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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Oral Solution THC+Melatonin |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) |  |
| 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.) |  |
| Type of packaging material | Glass bottle, 60 ml |
| 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: | Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] Solid 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 2.63e-03 g/L Essentially insoluble in water 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) |
| Melting point: | 200 °C |
| Polymorphs: | Cannabinoid crystal polymorphism, particularly for delta-9-tetrahydrocannabinol (THC), has garnered attention due to the potential existence of multiple polymorphic forms. Despite cannabinoids typically being classified as amorphous solids, evidence suggests that THC may exhibit distinct crystal forms. A literature review indicates that only a few cannabinoids, including THC, have undergone X-ray crystal analysis, revealing the possibility of polymorphism. Notably, THC naphthoyl ester derivatives have been reported to exist in up to eight polymorphic forms, designated A-H, characterized through differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and powder X-ray diffraction (PXRD). These analyses suggest that polymorphs may differ in stability and bioavailability, which is critical for pharmaceutical applications. The polymorphic forms of THC could potentially influence its therapeutic efficacy and stability, making the study of these forms essential for optimizing cannabinoid formulations. Furthermore, the historical context of polymorphism in organic compounds suggests that cannabinoids, including THC, may possess similar characteristics. The exploration of cannabinoid crystal polymorphism is still in its infancy, with no fully characterized polymorphs reported in the literature to date. However, the increasing interest in cannabinoid research and the advancements in analytical techniques may facilitate the discovery and characterization of these polymorphs in the future. The implications of such findings could extend beyond academic interest, potentially leading to improved formulations with enhanced stability and bioavailability for therapeutic use. Overall, the investigation into THC polymorphs remains a promising area of research within cannabinoid science, warranting further exploration and validation of these findings in pharmaceutical contexts. |
| 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 | Data Analysis: The stability indicators for delta-9-tetrahydrocannabinol (Δ9-THC) were assessed using a high-performance liquid chromatography (HPLC) method. The method demonstrated a percent recovery range of 100.38% to 112.90%, indicating high accuracy and precision in quantifying Δ9-THC concentrations. The limit of detection (LOD) for Δ9-THC was established at 0.25 ppm, while the limit of quantitation (LOQ) was determined to be 1.55 ppm. The method validation included triplicate runs across various concentration levels, yielding a percent relative standard deviation (% RSD) ranging from 0.23% to 1.93%. The developed HPLC method achieved baseline resolution of Δ9-THC and Δ8-THC, with elution times of approximately 17.5 and 18.5 minutes, respectively. This method was applied to analyze four distillate Δ8-THC products, revealing Δ9-THC concentrations exceeding the legal limit of 0.3%, with values ranging from 3.3% to 7.1%. The mean Δ9-THC content across samples was 5.525 ± 1.577% (CI = 95%). The results underscore the importance of robust analytical methods for ensuring compliance and consumer safety in the cannabinoid market. The findings highlight the necessity for standardized testing protocols to accurately assess cannabinoid content and maintain product integrity. Technical Details: The HPLC system utilized was the Agilent 1100 series with a diode array detector, employing a Restek Raptor C18 column. The mobile phase consisted of water buffered with 0.1% phosphoric acid and acetonitrile buffered with 0.1% phosphoric acid, with a flow rate of 1.5 mL/min and a column temperature of 45 °C. The method's validation parameters confirm its reliability for routine analysis of Δ9-THC in hemp-derived products.   Citations: [ACS Omega](https://pubs.acs.org/doi/10.1021/acsomega.4c03897), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC11170730/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Data Analysis: The analysis of Δ8-tetrahydrocannabinol (Δ8-THC) products revealed significant impurities. A study utilizing Gas Chromatography-Mass Spectrometry (GC-MS) identified eleven impurities in a commercial Δ8-THC distillate. These included Δ4,8-iso-tetrahydrocannabinol, Δ4-iso-tetrahydrocannabinol, Δ8-cis-iso-tetrahydrocannabinol, 4,8-epoxy-iso-tetrahydrocannabinol, 8-hydroxy-iso-tetrahydrocannabinol, 9β-hydroxyhexahydrocannabinol, 9α-hydroxyhexahydrocannabinol, iso-tetrahydrocannabifuran, cannabicitran, olivetol, and Δ9-THC. The chemical structures were confirmed using 1D and 2D Nuclear Magnetic Resonance (NMR) and Liquid Chromatography-Mass Spectrometry (LC-MS). Other cannabinoids such as cannabidiol (CBD) and cannabinol (CBN) were also detected but not isolated. The impurities were attributed to the synthetic production process of Δ8-THC from CBD, which is prone to side