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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?) | Others |
| Brand name / Generic name | THC+Melatonin Oral Solution |
| API(s) | THC  Melatonin |
| Strength(s) |  |
| Dosage form | Oral Solution |
| Route of administration | Oral |
| Dose(s) |  |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Type of packaging material | 60 ml glass bottle |
| 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: | - Appears as a brown amorphous semi-solid - May present as a viscous oil - Can also be observed as a chunky golden yellow solid |
| Solubility: | THC is extremely poorly soluble in water (2.8 mg/L at 73 °F or approximately 2.63×10⁻³ g/L) but is soluble in organic solvents and oils, which facilitates its formulation in lipid-based and polymeric delivery systems. |
| Melting point: | 200 °C |
| Polymorphs: | THC may exist in multiple polymorphic forms, as evidenced by its variable presentations: an amorphous semi-solid form and a more crystalline chunky golden yellow solid. Detailed thermodynamic, crystallographic, and density data are not provided in the current report. [PMC Article on THC Oxidation](https://pmc.ncbi.nlm.nih.gov/articles/PMC2921982/) |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | THC undergoes oxidative degradation when exposed to heat, light, and oxygen, resulting in decarboxylation and formation of oxidized products such as cannabinol (CBN) and other oxidized isomers. In formulations containing ascorbic acid, degradation was reduced from 31.6% in controls to 5.8% over two months at 40 °C. [Understanding Cannabinoid Degradation Pathways](https://www.broughton-group.com/blog/understanding-cannabinoid-degradation-pathways) [PMC Article on THC Oxidation](https://pmc.ncbi.nlm.nih.gov/articles/PMC2921982/) |
| Stability indicators | Stability studies using HPLC methods indicate significant degradation (up to 48.1% loss in some polymeric matrices at 40 °C under accelerated conditions) that can be mitigated by incorporating antioxidants such as ascorbic acid. These stability-indicating assays are critical in ensuring consistent potency over the product’s shelf life. [PMC Article on THC Oxidation](https://pmc.ncbi.nlm.nih.gov/articles/PMC2921982/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurity profiles include degradation products like cannabinol (CBN) and potential synthetic or excipient-derived byproducts, necessitating advanced analytical methods such as LC/MS and LC-NMR for accurate characterization. [ScienceDirect Article](https://www.sciencedirect.com/science/article/pii/S0022354915322097) [PMC Article](https://pmc.ncbi.nlm.nih.gov/articles/PMC2750308/) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Due to its extremely low aqueous solubility and high lipophilicity, THC is classified as a Class II drug under the Biopharmaceutical Classification System (BCS), signifying low solubility paired with high permeability. Formulation strategies typically include the use of lipid-based nanocarriers and polymeric matrices. [Biopharmaceutical Classification Study](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733) |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** THC  **Chemical names:**  **Structure:**  **Molecular formula:** C21H30O2  **Molecular mass:** 314.5  **Type of substance:**  **Dissociation constant (pKa):**  **Partition coefficient:** 6.97 (log Kow)  **Hygroscopicity:** While THC itself is non-hygroscopic because of its high lipophilicity, its formulations—especially those using amorphous or polymeric matrices—may exhibit hygroscopic behavior, thus requiring moisture-barrier coatings and controlled storage conditions. [Hygroscopicity in Formulated Dosage Forms](https://pmc.ncbi.nlm.nih.gov/articles/PMC9611293/)  **Chirality/Specific optical rotation:** THC contains two stereogenic centers and exists as enantiomers and diastereomers. Although specific optical rotation measurements are not provided, chiral HPLC and spectroscopic techniques such as circular dichroism confirm its stereochemical configuration. [Chirality in Cannabinoid Research](https://pmc.ncbi.nlm.nih.gov/articles/PMC7891190/)  **Degradation temperature:**Thermal analysis indicates that THC degrades at elevated temperatures within the range of 160 to 200 °C, while optimized processing conditions around 120 °C are recommended to minimize degradation. [PMC Article on THC Oxidation](https://pmc.ncbi.nlm.nih.gov/articles/PMC2921982/)  No explicit glass transition temperature (Tg) for isolated THC is provided. However, in polymeric formulations where THC is incorporated, Tg is a critical parameter often affected by plasticizing effects and is typically managed through controlled processing conditions. [Related Studies on Polymeric Formulations](https://pmc.ncbi.nlm.nih.gov/articles/PMC9611293/)  **Boiling point:** 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: | No physical description data available. |
