|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Oral Solution THC+Melatonin |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Others |
| Brand name / Generic name | THC+Melatonin |
| 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 | 60 mL glass bottles |
| Commercial presentations | Not defined |
| Expiration time required |  |
| **Observations:** | |

|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Delta-9-Tetrahydrocannabinol (THC) |
| CAS number: |  |
| Description: | • Exhibits multiple polymorphic forms and complex degradation behavior.  • Exists as a naphthoyl ester derivative with eight distinct crystalline forms (A-H).  • Degradation under environmental stress (heat, light, acidic conditions) affects potency and bioavailability.  References: [Veriheal](https://www.veriheal.com/blog/at-what-temperature-does-thc-degrade/) |
| Solubility: |  |
| Melting point: |  |
| Polymorphs: | Delta-9-THC naphthoyl ester exhibits eight polymorphic forms (designated A-H) as determined by Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), and Powder X-ray Diffraction (PXRD). Historical studies (e.g., Byrn et al. 1985) support the existence of cannabinoid polymorphism. References: [Hallow et al. 2021](https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-022-00131-2), [Byrn et al. 1985](https://www.nature.com/articles/s41598-022-13737-6) |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Quantitative stability data obtained via various HPLC methods indicate recoveries of 100.53 ± 3.12% (external calibration) and 99.3% (RP-HPLC). Further methods (HPLC-UV and HPLC-MS/MS) confirm assay specificity, linearity, and robustness for THC analysis. References: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0039914018309214), [Nature](https://www.nature.com/articles/s41598-022-13737-6), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27268223/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7819317/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Studies on Δ8-THC products reveal impurities such as Cannabidihexol (CBDH), Tetrahydrocannabihexol, 5''-hydroxy-CBD/THC, and Cannabidivarin (CBDV), along with other isomers. Impurities were quantified (up to ~14.76% relative to the Δ8-THC peak) using NMR, HPLC-UV, and MS. References: [ResearchGate](https://www.researchgate.net/publication/368788023\_Isolation\_and\_Characterization\_of\_Impurities\_in\_Commercially\_Marketed\_D8-THC\_Products), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC9608670/), [GMP Collective](https://gmpcollective.com/summary-of-isolation-and-characterization-of-impurities-in-commercially-marketed-δ8-thc-products/) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | THC is evaluated according to the Biopharmaceutical Classification System (BCS) based on solubility and permeability. Experimental methods include in vitro solubility tests in buffer systems, Caco-2 permeability assays, and Log P correlations. Approximately 67% of drugs are high-solubility, and permeability data is critical for bioequivalence. References: [Agno Pharmaceuticals](https://agnopharma.com/technical-briefs/biopharmaceutical-classification-system/), [Springer](https://link.springer.com/chapter/10.1007/978-0-387-74901-3\_28), [Charles River](https://www.criver.com/products-services/lab-sciences/bcs-classification-biowaivers), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC2782078/) |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Delta-9-Tetrahydrocannabinol (THC)  **Chemical names:**  **Structure:**  **Molecular formula:**  **Molecular mass:** None  **Type of substance:**  **Dissociation constant (pKa):**  **Partition coefficient:**  **Hygroscopicity:** THC's moisture absorption characteristics have been studied using oven drying, bench-top moisture analyzers, and water activity measurements via chilled mirror dew point hygrometers and capacitance sensors. The behavior follows Fick's law at relative humidity levels ≤60%, with an activation energy of approximately 0.56 eV. References: [IEEE Xplore](https://ieeexplore.ieee.org/document/5898541), [Technology Networks](https://www.technologynetworks.com/genomics/articles/testing-the-water-the-top-techniques-for-moisture-content-analysis-in-cannabis-390048), [AOAC](https://www.aoac.org/wp-content/uploads/2020/11/Laboratory-Guidance-Drying-Field-Fresh-Hemp-Plant-Samples-in-Preparation-for-Determination-of-Total-THC-on-Dry-Weight-Basis.pdf)  **Chirality/Specific optical rotation:** The specific optical rotation of THC is measured using polarimetry to assess its chiral properties and enantiomeric purity. Techniques involve defined concentrations, path length calibration, and may include advanced methods like surface plasmon resonance (SPR) with weak value amplification (WVA) for enhanced sensitivity. References: [Master Organic Chemistry](https://www.masterorganicchemistry.com/2017/02/07/optical-rotation-optical-activity-and-specific-rotation/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S2352492820327161), [ACS Publications](https://pubs.acs.org/doi/10.1021/acssensors.0c00346), [NCBI](https://pmc.ncbi.nlm.nih.gov/articles/PMC9607418/), [Science](https://www.science.org/doi/10.1126/sciadv.abm3749)  **Degradation temperature:**THC degradation is initiated at temperatures above 30 °C, with significant degradation observed around 43 °C (exposure for 30 minutes), leading to the formation of cannabinol (CBN) and other by-products. Optimal storage conditions range from 15 to 25 °C. Kinetic studies employing HPLC-DAD and LC-MS/MS confirm first-order degradation kinetics. References: [Veriheal](https://www.veriheal.com/blog/at-what-temperature-does-thc-degrade/), [ResearchGate](https://www.researchgate.net/publication/365019016\_Effect\_of\_temperature\_in\_the\_degradation\_of\_cannabinoids\_From\_a\_brief\_residence\_in\_the\_gas\_chromatography\_inlet\_port\_to\_a\_longer\_period\_in\_thermal\_treatments), [Journal of Cannabis Research](https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-022-00166-5), [PubMed](https://pubmed.ncbi.nlm.nih.gov/33420535/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/34096805/)  While specific Tg values for THC were not reported, literature outlines methods for its determination using DSC, TMA, and DMA. These methods reveal that Tg values are method-dependent and require standardized testing conditions. References: [Mettler Toledo](https://www.mt.com/us/en/home/applications/Application\_Browse\_Laboratory\_Analytics/Application\_Browse\_thermal\_analysis/glass-transition-measurement.html), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0009261407005271), [Springer](https://link.springer.com/chapter/10.1007/978-90-481-3150-1\_6), [TA Instruments](https://www.tainstruments.com/pdf/literature/TA082.pdf)  **Boiling point:** |

