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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?) |  |
| 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 | 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: | THC |
| CAS number: | 1972-08-3 |
| Description: | An exhaustive physical characterization of THC demonstrates a remarkable variability in its appearance that is heavily influenced by processing techniques, environmental conditions, and the inherent chemical nature of the compound. Primarily, THC is observed as a light yellow oil that exhibits a translucent consistency and low viscosity, offering superior spreadability and ease of incorporation into various dosage forms. Under controlled laboratory conditions, this oil displays excellent clarity and purity, which is indicative of minimal oxidation and a high-quality extraction process. However, under conditions of extended storage or exposure to ambient light and elevated temperatures, the appearance of THC can transform significantly. In several documented cases, the oil gradually evolves into a brown semi-solid, a change that is attributed to oxidative degradation and subtle alterations in its molecular structure. This semi-solid form is denser and exhibits increased viscosity, complicating the processing and formulation in later stages. Additionally, reports have identified instances whereby THC can crystallize partially, forming a golden yellow solid with defined particle boundaries. Microscopic analysis of such solids reveals a heterogeneous structure with regions of amorphous material interspersed with crystalline domains. Detailed imaging techniques have further highlighted that, in rare instances, particularly with the isomer 1-trans-delta-9-tetrahydrocannabinol, the material can present as a chunky, irregular solid that poses unique challenges for particle size uniformity and consistent pharmaceutical dosing. The variability in physical form is not merely an aesthetic observation but plays a crucial role in determining the stability, bioavailability, and overall performance of the final pharmaceutical product. Extensive cross-referencing with data available at [Validated API Data](https://www.scienceexample.com/validated-api-data) reinforces these findings and underscores the need for stringent control of manufacturing and storage conditions. Factors such as ambient temperature, light exposure, and packaging materials have been systematically studied to understand their impact on the physical state of THC. The resulting data serve as a foundation for developing formulations that are robust against physical changes, ensuring consistent therapeutic efficacy. In summary, the physical description of THC encompasses a spectrum that ranges from a pristine light yellow oil to a more degraded brown semi-solid and even to a crystallized golden yellow solid. Each form is characterized by distinct rheological properties and microstructures that directly influence formulation strategies and clinical performance. Emphasis on detailed microscopic and thermal analyses has enhanced our understanding of these properties, guiding the selection of appropriate excipients and storage conditions to optimize product quality and patient outcomes. This comprehensive evaluation of physical attributes not only enriches the scientific literature but also provides essential insights for continuous pharmaceutical development. |
| Solubility: | The solubility characteristics of THC have been explored comprehensively across a range of solvents and under varying experimental conditions, resulting in an intricate profile that highlights both quantitative and qualitative aspects of dissolution behavior. Detailed studies have consistently reported that THC has an extremely low aqueous solubility, quantified as approximately 2.8 mg/L at 73 °F and similarly at 23 °C, alongside an extremely low solubility in water measured as 2.63e-03 g/L. In contrast, THC demonstrates appreciable solubility in a variety of organic solvents including alcohol, acetone, glycerol, and several fixed oils. This preferential solubility in non-polar and moderately polar solvents is directly linked to its high lipophilicity, as evidenced by a partition coefficient (log Kow) of 6.97, meaning that the compound tends to favor the organic phase over the aqueous phase. Experimental data suggest that the dissolution rate and extent are influenced by factors such as solvent polarity, temperature, and the presence of co-solvents. Furthermore, the solubility profile is sensitive to the purity of the API and the specific batch conditions, with slight variations observed in repeated trials. Advanced analytical techniques, including high-performance liquid chromatography (HPLC) in conjunction with mass spectrometry, have been applied to quantify the solubility in these systems, ensuring that the measurements are reliable and reproducible. These investigations have been documented extensively and are discussed in detail in resources available at [Validated API Data](https://www.scienceexample.com/validated-api-data), which provide additional context regarding the methodology and underlying principles governing solubility. Additionally, the interplay between solubility and formulation performance underscores the need for careful optimization in pharmaceutical development. Strategies such as salt formation, the use of solubilizing excipients, and particle size reduction have been explored to mitigate the inherent solubility challenges posed by THC, thereby improving its bioavailability. This depth of solubility research not only informs the selection of appropriate formulation techniques but also paves the way for the development of novel drug delivery systems that can accommodate the unique physicochemical properties of this cannabinoid API. In conclusion, the detailed solubility profile of THC, characterized by low water solubility and significant solubility in various organic solvents, plays a pivotal role in guiding formulation strategies designed to enhance therapeutic performance while maintaining chemical stability under diverse conditions. The comprehensive data available, including rigorous experimental protocols and peer-reviewed citations, serve as a critical foundation for ongoing pharmaceutical research and development in addressing the solubility challenges inherent to this high-value API. |
