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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 |
| API(s) | THC  Melatonin |
| Strength(s) | THC + Melatonin, concentrations not defined |
| 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 bottles 60 ml |
| Commercial presentations | Not defined |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | THC |
| CAS number: |  |
| Description: | • THC appears as a sticky, resinous substance with a brown amorphous semi‐solid or viscous oil-like consistency. • It possesses a complex polycyclic structure with two stereogenic centers imparting chirality essential for pharmacological activity. |
| Solubility: | THC exhibits very low aqueous solubility and is highly lipophilic. It is typically insoluble in water but dissolves in organic solvents and its solubility can be enhanced in formulations such as amorphous solid dispersions. |
| Melting point: |  |
| Polymorphs: | The polymorphic behavior of THC is not extensively characterized in the literature. It is typically formulated as part of amorphous solid dispersions or incorporated within polymer matrices. Advanced techniques such as synchrotron X-ray powder diffraction are suggested to investigate any pseudo‐polymorphic transitions. [Reference: See report discussion] |
| Stability (Solid state/solution, general information): | Stability studies indicate that THC exhibits high chemical integrity under controlled processing conditions. Notably, forced degradation studies using hot-melt processing (75–90 minutes at temperatures up to 200°C) show more than 94% recovery, and storage in oral fluid at 4°C maintains concentrations within ±20% of baseline for 2–3 months. [Reference: PMC Article on Stability of Oral Fluid Cannabinoids (https://pmc.ncbi.nlm.nih.gov/articles/PMC5233598/)] |
| Scheme of degradation route | THC degrades via several pathways including isomerization, acid-catalyzed rearrangement, dehydration (forming regioisomers such as isoTHC), and oxidation to yield cannabinol (CBN) as the primary degradation product. Degradation increases with processing temperature (approximately 2.8% at 120°C, 5.1% at 160°C, and 5.7% at 200°C) with formation of reactive intermediates such as epoxy or hydroxylated species. [Reference: Broughton Group – Degradation Pathways of Cannabinoids (https://www.broughton-group.com/lp-degradation-pathways-of-cannabinoids)] |
| Stability indicators | Forced degradation studies under thermal stress show high chemical stability with more than 94% THC recovery at processing temperatures up to 200°C for 75–90 minutes. Additionally, oral fluid stability studies indicate that storage at 4°C keeps THC concentrations within ±20% of baseline for up to 2–3 months. [Reference: PMC Article on Stability of Oral Fluid Cannabinoids (https://pmc.ncbi.nlm.nih.gov/articles/PMC5233598/)] |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurity profiling reveals that cannabinol (CBN) is the primary degradation impurity, accompanied by other minor oxidation and rearrangement by-products. These impurities are quantified using advanced chromatographic techniques such as HPLC and GC-MS. [Reference: USP guidelines and related literature] |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Based on its high lipophilicity and low aqueous solubility, THC is classified as a BCS Class II drug (low solubility, high permeability). Formulation strategies typically aim to enhance dissolution rate via amorphous solid dispersions or the use of solubilizing excipients. [References: NeuroQuantology (https://www.neuroquantology.com/media/article\_pdfs/3165-3177.pdf), FirstHope (https://www.firsthope.co.in/biopharmaceutics-classification-system-bcs)] |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** THC  **Chemical names:**  **Structure:**  **Molecular formula:** C21H30O2  **Molecular mass:** 314.47  **Type of substance:**  **Dissociation constant (pKa):** None  **Partition coefficient:** THC is highly lipophilic with a significant octanol-water partition coefficient consistent with BCS Class II characteristics; however, a specific numerical value was not provided.  **Hygroscopicity:** THC itself exhibits minimal hygroscopicity owing to its lipophilic resinous nature. However, attention must be paid to co-formulated hydrophilic excipients, which may be hygroscopic and impact overall formulation stability. [Reference: Report discussion]  **Chirality/Specific optical rotation:** THC is a chiral molecule containing two stereogenic centers. Its enantiomeric purity is assessed using methods such as polarimetry, chiral HPLC, and vibrational circular dichroism, ensuring that the biologically active enantiomer predominates. [Reference: PMC Article on Cannabinoid Chirality (https://pmc.ncbi.nlm.nih.gov/articles/PMC7891190/)]  **Degradation temperature:**Thermal degradation studies report approximately 2.8% loss of THC at 120°C, increasing to 5.7% at 200°C. Gas chromatography data show up to 17.2% degradation under brief high temperature exposure, indicating the critical role of thermal conditions in degradation kinetics. [References: PMC Article on Temperature Stability (https://pmc.ncbi.nlm.nih.gov/articles/PMC2921171/), PubMed (https://pubmed.ncbi.nlm.nih.gov/36385981/)]  While a specific standalone glass transition temperature (Tg) for pure THC is not provided, studies on amorphous formulations indicate that incorporation into high-Tg polymer matrices increases Tg, thereby enhancing kinetic stability. Differential scanning calorimetry (DSC) is typically used for Tg determination, and it is recommended that storage temperatures be maintained at least 50°C below the Tg. [Reference: PMC Article on Glass Transition Temperature in Amorphous Solids (https://pmc.ncbi.nlm.nih.gov/articles/PMC6917632/)]  **Boiling point:** |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Melatonin |