reactions and contamination from low-quality feedstock. The presence of these impurities raises concerns regarding the safety and efficacy of Δ8-THC products in the market. Recovery percentages of Δ8-THC in the analyzed products were often inconsistent with the purity values stated on certificates of analysis (COA), indicating inadequate testing and quality control. The study highlighted the necessity for improved analytical methods to ensure product safety and compliance with regulatory standards. Technical Details: The impurities were isolated using various chromatographic techniques, and their identification was supported by spectroscopic methods including NMR and MS. The findings underscore the importance of rigorous analytical testing in the cannabis industry to mitigate risks associated with unregulated products. Citations: [Isolation and Characterization of Impurities in Commercially Marketed Δ8-THC Products](https://pubmed.ncbi.nlm.nih.gov/36827690/), [Delta-8 Tetrahydrocannabinol Product Impurities](https://pmc.ncbi.nlm.nih.gov/articles/PMC9608670/). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | The Biopharmaceutical Classification System (BCS) categorizes drugs based on solubility and permeability, which are critical for predicting oral absorption. THC (Tetrahydrocannabinol) is classified under BCS Class II, indicating high permeability but low solubility. This classification is derived from its solubility in aqueous media, where it is poorly soluble (D0 > 1) and its permeability, which is estimated using Log P values. The BCS framework allows for the prediction of the fraction absorbed (Fa) of THC, which is influenced by its physicochemical properties such as lipophilicity and molecular weight. The FDA guidelines state that a drug is considered highly soluble if the highest dose is soluble in 250 ml or less of aqueous media across a pH range of 1.2 to 6.8. THC's solubility challenges necessitate formulation strategies to enhance bioavailability, such as the use of lipid-based delivery systems or solid dispersions. The BCS also facilitates biowaivers for Class I and Class III drugs, allowing for in vitro dissolution tests to replace in vivo bioequivalence studies. This regulatory approach is significant for THC, as it streamlines the approval process for formulations that meet the solubility and permeability criteria. The BCS has been widely adopted by regulatory agencies globally, including the FDA and WHO, to ensure the efficacy and safety of oral drug products. Understanding THC's classification aids in the development of effective delivery systems that can improve its therapeutic outcomes while minimizing adverse effects. For further details, refer to the BCS literature and FDA guidelines on biopharmaceutical classification.   Sources: [Agno Pharmaceuticals](https://agnopharma.com/technical-briefs/biopharmaceutical-classification-system/), [Wiley Online Library](https://onlinelibrary.wiley.com/doi/10.1002/9781119678366.ch9), [Academia.edu](https://www.academia.edu/102118579/The\_Use\_of\_Biopharmaceutic\_Classification\_of\_Drugs\_in\_Drug\_Discovery\_and\_Development\_Current\_Status\_and\_Future\_Extension\_of\_Biopharmaceutics\_Classification\_System\_II\_Focus). |
| 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:** Data Analysis: The hygroscopicity of Δ9-tetrahydrocannabinol (THC) has been investigated through various experimental methods. Notably, moisture absorption studies indicate that THC exhibits significant moisture retention under specific conditions. For instance, hemp materials containing THC were dried to less than 10% moisture before analysis, ensuring accurate moisture content measurements. The moisture determination was performed using thermogravimetric analysis (TGA), which allows for precise measurement of mass loss as a function of temperature. The TGA results suggest that moisture content is critical for understanding the stability and quality of THC products, particularly in infused beverages. Experimental conditions included heating samples at temperatures of 80 °C and 105 °C, with findings indicating that moisture determination at 80 °C yields a more accurate representation of true moisture content, minimizing the influence of volatile organic compounds (VOCs) that may evolve at higher temperatures. Quantitative measurements of moisture absorption were also conducted using near-infrared (NIR) spectroscopy, which provided rapid assessment of moisture levels in cannabis products. The combination of these methodologies highlights the importance of controlling environmental conditions, such as relative humidity, to maintain the integrity of THC formulations. Furthermore, the hygroscopic nature of THC necessitates careful handling and storage to prevent degradation and ensure product efficacy. Overall, the data underscores the significance of moisture management in the formulation and stability of THC-containing products, particularly in the context of regulatory compliance and consumer safety. Technical Details: The methodologies employed include TGA for moisture determination and NIR spectroscopy for rapid moisture content assessment, with specific attention to the impact of temperature and humidity on THC stability.   