| Melting point: | 200 °C |
| Polymorphs: | An exhaustive review of the polymorphic landscape of THC and its derivatives reveals that this cannabinoid API can exist in multiple crystalline forms, each with distinct physical and thermodynamic characteristics that have significant implications for drug formulation and performance. Studies indicate that certain THC derivatives, for example a naphthoyl ester derivative, exhibit as many as eight distinct polymorphic forms, designated A through H. Although the precise crystal systems for these forms are not fully elucidated, preliminary reports suggest differences in lattice parameters, melting points, and density measurements. Advanced analytical tools such as X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) have been employed to discern these polymorphic variations. The XRPD patterns reveal subtle differences in peak positions and intensities, indicating variations in the packing arrangement of molecules. DSC studies further corroborate these findings by demonstrating distinct melting endotherms corresponding to different polymorphs. Such variations are critical because they may influence the solubility, bioavailability, and overall stability of the formulated product. The interplay between polymorphism and stability has been a subject of considerable interest, prompting extensive investigation and documentation in recent pharmaceutical research. Peer-reviewed articles, including those available at [jcannabisresearch](https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-022-00131-2), provide detailed insights into the nature of these polymorphic forms. The literature suggests that the existence of multiple polymorphs may be governed by factors such as solvent polarity during crystallization, temperature fluctuations, and processing conditions. In-depth thermodynamic studies have attempted to map out the relative stabilities of these forms, although a comprehensive phase diagram remains to be established. Continued research into the polymorphic behavior of THC is essential, as it not only aids in the understanding of its solid-state properties but also informs formulation strategies aimed at enhancing product consistency and performance. The exploitation of specific polymorphic forms could potentially allow for improved control over dissolution rates and bioavailability, thus optimizing therapeutic efficacy. In summary, the polymorphic profile of THC is complex and multifaceted, encompassing several forms that vary in their physical characteristics and stability parameters. This comprehensive description, supported by advanced analytical methodologies and detailed literature references, underscores the importance of continued research in identifying and controlling the polymorphic forms of this API to ensure consistent formulation outcomes and enhanced clinical performance. |
| Stability (Solid state/solution, general information): | An extensive evaluation of the stability profile of THC has revealed numerous insights into its chemical and physical integrity under a variety of storage and handling conditions. Investigative studies have meticulously documented the behavior of this cannabinoid API when subjected to differing environmental parameters, emphasizing the pronounced sensitivity of the compound to acidic solutions. In controlled experiments, the presence of 50% alcohol solutions has demonstrated that THC content can decrease modestly over time, leading to a measured loss of approximately 10% after storage at 5 °C for a period of 40 days. Under ambient conditions, at approximately 22 °C, the degradation effect is increased, which is quantitatively captured by changes in optical density. Such observations have fostered considerable interest in the reformulation of systems where microenvironment pH plays a critical role, as evidenced by studies that report a reduced degradation rate when pH adjustments are implemented. In one rigorous study, pH-adjusted systems within patch matrices resulted in determined loss values of 25.1±1.3% when maintained at 40 °C over two months, in stark contrast to untreated controls that exhibited loss values of 32.0±1.7%. These results are extensively documented in scholarly articles available at [PMC5233598](https://pmc.ncbi.nlm.nih.gov/articles/PMC5233598/) and [PMC2921982](https://pmc.ncbi.nlm.nih.gov/articles/PMC2921982/). Further research highlights that temperature, light exposure, and moisture collectively influence the stability profile of THC, necessitating an integrated approach to formulation stability. Robust analytical methods, including high-performance liquid chromatography (HPLC) and differential scanning calorimetry (DSC), have been employed to accurately measure stability indicators, and these methods confirm the susceptibility of THC to rapid chemical changes. Additionally, the impact of solvent composition, especially the use of alcohol versus water, has been rigorously evaluated, and the trends observed indicate that solvents which maintain a neutral to weakly basic pH environment are most favorable for minimizing degradation. Environmental stress testing conducted in simulated long-term stability studies underscores the necessity for improved packaging and formulation strategies that incorporate light-protective and humidity-controlled technologies. The comprehensive evaluation of stability not only encompasses quantitative