|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Melatonin |
| CAS number: | 73-31-4 |
| Description: | • Two polymorphic forms of a melatonin-piperazine cocrystal (MLT-PIP I and MLT-PIP II) with distinct hydrogen bonding and molecular packing arrangements.  • MLT-PIP I exhibits a melting point of approximately 127.9 °C and higher water solubility (0.4 mg/mL), while MLT-PIP II shows a melting point of approximately 147.0 °C and greater stability but lower water solubility (0.1 mg/mL).  • Recrystallization studies indicate that the active enantiomer is isolated only in the metastable form.  References: https://pubs.acs.org/doi/10.1021/acs.cgd.9b01405, https://pubs.acs.org/doi/abs/10.1021/cg300398a |
| Solubility: | Melatonin exhibits low aqueous solubility with variation across solvents at 298.15 K: Methanol (0.03570 g/mL), Ethanol (0.02536 g/mL), n-Propanol (0.01965 g/mL), n-Butanol (0.01524 g/mL), n-Pentanol (0.01450 g/mL), i-Butanol (0.01267 g/mL), n-Hexanol (0.01136 g/mL), Methyl Acetate (0.008498 g/mL), Ethyl Acetate (0.006587 g/mL), n-Propyl Acetate (0.004280 g/mL), n-Butyl Acetate (0.003410 g/mL), and n-Pentyl Acetate (0.002990 g/mL). Additionally, the polymorphs exhibit water solubility values of 0.4 mg/mL (MLT-PIP I) and 0.1 mg/mL (MLT-PIP II).  References: https://pubmed.ncbi.nlm.nih.gov/27865856/, https://www.sciencedirect.com/science/article/pii/S0167732220347164, https://healthinformaticsjournal.com/index.php/IJMI/article/view/733 |
| Melting point: | MLT-PIP I: 127.9 °C; MLT-PIP II: 147.0 °C |
| Polymorphs: | Two polymorphic forms of a melatonin-piperazine cocrystal are reported: MLT-PIP I, which features specific hydrogen bonding and a melting point of ~127.9 °C with higher water solubility (0.4 mg/mL), and MLT-PIP II, exhibiting different hydrogen bonding patterns, a higher melting point (~147.0 °C), and improved stability with lower water solubility (0.1 mg/mL). Characterization was performed using X-ray Powder Diffraction (PXRD) and Solid-State NMR.  References: https://pubs.acs.org/doi/10.1021/acs.cgd.9b01405, https://pubs.acs.org/doi/abs/10.1021/cg300398a |
| Stability (Solid state/solution, general information): | None |
| Scheme of degradation route |  |
| Stability indicators | Stability indicators from HPLC studies show melatonin recovery percentages ranging from 98.20% to 99.91%, with additional studies reporting mean recoveries of 100.47% (RSD = 1.25%) and 99.72 ± 0.682%. In capsule formulations, melatonin content was 93.6% ± 4.1% for 0.5 mg capsules and 98.7% ± 6.9% for 6 mg capsules. Analytical methods included RP-HPLC, HPTLC and were validated according to ICH guidelines.  References: https://www.researchgate.net/publication/383711992\_Development\_of\_RP-HPLC\_methods\_for\_the\_analysis\_of\_melatonin\_alone\_and\_in\_combination\_with\_sleep-enhancing\_dietary\_supplements, https://pmc.ncbi.nlm.nih.gov/articles/PMC5790749/, https://files.shroomery.org/attachments/20383466-HPTLC+Method+for+the+Analysis+of+Melatonin.pdf, https://pmc.ncbi.nlm.nih.gov/articles/PMC5790709/ |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Identified impurities of Melatonin include:  - Impurity A: CAS 50-67-9, Chemical Formula C10H12N2O, Molecular Weight 176.22 - Impurity B: CAS 1210-83-9, Chemical Formula C12H14N2O2, Molecular Weight 218.25 - Impurity C: CAS 608-07-1, Chemical Formula C11H14N2O, Molecular Weight 190.24 - Impurity D: CAS 28026-16-6, Chemical Formula C14H16N2O3, Molecular Weight 260.29 Additional impurities include 6-Hydroxy Melatonin (CAS 2208-41-5, C13H16N2O3, MW 248.28) and N-(2-(5-Methoxy-1-nitroso-1H-indol-3-yl)ethyl)acetamide (CAS 278783-22-5, C13H15N3O3, MW 261.28).  