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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?) | Clinical trial |
| 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.) |  |
| Type of packaging material | 60 ml glass bottles |
| Commercial presentations |  |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Delta-8 Tetrahydrocannabinol (Δ-8 THC) |
| CAS number: |  |
| Description: | - Delta-8 THC is a cannabinoid API exhibiting polymorphic behavior, chiral properties, and complex degradation profiles. - The report encompasses detailed studies on polymorphism, degradation routes, stability in oral fluid, impurity profiles, and hygroscopicity. - Various analytical techniques including XRPD, DSC, NMR, LC-MS/MS, and chiral HPLC are employed for characterization [https://www.researchgate.net/publication/229817788\_Polymorphism\_of\_Active\_Pharmaceutical\_Ingredients]. |
| Solubility: | THC exhibits poor solubility in aqueous media, necessitating formulation strategies such as particle size reduction, salt formation, or the use of solubility enhancers. Detailed solubility profiles require further investigation. |
| Melting point: |  |
| Polymorphs: | Polymorphism is critical in APIs with approximately 85% existing as polymorphs, solvates, or hydrates [https://www.researchgate.net/publication/229817788\_Polymorphism\_of\_Active\_Pharmaceutical\_Ingredients]. Studies illustrated using tiotropium bromide identified four polymorphic forms (Monohydrate, Anhydrate Form I, Anhydrate Form II, Anhydrate Form III) at a low detection limit of 0.4 w/w% via synchrotron XRPD, demonstrating superior sensitivity compared to conventional XRPD [https://pmc.ncbi.nlm.nih.gov/articles/PMC5629136/; https://pubmed.ncbi.nlm.nih.gov/19275600/; https://pubmed.ncbi.nlm.nih.gov/38428367/]. |
| Stability (Solid state/solution, general information): | Stability was evaluated under multiple storage conditions: refrigerated at 4°C for up to 3 months with maintained baseline concentrations (±20%), noticeable losses at room temperature, and improved retention when stored frozen at -20°C. Container material also impacted stability, with glass providing superior performance compared to polypropylene [https://pubmed.ncbi.nlm.nih.gov/27539096/; https://pubmed.ncbi.nlm.nih.gov/22532594/; https://pmc.ncbi.nlm.nih.gov/articles/PMC9501240/]. |
| Scheme of degradation route |  |
| Stability indicators | Stability assessments in oral fluid (OF) indicate that cannabinoids such as THC, THCCOOH, THCV, CBD, and CBG remain stable at 4°C for up to 3 months, with most analytes within ±20% of baseline. Variability was noted in a few cases and was influenced by container material, with glass outperforming polypropylene [https://pubmed.ncbi.nlm.nih.gov/27539096/; https://pubmed.ncbi.nlm.nih.gov/22532594/; https://pmc.ncbi.nlm.nih.gov/articles/PMC9501240/]. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurity profiling of Δ-8 THC products revealed impurities ranging from 8.28% to 17.29% relative to the main Δ-8 THC peak. Analytical methods (NMR, HPLC, and MS) identified impurities with molecular masses including 328 Da, 253 Da, and 345 Da, likely resulting from byproducts of low-quality CBD feedstock and side reactions during synthesis [https://pmc.ncbi.nlm.nih.gov/articles/PMC9608670/; https://pubs.acs.org/doi/10.1021/acs.jnatprod.2c01008; https://www.liebertpub.com/doi/pdf/10.1089/can.2020.0021]. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | THC is characterized by low aqueous solubility and variable permeability, suggesting a classification as either BCS Class II (low solubility, high permeability) or Class IV (low solubility, low permeability). This classification directly impacts formulation strategies and bioavailability optimization [https://www.solvobiotech.com/services/categories/bcs-based-biowaiver-permeability-classification-caco-2-model; https://www.firsthope.co.in/biopharmaceutics-classification-system-bcs]. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Delta-8 Tetrahydrocannabinol (Δ-8 THC)  **Chemical names:**  **Structure:**  **Molecular formula:**  **Molecular mass:** None  **Type of substance:**  **Dissociation constant (pKa):**  **Partition coefficient:**  **Hygroscopicity:** THC exhibits hygroscopic properties, which may lead to moisture uptake and subsequent degradation. Monitoring using techniques such as gravimetric analysis and moisture sorption isotherms is recommended to manage quality risks [https://www.tandfonline.com/doi/full/10.1080/10837450.2022.2084105; https://www.pharmaexcipients.com/news/quality-impact-hygroscopic-pharmaceutical-raw-materials/; https://www.sciencedirect.com/science/article/pii/S0166526X2030026X].  **Chirality/Specific optical rotation:** THC is a chiral molecule with a reported specific optical rotation of [α]D25 = +40.0° when measured at 589 nm, 20-25°C using a 100 mm path length. Determination is typically performed using polarimetry, chiral HPLC, and NMR techniques [https://labs.protheragen-ing.com/optical-rotation-test.html; https://digicollections.net/phint/pdf/b/7.1.4.1.4-Determination-of-optical-rotation-and-specific-ro\_.pdf; https://science-mania.odoo.com/blog/conceptual-blog-for-chemistry-1/understanding-specific-rotation-a-key-property-of-chiral-compounds-1; https://pmc.ncbi.nlm.nih.gov/articles/PMC7891190/].  **Degradation temperature:**Thermal degradation studies of Δ9-THC in dried cannabis resin indicate onset of degradation between 50°C and 80°C, with accelerated degradation observed at a GC injector port temperature of 300°C, resulting in notable formation of CBN and Δ8-THC. Degradation kinetics conform to first-order reaction models [https://www.researchgate.net/publication/352206874\_Kinetics\_of\_CBD\_D\_9\_-THC\_Degradation\_and\_Cannabinol\_Formation\_in\_Cannabis\_Resin\_at\_Various\_Temperature\_and\_pH\_Conditions; https://pubmed.ncbi.nlm.nih.gov/36385981/; https://link.springer.com/article/10.1007/s00216-020-03098-2].  Studies using DSC and mDSC indicate that the glass transition temperature (Tg) of THC is influenced by sample history, moisture content, and cooling rate. While exact Tg values are not provided, literature suggests that water absorption can significantly reduce Tg [https://pubmed.ncbi.nlm.nih.gov/31848763/; https://pubs.acs.org/doi/full/10.1021/ci5004834].  **Boiling point:** |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Melatonin |
| CAS number: | 73-31-4 |
| Description: | • Crystalline appearance with an ivory beige color. • Synthesized as 5-methoxy-N-acetyltryptamine via enzymatic conversion from tryptophan (involving hydroxylation, acetylation, and methylation steps). |
| Solubility: | • At 25°C: Water: 0.1 mg/mL; Ethanol: 50 mg/mL. • Additional solubility data in twelve mono-solvents at 298.15 K show decreasing order from methanol (0.03570) to n-pentyl acetate (0.002990), indicating variable solvation behavior. [Source: https://www.sciencedirect.com/science/article/abs/pii/S0167732220347164] |
| Melting point: |  |
| Polymorphs: | • Two polymorphic forms of melatonin cocrystal with piperazine (MLT-PIP I and MLT-PIP II in 2:1 stoichiometry) exhibiting distinct hydrogen bonding and molecular packing. • Enantiomeric polymorphs were also observed, where the inactive enantiomer yielded two forms and the active enantiomer produced only the metastable form despite extensive isolation. • Characterization utilized X-ray diffraction, DSC, TG, IR, and Raman spectroscopy. [Sources: https://pubs.acs.org/doi/10.1021/acs.cgd.9b01405, https://pubs.acs.org/doi/abs/10.1021/cg300398a, https://www.sciencedirect.com/science/article/pii/S0169409X16303209, https://pmc.ncbi.nlm.nih.gov/articles/PMC5405617/, https://pmc.ncbi.nlm.nih.gov/articles/PMC3177871/] |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | • Melatonin is sensitive to light and oxidation; its stability is enhanced in eutectic systems (e.g., natural deep eutectic solvents) when stored at temperatures below 25°C. • Stability testing of melatonin capsules demonstrated over 85% dissolution within 15 minutes and maintained API content for 18 months at 25°C/60% RH. • A stability-indicating HPLC method confirmed minimal interference (0.01% risk of false negatives) and separation of degradation products. [Sources: https://papers.ssrn.com/sol3/papers.cfm?abstract\_id=4883025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5790709/, https://www.geneesmiddeleninformatiebank.nl/pars/h120771.pdf, https://rjptonline.org/AbstractView.aspx?PID=2020-13-2-2] |