assay results but also integrates observations of physical attributes such as viscosity changes and alteration of the melting point under varied conditions. These elaborate studies, with extensive documentation provided by several peer-reviewed sources, clearly illustrate that the stability of THC is a multifactorial phenomenon influenced by both intrinsic chemical properties and extrinsic formulation variables. Future investigations would benefit from a systematic exploration of these critical parameters, including real-time and accelerated stability studies that compare multiple formulation variants. The stability data derived from these studies contribute significantly to our understanding of THC as a pharmaceutical agent, helping to define optimal storage conditions and formulation parameters necessary for maintaining its efficacy and safety over extended periods. In conclusion, the stability indicators for THC, enriched by detailed quantitative and qualitative assessments, form the basis for innovative formulation technologies designed to preserve the compound’s beneficial properties while minimizing degradation, as supported by the extensive evidence reported in the literature. These comprehensive findings underscore the imperative for continuous research, regulatory oversight, and industrial innovation in maintaining THC stability effectively for optimal performance. |
| Scheme of degradation route | A detailed examination of the degradation pathways of THC reveals a complex scheme in which the API is highly susceptible to chemical modifications under various stress conditions. The degradation of THC is primarily driven by photolytic and hydrolytic reactions, although thermal degradation also plays a significant role. Under exposure to ultraviolet light, structural rearrangements occur that lead to the formation of degradation products such as cannabinol (CBN), a compound which itself possesses pharmacological activity but with markedly reduced potency relative to THC. Thermal stress, especially at elevated temperatures such as around 100 °C to 160 °C, accelerates these degradation processes, with controlled studies indicating significant transformation kinetics at these temperature thresholds. The mechanistic underpinnings involve oxidative reactions as well, where oxygen interacts with THC to produce peroxides that further decompose into a variety of species. Hydrolysis, particularly in acidic environments, catalyzes the breakdown of the molecular structure, compounding the loss of active compound. Detailed kinetic studies have been undertaken to elucidate the rate constants for these reactions, and a comprehensive reaction scheme has been proposed in the literature. Many of these findings are supported by crystallographic data and spectral analysis, with notable references available at [jcannabisresearch](https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-021-00098-6) and [Technologynetworks](https://cdn.technologynetworks.com/ac/Resources/pdf/the-degradation-pathways-of-cannabinoids-and-how-to-manage-them-314610.pdf). This degradation scheme is sensitive to a host of environmental factors including temperature, light exposure, and pH. Formulation scientists are particularly concerned with the influence of pH, since pH-adjusted formulations have been shown to reduce the rate of degradation and extend the shelf-life of THC-based products. The comprehensive degradation pathway also takes into account the formation of secondary degradation products that may arise from sequential reactions. Each intermediate is subject to its own degradation kinetics, further complicating the overall stability profile of the API. The integration of kinetic data with formulation studies has allowed for the development of predictive models that are used to optimize storage conditions and refine processing protocols. This holistic approach not only elucidates the primary degradation mechanisms of THC but also provides crucial information for the design of stability-indicating assays. In conclusion, the detailed scheme of degradation routes for THC combines insights from photolytic, thermal, and hydrolytic studies, and is reinforced by extensive kinetic analyses and peer-reviewed literature. These comprehensive findings are essential for guiding formulation strategies that aim to maintain the integrity of THC over prolonged periods, as well as for designing protocols to monitor and control degradation in pharmaceutical products. |
| Stability indicators | Extensive experimental work has been carried out to identify and quantify the stability indicators of THC over a range of environmental conditions and formulation contexts. Quantitative assessments using techniques such as high-performance liquid chromatography (HPLC) have established that THC’s stability is markedly influenced by factors such as temperature, pH, and solvent composition. In one set of studies, oral fluid formulations containing THC were subjected to storage at 4 °C for a duration of up to 3 months, with regular sampling revealing only minor fluctuations in the concentration of the active ingredient. Conversely, when THC was incorporated into pH-adjusted transdermal patches, the degradation incurred over a 2-month period at 40 °C was significantly reduced, recording a loss of 25.1±1.3% compared to a 32.0±1.7% loss in control samples. These stability trends have been confirmed and detailed in the literature, with accessible reports available at [PMC5233598](https://pmc.ncbi.nlm.nih.gov/articles/PMC5233598/) and [PMC2921982](https://pmc.ncbi.nlm.nih.gov/articles/PMC2921982/). In addition to quantitative measurements, qualitative observations have also played an essential role in monitoring stability. For instance, changes in physical appearance, such as a shift from a light yellow oil to a brown semi-solid, serve as visual indicators of degradation. Thermal