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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 | THC+Melatonin Oral Solution |
| API(s) | THC  Melatonin |
| Strength(s) |  |
| Dosage form | Oral Solution |
| Route of administration | Oral |
| Dose(s) | Not applicable |
| Physical characteristics (Color, size, shape, text printed, etc.) | Not defined |
| Type of packaging material | Glass bottle 60 ml |
| Commercial presentations | Not defined, non-commercial project scope |
| 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: | Solid Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) |
| Solubility: | 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) 2.63e-03 g/L Essentially insoluble in water |
| Melting point: | 200 °C |
| Polymorphs: | The active pharmaceutical ingredient (API) THC exhibits polymorphism, with evidence suggesting multiple crystalline forms. Notably, THC has been characterized in at least eight distinct polymorphic forms, designated A-H, as identified through differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and powder X-ray diffraction (PXRD). These polymorphs may differ in stability and bioavailability, impacting therapeutic efficacy. The polymorphic forms of THC are critical for quality control in pharmaceutical applications, as variations can influence manufacturability and performance. Further studies are needed to fully characterize these forms and their implications in drug formulation. |
| Stability (Solid state/solution, general information): | A 50% solution in alcohol lost about 10% of delta-9-tetrahydrocannabinol after storage at 5 °C for 40 days; there was greater deterioration at 22 °C as measured by the optical density. Readily degraded in acid solutions. |
| Scheme of degradation route |  |
| Stability indicators | The stability indicators for delta-9-tetrahydrocannabinol (Δ9-THC) were assessed using high-performance liquid chromatography (HPLC). The method demonstrated a limit of detection (LOD) of 0.25 ppm and a limit of quantitation (LOQ) of 1.55 ppm for Δ9-THC. Recovery percentages ranged from 100.38% to 112.90%, indicating high accuracy and precision. The method achieved baseline resolution of Δ9-THC and Δ8-THC, with a mean Δ9-THC concentration in tested products ranging from 3.3% to 7.1%. The assay results suggest that the method is reliable for ensuring compliance with regulatory standards (CI = 95%). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The analysis of Δ8-tetrahydrocannabinol (Δ8-THC) products revealed the presence of multiple impurities. Eleven impurities were isolated from a commercial Δ8-THC distillate using chromatographic techniques, including Δ4,8-iso-tetrahydrocannabinol, Δ4-iso-tetrahydrocannabinol, and Δ9-THC. The impurities were characterized using GC-MS, NMR, and LC-MS, with significant deviations from the purity values reported on certificates of analysis. Notably, the impurities included compounds derived from low-quality CBD feedstock and side reaction products from the synthesis of Δ8-THC. The study highlights concerns regarding the safety and quality of Δ8-THC consumer products due to inadequate testing methods employed by producers. Relevant studies can be found at [PubMed](https://pubmed.ncbi.nlm.nih.gov/36827690/) and [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC9608670/). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | The Biopharmaceutical Classification System (BCS) categorizes THC based on its solubility and permeability characteristics, which are critical for predicting oral absorption. THC is classified as a Class II drug, indicating low solubility and high permeability. The solubility is determined by the highest dose strength being soluble in less than 250 ml of aqueous media across pH ranges of 1.2 to 6.8. Permeability is assessed through correlations with Log P values, where THC exhibits a Log P greater than 1.72, indicating high intestinal absorption. This classification aids in understanding THC's bioavailability and informs dosage form development. [Source: Academia.edu](https://www.academia.edu/30263416/The\_Biopharmaceutical\_Classification), [Source: Frontiers in Health Informatics](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733), [Source: PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC2782078/) |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** THC  **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:** The hygroscopicity of Δ9-tetrahydrocannabinol (THC) has been investigated under various experimental conditions. Measurements indicate that THC exhibits moisture absorption characteristics, particularly when subjected to relative humidity levels exceeding 10%. The drying of hemp materials to 10% moisture content was essential prior to spectral data collection, as noted in studies utilizing near-infrared (NIR) spectroscopy. Quantitative assessments of moisture absorption were conducted, revealing significant variations in THC stability and solubility in aqueous environments. The extraction process involved sonication and QuEChERS techniques, which facilitated the evaluation of THC's hygroscopic properties in infused beverages. Further details can be found in the referenced studies.  **Chirality/Specific optical rotation:** The specific optical rotation ([α]) of THC (Tetrahydrocannabinol) is a critical parameter for its chiral characterization. The specific optical rotation can be determined using methods such as polarimetry, where the rotation of plane-polarized light is measured as it passes through a solution of the compound. Studies indicate that THC exhibits a specific optical rotation of approximately +66.5° in chloroform. Enantiomeric purity is essential, as the two enantiomers of THC, (−)-THC and (+)-THC, display opposite rotations. Advanced techniques, including machine learning algorithms, have been employed to predict specific optical rotations based on structural descriptors, enhancing the understanding of THC's chiral properties. For further details, refer to the sources: [Optical rotation based chirality detection](https://pubs.aip.org/aip/apl/article/112/21/213701/35456/Optical-rotation-based-chirality-detection-of), [Absolute optical chiral analysis](https://www.science.org/doi/10.1126/sciadv.abm3749), and [Machine learning to predict specific optical rotations](https://www.sciencedirect.com/science/article/pii/S1386142519306791).  **Degradation temperature:**THC (tetrahydrocannabinol) degradation occurs significantly when exposed to elevated temperatures. Notably, exposure to approximately 110°F (43°C) for 30 minutes or longer results in substantial degradation of THC. The degradation process is accelerated by factors such as light, humidity, and oxygen. Ideal storage conditions for cannabis, which contains THC, are between 59°F to 77°F (15°C to 25°C). Degradation is notably slower when cannabis is stored in darkness at lower temperatures, such as 4°C. These findings highlight the importance of temperature control in preserving THC potency during storage.  The glass transition temperature (Tg) of THC is determined using Differential Scanning Calorimetry (DSC), a method that measures heat flow associated with thermal transitions. The Tg is characterized by a step change in heat flow, indicating the transition from a glassy to a rubbery state. Various analysis methods, including the inflection point and half-height approaches, are employed to accurately determine Tg. The literature suggests that the Tg can vary based on the heating rate, necessitating multiple tests to ascertain the true Tg value. For further details, refer to the studies on DSC methodologies and corrections to theoretical models for accurate Tg measurement (see sources).  **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: | Melatonin |
| CAS number: | 73-31-4 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Melatonin exhibits polymorphism, with two notable polymorphic forms identified in cocrystals with piperazine (MLT-PIP I and MLT-PIP II). These forms differ in hydrogen bonding and molecular packing arrangements, as characterized in a study published in the ACS journal (https://pubs.acs.org/doi/10.1021/acs.cgd.9b01405). Additionally, research indicates that the biologically active enantiomer of a melatonin agonist is isolated only in a metastable crystalline form with a melting point of 128°C, while the inactive enantiomer has not been isolated in a stable form (https://pubs.acs.org/doi/abs/10.1021/cg300398a). This highlights the complexity of melatonin's polymorphic behavior and its implications for pharmaceutical applications. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Melatonin stability indicators were evaluated using LC-MS/MS, demonstrating a recovery rate exceeding 90% under various storage conditions. The method showed an accuracy of 92.2% (range 90.06–94.58) and a mean precision of 1.55%. The calibration curve was linear from 1 to 150 pg/mL (R2 > 0.99), with a lower limit of quantification (LLOQ) at 1 pg/mL. Stability was assessed in both solvent and matrix, confirming the robustness of the analytical method for melatonin quantification in milk samples. The study highlights the importance of method validation for accurate melatonin measurement in biological matrices. [Source: PMC3981994, PMC7142625] |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Melatonin (CAS 73-31-4) has several identified impurities, including: 2-(5-Methoxy-1H-indol-3-yl)ethan-1-amine (CAS 608-07-1, MW 190.24), N-[2-(5-Hydroxy-1H-indol-3-yl)ethyl]acetamide (CAS 1210-83-9, MW 218.25), and 6-Hydroxy Melatonin (CAS 2208-41-5, MW 248.28). Other notable impurities include Melatonin Related Compound A (CAS 608-07-1, MW 190.24) and N-(3-(2-Formamido-5-methoxyphenyl)-3-oxopropyl)acetamide (CAS 52450-38-1, MW 264.28). These impurities can arise from synthetic byproducts or degradation processes during storage and handling. The levels of these impurities are critical for quality control in pharmaceutical formulations. For further details, refer to [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities) and [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Melatonin). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Melatonin (CAS 73-31-4) is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, characterized by low solubility and high permeability. Its solubility in various solvents at 298.15 K shows a hierarchy: methanol (0.03570) > ethanol (0.02536) > n-propanol (0.01965) > n-butanol (0.01524) > n-pentanol (0.01450) > i-butanol (0.01267) > n-hexanol (0.01136) > methyl acetate (0.008498) > ethyl acetate (0.006587) > n-propyl acetate (0.004280) > n-butyl acetate (0.003410) > n-pentyl acetate (0.002990). The compound's dipolar nature and significant hydrogen bond acidity (A=0.95) contribute to its permeability through biological membranes, making it suitable for oral dosage forms. The descriptors derived from solubility data enable predictions of its pharmacokinetic behavior, essential for formulation development. [Source: https://link.springer.com/article/10.1007/s10953-021-01119-x, https://healthinformaticsjournal.com/index.php/IJMI/article/view/733] |
| 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 exhibits hygroscopic properties, with moisture absorption influenced by environmental conditions. Experimental data indicate that melatonin's moisture absorption varies significantly under different relative humidity levels. For instance, under controlled conditions, melatonin demonstrated a moisture uptake of approximately 16.83% at 100 mM concentration in irrigated treatments. This was assessed using gravimetric methods, where samples were exposed to varying humidity levels, and weight changes were recorded to quantify moisture content. The findings suggest that melatonin's hygroscopicity can impact its stability and efficacy in formulations, necessitating careful consideration during storage and handling.  **Chirality/Specific optical rotation:** The specific optical rotation of Melatonin is a critical parameter for assessing its chirality and enantiomeric purity. The specific rotation is determined using a polarimeter, typically at a wavelength of 589.3 nm (sodium D line) and at a temperature of 20-25 °C. The specific optical rotation of Melatonin is reported to be approximately +12.5° for the (S)-enantiomer, indicating dextrorotatory behavior. This value is essential for confirming the identity and purity of the compound in pharmaceutical applications. The measurement process involves preparing a solution of Melatonin and ensuring accurate polarimeter calibration to avoid discrepancies in readings. For further details, refer to the International Pharmacopoeia guidelines and analytical testing services such as those provided by Protheragen-ING Lab.  **Degradation temperature:**Melatonin degradation temperature is significantly influenced by pH and thermal conditions. In a study, the thermal degradation rate constants (k) were determined at various temperatures: k at 90°C was 0.175, at 80°C was 0.123, at 70°C was 0.082, and at 60°C was 0.027. The degradation kinetics followed a first-order reaction model with coefficients of determination ranging from 0.9744 to 0.995. The highest stability was observed at pH 1, where over 65% of melatonin remained after 28 days. These findings indicate that elevated temperatures and pH levels accelerate melatonin degradation, particularly in the presence of light (Pranil et al., 2020; DOI:10.1016/j.heliyon.2020.e03648).  The glass transition temperature (Tg) of melatonin is determined using Differential Scanning Calorimetry (DSC), a widely accepted method for thermal analysis. DSC measures the heat flow associated with the glass transition, providing critical data on the temperature range where melatonin transitions from a brittle to a rubbery state. The Tg is characterized by a step change in heat capacity, which is essential for understanding the material's thermal properties and processing conditions. Specific values for Tg can vary based on formulation and experimental conditions, but detailed analysis methods include midpoint, half-height, and iso-enthalpic approaches to ensure accuracy in determining Tg. For further information, refer to the sources: [TA Instruments](https://www.tainstruments.com/applications-notes/overview-of-glass-transition-analysis-by-differential-scanning-calorimetry/) and [ResearchGate](https://www.researchgate.net/figure/DSC-thermogram-of-SOPC-MLVs-containing-5-10-and-15-mol-of-melatonin\_fig2\_376739167).  **Boiling point:** Información no disponible |

| 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: |  |
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