| Solubility: | No specific solubility information is provided. |
| Melting point: | 116–118 °C |
| Polymorphs: | Studies investigating the solid-state properties of melatonin have shown that when melatonin is entrapped in lipid matrices (e.g., in solid lipid nanoparticles), there is a conversion from its crystalline form to an amorphous form. This observation, made through thermal and polymorphic studies using techniques such as DSC and PXRD, indicates that the crystalline structure of melatonin can be altered depending on its formulation environment, impacting dissolution and bioavailability [PubMed](https://pubmed.ncbi.nlm.nih.gov/37809765/). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Melatonin degrades under conditions of elevated temperature with first-order reaction kinetics. Degradation rate constants (k) have been reported as 0.027, 0.082, 0.123, and 0.175 at 60, 70, 80, and 90 °C respectively, with a corresponding reduction in half-life at higher temperatures. Factors such as pH and light exposure (e.g., in fruit juices) also accelerate degradation via mechanisms including photolysis and hydrolysis [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S240584402030493X). |
| Stability indicators | The stability of melatonin is characterized by degradation rate constants and half-life measurements, with stability-indicating HPLC methods showing assay values and recovery percentages under forced degradation conditions. Coefficients of determination (R²) ranging from 0.9744 to 0.995 support the adherence to first-order kinetics, indicating significant impact of temperature and environmental stressors on stability [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S2772422024000351). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Several impurities, originating either as synthetic byproducts or as degradation products, have been identified in melatonin formulations. Advanced analytical techniques such as high-resolution time-of-flight mass spectrometry have been utilized to characterize these impurities, which are essential for quality control in both commercial and OTC formulations [Pharma Affiliates](https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Biopharmaceutical studies indicate that oral melatonin exhibits an absolute bioavailability of approximately 15% at 2 mg and 4 mg doses, likely due to poor absorption and extensive first-pass metabolism. This suggests a classification as a drug with limited oral bioavailability, necessitating formulation strategies to enhance systemic exposure [PubMed](https://pubmed.ncbi.nlm.nih.gov/10883420/), [NEJM](https://www.nejm.org/doi/full/10.1056/NEJM199704033361418). |
| 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):**  **Partition coefficient:** Información no disponible  **Hygroscopicity:** No experimental data regarding the hygroscopicity or moisture absorption properties of melatonin is provided.  **Chirality/Specific optical rotation:** Chiral separation techniques, such as preparative HPLC on polysaccharide-based chiral stationary phases, have been employed to resolve enantiomers of melatonin derivatives. The studies indicate that the (-)-(S) enantiomer exhibits higher receptor affinity for MT1 and MT2, underscoring the importance of stereochemistry, although precise rotation values are not provided [EuropePMC](https://europepmc.org/article/MED/11284025/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/11284025/).  **Degradation temperature:**Thermal degradation studies indicate that melatonin is highly sensitive to temperature increases. The degradation rate constants increase from 0.027 at 60 °C to 0.175 at 90 °C, demonstrating accelerated degradation with rising temperature. First-order kinetic parameters and high R² values (0.9744 to 0.995) confirm the critical role of temperature in degradation behavior [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S240584402030493X), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32258489/).  No data regarding the glass transition temperature (Tg) of melatonin is provided.  **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: |  |
| Job title: |  |  | Job title: |  |  | Job title: |  |
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| Date: |  |  | Date: |  |  | Date: |  |