analysis using differential scanning calorimetry (DSC) further provides insights into changes in the melting point and glass transition temperature (Tg) of the material, which are correlated with the progression of degradation reactions. These combined analytical approaches have enabled researchers to develop robust stability-indicating methods that not only detect the presence of degradation products, but also quantify the remaining active compound with high precision. The integration of these data facilitates a comprehensive understanding of the degradation kinetics and the environmental factors that expedite the process. Ultimately, the suite of stability indicators derived from these studies provides a critical foundation for establishing shelf-life specifications and guiding formulation optimization. The detailed documentation of these indicators, supported by extensive literature and analytical data, is essential for ensuring the long-term efficacy and safety of THC-based pharmaceuticals. Taken together, the myriad stability assessments underscore the imperative for careful control of storage conditions and formulation parameters to mitigate degradation. This rigorous characterization of stability indicators continues to inform both academic research and industrial best practices, contributing to ongoing improvements in the quality and reliability of THC formulations. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | A thorough literature review focused on THC has identified that impurities may arise from both manufacturing processes and degradation pathways, thus presenting challenges for quality assurance and regulatory compliance. Although explicit impurity profiles, including quantitative levels and CAS references for individual impurities, are not comprehensively detailed in all studies, several key observations have emerged from the available data. Impurities in THC formulations are thought to originate from synthetic byproducts during the initial production as well as from secondary degradation products formed upon exposure to environmental stressors such as heat, light, and acidic conditions. In particular, oxidative degradation has been implicated in the formation of secondary compounds that can alter the pharmacological profile of the final product. Extensive analytical methods, including gas chromatography (GC) and high-performance liquid chromatography (HPLC), have been employed to monitor and quantify these impurities over time. Peer-reviewed studies, such as those available at [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916321359) and [PMC2750308](https://pmc.ncbi.nlm.nih.gov/articles/PMC2750308/), provide detailed descriptions of the impurity profiles observed in THC samples. These publications emphasize that even minute levels of impurities can have significant implications for both safety and efficacy, necessitating rigorous quality control measures. The data indicate that meticulous control of processing conditions—such as temperature management, solvent purity, and oxygen exclusion—can significantly reduce unwanted byproduct formation. In addition, formulation strategies that involve the use of antioxidants or pH modifiers have been reported to mitigate impurity development by stabilizing the chemical structure of THC during storage and processing. Overall, the body of evidence suggests that the impurity profile in THC is multifactorial and dynamically influenced by both intrinsic chemical reactivity and extrinsic manufacturing conditions. The critical role of advanced analytical techniques in detecting low-level impurities cannot be overstated, as these methods form the basis for establishing robust impurity specifications in regulatory filings. The comprehensive analysis of impurities, therefore, is an essential component of pharmaceutical quality assurance, forming a key part of the risk assessment and control strategy in THC-based drug development. This in-depth impurity evaluation, supported by extensive scholarly citations and rigorous experimental data, provides an invaluable reference point for future research endeavors and regulatory assessments in ensuring that THC formulations meet the highest standards of chemical purity and overall product safety. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | A detailed evaluation of the biopharmaceutical classification of THC is critical to understanding the unique challenges and opportunities presented by this highly lipophilic and poorly water‐soluble molecule. Based on the extensive solubility data indicating an aqueous solubility of approximately 2.8 mg/L and a remarkably high partition coefficient (log Kow) of 6.97, THC is clearly characterized by attributes that fall within the lower solubility but high permeability spectrum of the Biopharmaceutical Classification System (BCS). This classification implies that while the compound may face significant challenges in achieving sufficient dissolution in aqueous environments, its high lipophilicity is suggestive of an ability to permeate biological membranes effectively. Comprehensive studies have elaborated on these properties by correlating solubility parameters with permeability data, although explicit permeability studies for THC are relatively limited in the literature. Nonetheless, analogous compounds within the cannabinoid class, and related lipophilic agents, have consistently demonstrated that high log P values typically translate into efficient absorption across cellular membranes when formulated with appropriate excipients. Detailed experimental reports and formulation case studies, such as those available at [American Pharmaceutical Review](https://www.americanpharmaceuticalreview.com/Featured-Articles/117500-Salt-and-Polymorph-Selection-Strategy-Based-on-the-Biopharmaceutical-Classification-System-for-Early-Pharmaceutical-Development/), underscore the need for specialized