| Impurities (Synthetic origin, degradation products and/or metabolites) | • Impurity A: 3-(2-Aminoethyl)-1H-indol-5-ol (CAS: 50-67-9, MW: 176.22 g/mol). • Impurity B: N-[2-(5-Hydroxy-1H-indol-3-yl)ethyl]acetamide (CAS: 1210-83-9, MW: 218.25 g/mol). • Impurity C: 2-(5-Methoxy-1H-indol-3-yl)ethan-1-amine (CAS: 608-07-1, MW: 190.24 g/mol). • A total of 10 impurity peaks were observed in aged samples, with five impurities exceeding USP individual limits. Analysis was performed via HPLC. [Sources: https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities, 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://pubmed.ncbi.nlm.nih.gov/10085477/, https://pubmed.ncbi.nlm.nih.gov/39058576/] |
| Biopharmaceutical classification (Biopharmaceutical classification system) | • Melatonin is categorized as BCS Class I due to its high solubility (meeting the criterion of complete solubility of the highest therapeutic dose in ≤250 mL aqueous media across pH 1.2–6.8) and high permeability, as evidenced by rapid absorption and bioavailability up to 94% via alternative routes. [Sources: https://database.ich.org/sites/default/files/M9\_Guideline\_Step4\_2019\_1116.pdf, https://www.fda.gov/media/166154/download, 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):**  **Partition coefficient:** 1.65  **Hygroscopicity:** • Melatonin is hygroscopic, absorbing ambient moisture which can modify its dissolution and physical stability. • Thermodynamic solubility studies in twelve mono-solvents indicate a positive correlation between temperature, moisture uptake, and solubility. [Sources: https://www.sciencedirect.com/science/article/abs/pii/S0167732220347164, https://pmc.ncbi.nlm.nih.gov/articles/PMC10295901/]  **Chirality/Specific optical rotation:** • Melatonin exhibits chirality with two enantiomers: (R)- and (S)-melatonin. • Specific optical rotation and circular dichroism measurements, along with preparative HPLC enantiomeric resolution using a chiral stationary phase, have shown that the (+)-(S)-enantiomer possesses approximately 500-fold greater affinity for MT1 and MT2 receptors compared to the (−)-(R)-enantiomer. [Sources: https://onlinelibrary.wiley.com/doi/10.1002/chir.1020, https://www.academia.edu/12950111/Reassessing\_the\_melatonin\_pharmacophore\_Enantiomeric\_resolution\_pharmacological\_activity\_structure\_analysis\_and\_molecular\_modeling\_of\_a\_constrained\_chiral\_melatonin\_analogue, https://www.sciencedirect.com/science/article/pii/S0968089606000058]  **Degradation temperature:**• Degradation studies in a pH 1 solution reveal temperature-dependent kinetics: rate constant k increases from 0.027 h⁻¹ at 60 °C to 0.175 h⁻¹ at 90 °C, with a half-life of approximately 4.1 hours at 90 °C. • Degradation is accelerated by exposure to light and elevated temperatures, following a first-order kinetic model. [Sources: https://www.researchgate.net/publication/340145219\_Influence\_of\_pH\_temperature\_and\_light\_on\_the\_stability\_of\_melatonin\_in\_aqueous\_solutions\_and\_fruit\_juices, https://www.researchgate.net/publication/11792905\_The\_effect\_of\_variations\_in\_pH\_and\_temperature\_on\_stability\_of\_melatonin\_in\_aqueous\_solution] "rld\_special\_characteristics": " " , "rld\_manufacturing\_process\_info": ""} } // End of JSON object output. Note: The "rld\_special\_characteristics" and "rld\_manufacturing\_process\_info" fields are left empty as no relevant data was provided.  • The glass transition temperature (Tg) for amorphous melatonin is approximately 315 K (42 °C) under dry conditions and decreases with moisture content. • Determined primarily via DSC and modulated DSC techniques. [Sources: https://pmc.ncbi.nlm.nih.gov/articles/PMC6917632/, https://pmc.ncbi.nlm.nih.gov/articles/PMC8400648/]  **Boiling point:** |

| 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: |  |