. Inactive ingredients include glycerin and water. |
| 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** | |
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| Official monographs for the API: | Dronabinol USP monograph [32]  Acetazolamide USP monograph [16]  Acetazolamide Ph. Eur. monograph [33]  Acetazolamide BP monograph [34]  Acetazolamide JP monograph [35] |
| Official monographs for the finished products: | Dronabinol, capsules USP monograph [26]  Acetazolamide, tablets USP monograph [31]  Acetazolamide, tablets BP monograph [36] |
| Other information:   1. **API monographs**  |  |  |  | | --- | --- | --- | | **Dronabinol USP monograph [32]** | | | | **Description:** Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration.  **Solubility:** Insoluble water. | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Identification b | The color and *R*F value of the spots from the *Test solution* correspond to those obtained from the *Identification solution*. | Chromatography 〈621〉: Thin-layer Chromatography | | Related compounds | Cannabinol: Not more than 1.5 %.  *Exo*-tetrahydrocannabinol: Not more than 0.5 %.  Δ8-Tetrahydrocannabinol: Not more than 2.0 %.  Any other individual impurity: Not more than 1.0 %.  Total impurities: Not more than 5.0 %. | Chromatography 〈621〉: Liquid Chromatography | | Assay | Not less than 95.0 percent of C21H30O2. | Chromatography 〈621〉: Liquid Chromatography |  |  |  |  | | --- | --- | --- | | **Acetazolamide USP monograph [16]** | | | | **Description:** White to faintly yellowish-white, crystalline, odorless powder.  **Solubility:** Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water. | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*. | Spectroscopic Identification Tests 〈197〉, *Infrared Spectroscopy*: 197K | | Identification b | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Assay | 98.0 % – 102.0 % on the anhydrous basis | Chromatography 〈621〉: Liquid Chromatography | | Residue on ignition 〈281〉 | Not more than 0.1 % | None | | Chloride | A 25-mL portion of the filtrate shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid 0.014%). | Chloride and Sulfate 〈221〉 | | Sulfate | It shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (0.04%). | Chloride and Sulfate 〈221〉 | | Selenium 〈291〉 | Not more than 30 rpm. | None |  |  |  |  | | --- | --- | --- | | **Test** | **Acceptance criteria** | **Observations** | | Organic impurities | Desacetyl acetazolamide: Not more than 0.3 %.  Acetazolamide acid analog: Not more than 0.5 %.  Acetamidothiadiazole: Not more than 0.5 %.  Mercaptothiadiazole analog: Not more than 0.5 %.  Chlorothiadiazole analog: Not more than 0.5 %.  Acetazolamide dimer: Not more than 0.5 %.  Any unspecified impurity: Not more than 0.1 %.  Total impurities: Not more than 1.0 %. | Chromatography 〈621〉: Liquid Chromatography |  |  |  |  | | --- | --- | --- | | **Acetazolamide BP monograph / Ph. Eur. monograph 0454 [33, 34]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Appearance | White or almost white, crystalline powder. | None | | Solubility | Very slightly soluble in water, slightly soluble in ethanol (96 percent). It dissolves in dilute solutions of alkali hydroxides. | None | | Identification A | The UV absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide. | Ultraviolet and visible absorption spectrophotometry (2.2.25) | | Identification B | The infrared absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide. | Infrared absorption spectrophotometry (2.2.24) | | Identification C | The paper shows a brownish-black color. | None | | Identification D | A greenish-blue precipitate is formed. | None | | Appearance of solution | The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely colored than reference solution Y5 or BY5 (2.2.2, Method II). | None | | Related substances | Impurities A, B, C, D, E, F: For each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 percent)  Unspecified impurities: For each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 percent)  Total: Not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 percent) | None | | Sulfates (2.4.13) | Maximum 500 ppm. | None | | Loss on drying (2.2.32) | Maximum 0.5 percent | Determined on 1.000 g by drying in an oven at 105 °C. | | Sulfated ash (2.4.14) | Maximum 0.1 percent | Determined on 1.0 g. | | Assay | 98.5 per cent to 101.0 per cent (dried substance) | Potentiometric titration (2.2.20) |  |  |  |  | | --- | --- | --- | | **Acetazolamide JP monograph [35]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Description | Acetazolamide occurs as a white to pale yellowish white crystalline powder. It is odorless and has a slight bitter taste. | None | | Solubility | It is slightly soluble in ethanol (95), very slightly soluble in water, and practically insoluble in diethyl ether. | None | | Melting point | About 255 °C (with decomposition). | None | | Identification 1 | A deep yellow color is produced gradually. | None | | Identification 2 | Responds to the Qualitative Tests 〈1.09〉 for primary aromatic amines. | None | | Identification 3 | The gas evolved darkens moistened lead (II) acetate paper. | None | | Clarity and color of solution | The solution is clear and colorless to pale yellow | None | | **Test** | **Acceptance criteria** | **Observations** | | Chloride 〈1.03〉 | Not more than 0.014 %. | None | | Sulfate 〈1.14〉 | Not more than 0.038 %. | None | | Heavy metals 〈1.07〉 | Not more than 20 ppm. | None | | Silver-reducing agents | Not less than 4.8 mL of 0.1 mol/L ammonium thiocyanate VS is consumed | Titration 〈2.50〉 | | Loss on drying (2.41) | Not more than 0.5 %. | Determined on 0.5 g, 105 °C, 3 hours. | | Residue on ignition (2.44) | Not more than 0.1 %. | Determined on 0.5 g. | | Assay | Not less than 98.0 % and not more than 102.0 % of acetazolamide (C4H6N4O3S2), calculated on the dried basis. | Ultraviolet-visible Spectrometry 〈2.24〉 |  1. **Drug product monographs**  |  |  |  | | --- | --- | --- | | **Dronabinol, capsules USP monograph [26]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.* | Chromatography 〈621〉: Liquid Chromatography | | Assay | Not less than 90.0 % and not more than 110.0 % of the labeled amount of dronabinol (C21H30O2). | Chromatography 〈621〉: Liquid Chromatography | | Dissolution 〈711〉 | The requirements are met if all of the capsules tested rupture in NMT 15 min. If 1 or 2 of the capsules rupture in NLT 15 but NMT 30 min, repeat the test on 12 additional Capsules. NMT 2 of the total of 18 capsules tested rupture in NLT 15 min but NMT 30 min. | Medium: Water  Volume: 500 mL  Apparatus: 2  Speed: 50 rpm  Time: 15 minutes | | Uniformity of Dosage Units 〈905〉 | Meet the requirements. | None |  |  |  |  | | --- | --- | --- | | **Acetazolamide tablets, USP monograph [31]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*. | Spectroscopic Identification Tests 〈197〉, *Infrared Spectroscopy*: 197K | | Identification b | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Assay | 95.0 % - 105.0 % | Chromatography 〈621〉: Liquid Chromatography | | Dissolution 〈711〉 | NLT 75% (Q) of the labeled amount of acetazolamide (C4H6N4O3S2) is dissolved. | Medium: 0.01 N HCl  Volume: 900 mL  Apparatus: 1  Speed: 100 rpm  Time: 60 minutes | | Uniformity of Dosage Units 〈905〉 | Meet the requirements. | None |  |  |  |  | | --- | --- | --- | | **Acetazolamide tablets, BP monograph [36]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The infrared spectrum of the residue is concordant with the reference spectrum of acetazolamide. | Infrared spectrometry | | **Test** | **Acceptance criteria** | **Observations** | | Identification b | The paper exhibits a brownish black color. | None | | Identification b | A greenish blue color or precipitate is produced. | None | | Related substances | Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1 %). | Thin-layer chromatography | | Assay | 95.0 to 105.0 % of the stated amount of acetazolamide. | Potentiometric titration | | |

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| 1. **REVISION OF PATENTS (BACKGROUND AND RESTRICTIONS)** |
| See patent revision report. |

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| 1. **REFERENCES** (Specify the references throughout the document with numbers between brackets i.e. [1]) |
| **[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:** | |
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