References: https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities, https://www.synzeal.com/en/melatonin-ep-impurity-c-2, https://www.lgcstandards.com/FM/en/Melatonin-Assay-Standard/p/BP+1077 |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Melatonin is classified as a BCS Class II drug, which indicates low water solubility and high permeability. It has a very short half-life and variable bioavailability that poses challenges for its therapeutic use.  Reference: https://healthinformaticsjournal.com/index.php/IJMI/article/view/733 |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Melatonin  **Chemical names:**  **Structure:**  **Molecular formula:** C13H16N2O2  **Molecular mass:** 232.28  **Type of substance:**  **Dissociation constant (pKa):** None  **Partition coefficient:**  **Hygroscopicity:** Studies indicate that melatonin exhibits hygroscopic behavior. Infrared spectroscopy identifies water absorption bands between 3050-2800 cm-1. Quantitative measurements in tea show moisture content ranging from 3.7 g/kg to 196 g/kg with relative expanded uncertainties between 28% and 40%.  References: https://pubmed.ncbi.nlm.nih.gov/39466022/, https://www.sciencedirect.com/science/article/pii/S0022286006009859, https://pubmed.ncbi.nlm.nih.gov/32183489/  **Chirality/Specific optical rotation:** Melatonin, as a chiral molecule, displays specific optical rotation measurable by polarimetry in solvents such as chloroform. This property is essential for assessing enantiomeric purity and differentiating between enantiomers.  References: https://www.sciencedirect.com/science/article/pii/S1386142519306791, https://pubmed.ncbi.nlm.nih.gov/9856945/, https://www.sciencedirect.com/science/article/pii/S0167732217348638, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9166628/, https://pmc.ncbi.nlm.nih.gov/articles/PMC9900718/  **Degradation temperature:**Thermal degradation studies of melatonin show first-order kinetics with degradation rate constants of 0.027 at 60 °C, 0.082 at 70 °C, 0.123 at 80 °C, and 0.175 at 90 °C. At 90 °C, the half-life is approximately 4.1 hours. Degradation is further accelerated by light exposure via photo-oxidation, as studied using LC-MS/MS and HPTLC under various pH conditions (1 to 13).  References: https://www.sciencedirect.com/science/article/pii/S240584402030493X, https://pubmed.ncbi.nlm.nih.gov/32258489/  The glass transition temperature (Tg) of melatonin has been evaluated using Differential Scanning Calorimetry (DSC), Temperature-Modulated DSC (TMDSC), Dynamic Mechanical Thermal Analysis (DMTA), and dilatometry. DSC measurements typically use a heating rate of 10 K/min, though reported Tg values vary with sample preparation and methodology.  References: https://link.springer.com/article/10.1007/s10973-009-0268-0, https://glassproperties.com/tg/, https://link.springer.com/chapter/10.1007/978-90-481-3150-1\_6, https://www.sciencedirect.com/science/article/abs/pii/S0378517311010453, https://www.sciencedirect.com/science/article/pii/S0009261407005271  **Boiling point:** |

| 1. **ANNEXES** | |
| --- | --- |
| **ANNEX** | **DESCRIPTION** |
| 1 | IHL-42X formulation brief August 2021 |

| 1. **RELATED DOCUMENTS** | |
| --- | --- |
| **CODE** | **DESCRIPTION** |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

|  |
| --- |
| 1. **AUTHORIZATIONS** |

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