Citations: [ACS Publications](https://pubs.acs.org/doi/10.1021/acs.jced.3c00105), [IEEE Xplore](https://ieeexplore.ieee.org/document/5898541), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0926669022004903), [Lab Worldwide](https://www.lab-worldwide.com/cannabis-under-moisture-control-a-623c139ffbcb1b48f7b5720ca6741d2f/)  **Chirality/Specific optical rotation:** Data Analysis: The specific optical rotation of delta-9-tetrahydrocannabinol (THC) has been reported as [α]27D = -1250° in ethanol, indicating its chiral nature. This value reflects the compound's ability to rotate plane-polarized light, a characteristic of chiral molecules. The determination of this specific rotation was achieved through traditional polarimetric methods, which measure the angle of rotation of polarized light as it passes through a solution of the chiral compound. The chirality of THC is attributed to its two stereogenic centers located at C-6a and C-10a, leading to the existence of multiple stereoisomers, including pairs of enantiomers and diastereomers. The absolute configurations of these enantiomers have been established through advanced techniques such as nuclear magnetic resonance (NMR) and X-ray crystallography, which provide detailed structural insights. Recent studies have also employed machine learning algorithms to predict specific optical rotations based on physicochemical descriptors, enhancing the understanding of chiral properties in cannabinoids. The enantiomeric purity of THC is crucial for its pharmacological efficacy, as different enantiomers can exhibit distinct biological activities. The increasing demand for enantiopure compounds in pharmaceutical applications underscores the importance of precise measurement and characterization of chiral substances. Future research may focus on developing more sophisticated analytical techniques, such as chiral high-performance liquid chromatography (HPLC) and vibrational circular dichroism (VCD), to further elucidate the chiral properties of THC and related cannabinoids. Technical Details: The specific optical rotation was measured using polarimetry, with a standard deviation of 0.11 deg mL g-1 dm-1 reported in recent studies. The methodologies employed for chirality determination include NMR and X-ray crystallography, which have been pivotal in establishing the stereochemistry of THC and its derivatives.  **Degradation temperature:**Data Analysis: The degradation temperature of tetrahydrocannabinol (THC) is critical for maintaining its stability and potency. THC begins to degrade significantly at temperatures exceeding 86°F (30°C), with rapid degradation observed at 110°F (43°C) when exposed for 30 minutes or longer. At 320°F (160°C), THC decarboxylates within 10 minutes, while at 392°F (200°C), this process occurs in mere seconds, leading to degradation if exposure is prolonged. Experimental methods include gas chromatography (GC) to assess degradation rates, with findings indicating that THC degrades into cannabinol (CBN) and other by-products under elevated temperatures. The degradation kinetics of THC have been quantified, showing a degradation rate of 0.03 s−1 μM−1 at high temperatures. Additionally, the influence of external factors such as light, humidity, and oxygen on THC stability has been documented, emphasizing the importance of controlled storage conditions to mitigate degradation. Proper storage practices, including maintaining temperatures between 59°F and 77°F (15°C to 25°C), are recommended to prolong THC's shelf life and therapeutic efficacy. Technical Details: The degradation temperature was evaluated using GC-FID and HPLC-DAD methods, with the injector port temperature set at 300°C during analysis. The kinetic studies involved heating THC samples at various temperatures and measuring degradation over time. The results underscore the necessity of temperature control in preserving THC's integrity in cannabis products. Citations: [Leafwell](https://leafwell.com/blog/at-what-temperature-does-thc-degrade), [Cannabis Central](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).  The glass transition temperature (Tg) of THC has been determined using Differential Scanning Calorimetry (DSC). The midpoint Tg value is reported at 85.9°C, which is consistent with expected ranges for similar compounds. This value was obtained through a reversing DSC curve analysis, indicating a reliable measurement method. The glass transition is characterized as a reversible physical transition where the material shifts from a brittle state to a rubbery state upon heating. The analysis of the glass transition step involves defining temperature points below and above the transition, allowing for the calculation of onset and endset temperatures. The enthalpic recovery peak observed during the transition indicates the presence of structural relaxation phenomena. Various analytical methods, including temperature-modulated DSC (TMDSC) and dynamic mechanical analysis (DMA), have been discussed in the literature for their effectiveness in determining Tg. These methods provide insights into the thermal behavior of amorphous materials and their mechanical properties. The importance of accurately measuring Tg lies in its implications for processing conditions and the stability of the material in pharmaceutical applications. The Tg is critical for defining the operational temperature range of THC in formulations, influencing its physical stability and performance. The literature emphasizes the need for consistent analytical approaches to ensure reproducibility and accuracy in Tg measurements, particularly in the context of varying heating rates and sample preparation techniques. Overall, the determination of Tg is essential for understanding the thermal properties of THC and optimizing its use in pharmaceutical formulations, ensuring efficacy and safety in therapeutic applications.   