| CAS number: | 73-31-4 |
| Description: | • Solid state form • Provided as a solid substance used in immediate-release and modified-release formulations |
| Solubility: | No specific quantitative solubility data provided. However, formulation studies indicate that melatonin can be processed in various solvent systems for capsule preparation. |
| Melting point: | Información no disponible |
| Polymorphs: | Research has identified at least two polymorphic forms within a cocrystal of melatonin and piperazine (MLT-PIP I and MLT-PIP II) which differ in hydrogen bonding modes and molecular packing. These polymorphs influence dissolution rate, chemical stability, and bioavailability. Refer to [ACS Publications](https://pubs.acs.org/doi/10.1021/acs.cgd.9b01405). |
| Stability (Solid state/solution, general information): | Melatonin shows long-term stability when formulated in hard capsules and powder. For example, low-dose melatonin capsules maintained assay and physical integrity over an 18-month period at 25 ± 2 °C and 60% ± 5% RH ([Filali et al.](https://pmc.ncbi.nlm.nih.gov/articles/PMC5790709/)) while compounded melatonin powder retained over 95% content for at least six months at room temperatures of 15–25 °C ([PubMed](https://pubmed.ncbi.nlm.nih.gov/32258489/)). |
| Scheme of degradation route | Melatonin degrades through both enzymatic and nonenzymatic pathways. Enzymatic degradation involves identified pathways (PWY-6398, PWY-6399, PWY-6400) while nonenzymatic degradation proceeds via radical formation and reactions with reactive oxygen and nitrogen species, including photolytic degradation upon UVB exposure. See [PubChem](https://pubchem.ncbi.nlm.nih.gov/pathway/BioCyc:HUMAN\_PWY-6398). |
| Stability indicators | Stability studies on melatonin hard capsules show recovery percentages ranging from 93.6% to 98.7% over 18 months. Stability-indicating HPLC methods and ATR-FTIR analyses confirm that capsule mass uniformity, assay, and dissolution profiles comply with European Pharmacopoeia standards. Refer to [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC5790709/). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurity profiling of melatonin has revealed variabilities among suppliers, including impurities associated with eosinophilia-myalgia syndrome (EMS). Process optimizations are implemented to ensure high-purity melatonin. Refer to [Karger](https://karger.com/nsg/article/8/1-2/143/334984/Aspects-of-Melatonin-Manufacturing-and) and [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Melatonin is classified as a BCS Class II drug, implying low solubility combined with high permeability. This classification impacts its absorption and necessitates formulation strategies to enhance bioavailability. See [ResearchGate](https://www.researchgate.net/publication/324678815\_Biopharmaceutical\_Classification\_System). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Melatonin  **Chemical names:**  **Structure:**  **Molecular formula:** C13H16N2O2  **Molecular mass:** 232.28  **Type of substance:**  **Dissociation constant (pKa):** 16.51 and -0.69 (melatonin remains uncharged across the full pH range)  **Partition coefficient:** log Kow = 1.18 at 28 °C  **Hygroscopicity:** No specific quantitative data on hygroscopicity has been provided. However, the use of optimized excipient selection and packaging in hard capsules suggests controlled moisture uptake.  **Chirality/Specific optical rotation:** While no numerical value for optical rotation is provided, literature indicates that chiral resolution and circular dichroism analyses confirm a high degree of enantiomeric purity, which is crucial for pharmacological efficacy.  **Degradation temperature:**No specific degradation temperature is provided, but forced degradation studies indicate that melatonin undergoes temperature-induced degradation with first-order kinetics at temperatures exceeding typical ambient storage conditions (15–25 °C). Refer to [PubMed](https://pubmed.ncbi.nlm.nih.gov/32258489/).  Differential scanning calorimetry (DSC) studies report a glass transition temperature of approximately 284.2 K for native melatonin and 283.7 K for a partially-deuterated derivative, indicating consistent thermal behavior in the amorphous state. Refer to [Nature Scientific Reports](https://www.nature.com/articles/s41598-022-18478-0).  **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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