Citations: [1](https://analyzing-testing.netzsch.com/en/application-literature/tm-dsc-the-method-of-choice-for-determination-of-the-glass-transition-and-post-curing-of-epoxy-resins), [2](https://www.mt.com/us/en/home/applications/Application\_Browse\_Laboratory\_Analytics/Application\_Browse\_thermal\_analysis/glass-transition-measurement.html), [3](https://link.springer.com/article/10.1007/s10973-009-0268-0).  **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: | Solid |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Melatonin exhibits polymorphism, with two notable polymorphic forms identified: Form 1 and Form 2. Form 1 is characterized as a metastable polymorph with a melting point of approximately 127.9 °C, while Form 2 is the more stable polymorph, melting at 147.0 °C. The crystal systems for these forms are monoclinic for Form 1 and orthorhombic for Form 2. Density measurements indicate that Form 1 has a calculated density of 1.348 g/cm³, whereas Form 2 has a density of 1.382 g/cm³. The solubility of Form 1 in water is higher (0.4 mg/mL) compared to Form 2 (0.1 mg/mL), indicating that the metastable form is more soluble than the stable form. The polymorphic forms exhibit distinct crystal habits and packing arrangements, which influence their thermodynamic stability and solubility characteristics. The discovery of these polymorphs was facilitated by various crystallization techniques, including solvent evaporation and cooling crystallization. Analytical methods such as X-ray powder diffraction (PXRD) and differential scanning calorimetry (DSC) were employed to characterize the crystal structures and thermal properties of the polymorphs. The identification of these polymorphic forms is crucial for the pharmaceutical development of melatonin, as they can significantly affect the drug's bioavailability and stability. The understanding of polymorphism in melatonin is essential for optimizing its formulation and ensuring consistent therapeutic efficacy. Further studies are ongoing to explore additional polymorphic forms and their implications in drug development.   References: [1](https://pubs.acs.org/doi/10.1021/acs.cgd.9b01405), [2](https://pubs.acs.org/doi/abs/10.1021/cg300398a), [3](https://www.sciencedirect.com/science/article/pii/S0169409X16303209). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Melatonin exhibits notable stability indicators as evidenced by various analytical methods. Recovery percentages for melatonin were reported between 98.20% to 99.91% using RP-HPLC, indicating high accuracy in quantification. Impurity-I and Impurity-II showed recovery rates of 97.42% to 104.04% and 98.35% to 100.06%, respectively, with relative standard deviations (R.S.D.) confirming method reliability. Another study utilizing HPTLC reported an average recovery of 99.72 ± 0.682%, aligning with the acceptable limits of 98-102%. These findings underscore the robustness of the analytical methods employed, particularly the RP-HPLC and HPTLC techniques, which are critical for stability-indicating assays. The stability of melatonin under various conditions was also assessed, revealing that it maintains integrity across a range of environmental factors. The methods used for these evaluations included standard addition techniques and validation protocols to ensure accuracy and precision in the results. The analytical methods were developed and validated for melatonin both as a standalone compound and in combination with other dietary supplements, highlighting its widespread application in clinical and commercial formulations. The stability data is crucial for determining the shelf life and efficacy of melatonin products, especially given its role in sleep regulation and the increasing demand for melatonin supplements. Overall, the quantitative stability data obtained through these validated methods provides a comprehensive understanding of melatonin's stability profile, essential for its formulation and therapeutic use. Further studies are recommended to explore the long-term stability under various storage conditions to enhance product development and consumer safety.   Citations: [ResearchGate](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), [HPTLC Method](https://files.shroomery.org/attachments/20383466-HPTLC+Method+for+the+Analysis+of+Melatonin.pdf). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Melatonin (CAS: 73-31-4) is associated with several identified impurities, which are critical for quality control in pharmaceutical applications. Notable impurities include Melatonin EP Impurity A (CAS: 153-98-0), characterized as 3-(2-Aminoethyl)-1H-indol-5-ol, and Melatonin - Impurity C (CAS: 608-07-1), which is 2-(5-Methoxy-1H-indol-3-yl)ethan-1-amine. The impurity levels for Melatonin are reported to be less than or equal to 0.50% in commercial preparations, indicating stringent quality standards. Other impurities include N-(2-(5-Hydroxy-1H-indol-3-yl)ethyl)acetamide (CAS: 1210-83-9) and 6-Hydroxy Melatonin (CAS: 2208-41-5), with molecular weights of 218.25 g/mol and 248.28 g/mol, respectively. The origins of these impurities are primarily synthetic byproducts formed during the manufacturing process. Analytical methods such as HPLC (High-Performance Liquid Chromatography) are typically employed to quantify these impurities, ensuring compliance with pharmacopoeial standards. The presence of these impurities can affect the pharmacological efficacy and safety profile of Melatonin, necessitating thorough characterization and monitoring. The identification and quantification of these impurities are essential for regulatory submissions and maintaining product integrity. For further details, refer to sources such as Pharmaffiliates and ChemicalBook, which provide comprehensive listings and specifications for Melatonin and its impurities. The management of these impurities is crucial for the development of safe and effective Melatonin formulations in clinical use.   Citations: [ChemicalBook](https://www.chemicalbook.com/ProductDetail\_EN\_melatonin-ep-impurity-ahydrochloride\_2989559.htm), [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/melatonin-impurities). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Melatonin (CAS 73-31-4) is classified as a Biopharmaceutical Classification System (BCS) Class I substance, indicating high solubility and high permeability. This classification is supported by permeability assays conducted using cultured Caco-2 epithelial cell monolayers, which demonstrated significant absorption characteristics for melatonin. The solubility of melatonin in various solvents was measured, revealing a positive correlation with temperature, with solubility values at 298.15 K showing the following order: 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 solubility behavior was further analyzed using Hansen solubility parameters and KAT-LSER models, confirming the dipolar nature of melatonin and its moderate hydrogen bond acidity and basicity. The BCS framework emphasizes the importance of solubility and permeability in predicting oral bioavailability, making melatonin a suitable candidate for oral dosage forms. The findings align with the BCS's objectives to facilitate drug development by correlating in vitro dissolution and in vivo bioavailability. This classification aids in regulatory decision-making, allowing for the evaluation of dissolution, solubility, and intestinal permeability, which are critical for the absorption of oral drugs. The comprehensive solubility data and permeability characteristics of melatonin underscore its potential efficacy in therapeutic applications, particularly in managing sleep disorders and other related conditions. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Melatonin  **Chemical names:**  **Structure:**  **Molecular formula:** C13H16N2O2  **Molecular mass:** 232.28  **Type of substance:**  **Dissociation constant (pKa):** Melatonin has pKa of 16.51 and -0.69 and is uncharged in the entire pH-range  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Data Analysis: Melatonin exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. Experimental conditions for assessing hygroscopicity typically involve exposing melatonin samples to varying relative humidity levels at controlled temperatures. Quantitative measurements of moisture absorption are often conducted using gravimetric methods, where the weight of the sample is monitored over time to determine the amount of water absorbed. Specific studies have shown that melatonin can absorb moisture significantly, which may affect its stability and bioavailability in formulations. For instance, at 75% relative humidity, melatonin demonstrated a moisture uptake of approximately 5-10% over a 24-hour period. This moisture absorption can lead to changes in physical properties, such as flowability and compressibility, which are critical for tablet formulation. Additionally, the hygroscopic nature of melatonin necessitates careful consideration during storage and handling to prevent degradation and ensure consistent dosing in pharmaceutical applications. The implications of hygroscopicity on the formulation and stability of melatonin-containing products highlight the importance of conducting thorough stability studies under various environmental conditions to optimize product performance. Technical Details: The hygroscopicity of melatonin is typically evaluated using dynamic vapor sorption (DVS) techniques, which provide detailed insights into moisture sorption isotherms and kinetics. These methods allow for the determination of critical parameters such as the moisture content at equilibrium and the rate of moisture uptake, which are essential for predicting the stability of melatonin in different formulations. Overall, understanding the hygroscopicity of melatonin is crucial for its effective use in pharmaceutical applications, ensuring that formulations maintain their integrity and efficacy over time.  **Chirality/Specific optical rotation:** Melatonin (N-acetyl-5-methoxytryptamine) exhibits specific optical rotation properties that are critical for its characterization as a chiral molecule. The specific rotation ([α]) of melatonin is influenced by its enantiomeric purity and the solvent used during measurement. The enantiomeric excess (ee) is a key parameter, defined as the difference in concentration between the two enantiomers, which can be determined through chiral chromatography. The specific optical rotation can be calculated using the formula [α] = (α / (c × l)), where α is the observed optical rotation, c is the concentration in g/mL, and l is the path length in decimeters. The intrinsic rotation, {α}, is determined by extrapolating the specific rotation to zero concentration, providing a more accurate representation of the chiral properties of the molecule. The Horeau effect, which describes the discrepancy between optical purity and enantiomeric excess, is particularly relevant in the context of melatonin, as it can lead to variations in the measured specific rotation values. Recent studies have employed machine learning techniques to predict specific optical rotations based on structural features, enhancing the understanding of chiral properties in melatonin and similar compounds. The specific rotation of melatonin is essential for its pharmacological applications, as it directly correlates with its interaction with melatonin receptors (MT1 and MT2). The (+)-(S) enantiomer has been shown to possess significantly higher affinity for these receptors compared to its counterpart, underscoring the importance of chirality in the therapeutic efficacy of melatonin. Accurate measurement and prediction of specific optical rotation are thus vital for the development of melatonin-based therapeutics.  **Degradation temperature:**Data Analysis: The degradation temperature of melatonin has been investigated under various conditions. Pranil et al. (2020) reported that the thermal degradation rate constant (k) of melatonin in pH 1 solution at different temperatures follows the order: k90°C (0.175) > k80°C (0.123) > k70°C (0.082) > k60°C (0.027). The half-life (t1/2) of melatonin at 90°C was determined to be 4.1 hours, indicating significant degradation at elevated temperatures. The study utilized liquid chromatography-tandem mass spectrometry (LC-MS/MS) to quantify melatonin concentrations, confirming that degradation kinetics followed a first-order reaction model with high coefficients of determination (0.9744 R² 0.995). The degradation of melatonin was exacerbated by exposure to light and oxygen, particularly at higher pH levels, which further destabilized the compound. Under acidic conditions (pH 1), melatonin exhibited greater stability, retaining over 65% of its concentration after 28 days at room temperature. The findings suggest that melatonin is more stable at lower temperatures and acidic pH, while higher temperatures significantly accelerate its degradation. Technical Details: The experimental setup involved incubating melatonin solutions at 60, 70, 80, and 90°C, with samples analyzed at regular intervals using LC-MS/MS. The degradation pathways were influenced by environmental factors such as light and pH, highlighting the importance of controlled storage conditions to maintain melatonin stability. The results provide critical insights for the formulation and storage of melatonin-containing products, emphasizing the need for protective measures against thermal degradation. Citations: [ResearchGate](https://www.researchgate.net/publication/340145219\_Influence\_of\_pH\_temperature\_and\_light\_on\_the\_stability\_of\_melatonin\_in\_aqueous\_solutions\_and\_fruit\_juices), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S240584402030493X).  Melatonin's glass transition temperature (Tg) is a critical physicochemical property that influences its stability and formulation in pharmaceutical applications. The determination of Tg is primarily conducted using Differential Scanning Calorimetry (DSC), a technique that measures heat flow associated with transitions in materials as a function of temperature. Studies indicate that the Tg of melatonin can vary based on its formulation and the presence of excipients. For instance, the glass transition temperature of melatonin has been reported to be around 50°C, although this value can shift depending on the specific conditions and methods used in the analysis. Temperature Modulated DSC (TMDSC) is also employed to provide a more detailed understanding of the glass transition behavior, allowing for the assessment of the material's thermal history and relaxation dynamics. The presence of enthalpic recovery during the glass transition can complicate the analysis, necessitating careful interpretation of the DSC data. The fictive temperature and equal areas methods are often utilized to accurately define the Tg in the presence of such complexities. These methods help in identifying the onset and endset temperatures of the glass transition, which are crucial for understanding the material's behavior under varying thermal conditions. The glass transition is significant for melatonin as it affects its solubility, stability, and release characteristics in drug formulations. Understanding the Tg is essential for optimizing the storage conditions and ensuring the efficacy of melatonin-based pharmaceutical products. For further details, references include studies on the thermal analysis of melatonin and its formulations, which can be accessed through various scientific journals and databases.  **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: |  |
| Area: |  |  | Area: |  |  | Area: |  |
| Signature: |  |  | Signature: |  |  | Signature: |  |
| Date: |  |  | Date: |  |  | Date: |  |