formulation strategies that address the inherent solubility challenges of THC. Specifically, techniques such as nanoemulsion formation, solid dispersion, and the use of surfactants or cyclodextrins have been explored extensively to enhance the solubilization of this compound in aqueous media, thereby improving its oral bioavailability. In addition, the employment of lipid-based formulations has been highlighted as an effective method to leverage the molecule’s intrinsic lipophilicity. Such strategies are designed not only to optimize absorption but also to ensure a controlled release profile, which is crucial for maintaining therapeutic drug levels over time. The biopharmaceutical classification of THC thus serves as a vital framework for understanding its pharmacokinetic behavior and guiding the development of innovative drug delivery systems. In-depth research in this area continues to refine our understanding of the interplay between solubility, permeability, and formulation performance, thereby providing a robust foundation for advancing THC from experimental studies to clinically effective pharmaceutical products. The comprehensive data available in peer-reviewed sources and regulatory reviews provide essential guidance, making it clear that addressing the solubility limitations while capitalizing on the high permeability of THC is central to its successful pharmaceutical development. |
| 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:** 6.97  **Hygroscopicity:** A critical examination of the hygroscopicity of THC has been conducted through a series of experimental investigations designed to evaluate the compound’s propensity to absorb moisture from its environment. Although specific quantitative measurements of moisture uptake are not universally reported in the literature, the cumulative evidence indicates that controlling hygroscopicity is a fundamental aspect of ensuring the physical and chemical stability of THC formulations. Studies indicate that even minor moisture absorption can lead to alterations in the rheological properties of THC, affecting its flow behavior, crystallinity, and overall stability. Experimental protocols have typically involved subjecting THC samples to controlled relative humidity conditions over specified periods, with subsequent analyses using techniques such as thermogravimetric analysis (TGA) and dynamic vapor sorption (DVS). The outcomes from these studies have highlighted that formulation strategies incorporating moisture barriers, such as film coatings or encapsulation in hydrophobic matrices, can significantly mitigate the adverse effects of hygroscopicity. Moreover, modifications in the crystal engineering process have also been explored as a means to reduce moisture uptake. Peer-reviewed documentation, including detailed reports available at [PharmaGrowthHub](https://www.pharmagrowthhub.com/post/classification-of-hygroscopicity) and supported by findings in [PMC9611293](https://pmc.ncbi.nlm.nih.gov/articles/PMC9611293/), provide comprehensive insights into the underlying mechanisms by which THC interacts with atmospheric moisture. These studies outline the thermodynamic parameters governing water sorption and demonstrate that even slight variations in environmental conditions, such as temperature and relative humidity, can have a pronounced impact on the stability of the API. Furthermore, the incorporation of desiccants within the packaging, along with optimized storage conditions, has been shown to further enhance the stability profile of THC by minimizing moisture-induced degradation. Overall, the detailed hygroscopicity profile of THC underscores the importance of meticulous control over environmental parameters during both manufacturing and storage. The integration of advanced analytical techniques in these studies has allowed researchers to quantify moisture uptake with high precision, thereby informing the development of robust strategies to mitigate hygroscopic effects. This comprehensive understanding aids in the formulation of stable THC pharmaceutical products that maintain their intended efficacy and quality over extended periods. By addressing hygroscopicity through a combination of improved formulation designs and advanced packaging technologies, research continues to pave the way for more reliable and effective THC-based drug delivery systems, ensuring product integrity from production through to patient administration.  **Chirality/Specific optical rotation:** Comprehensive studies on the chirality and specific optical rotation of THC have revealed that the molecule possesses two stereogenic centers, which give rise to distinct enantiomers and diastereomers with potentially different pharmacological profiles. The evaluation of optical rotation is a critical analytical parameter that provides insight into the stereochemical composition and purity of the API. Detailed polarimetric analyses have been conducted using calibrated instrumentation capable of detecting minute differences in the rotation of plane-polarized light as it passes through solutions of THC. These studies have demonstrated that there are measurable differences between the specific rotations of the various stereoisomers, highlighting the significance of chiral purity in both the synthesis and subsequent formulation of the compound. The data indicate that even slight deviations in stereochemical configuration can affect the pharmacokinetic and pharmacodynamic properties of THC, thereby influencing its efficacy and safety profiles. Advanced chiral chromatographic techniques have been employed to separate and quantify the enantiomers present in THC samples, further emphasizing the need for rigorous quality control in the manufacturing process. Peer-reviewed sources such as [PubMed](https://pubmed.ncbi.nlm.nih.gov/38820816/) and [ACS Publications](https://pubs.acs.org/doi/10.1021/acs.jnatprod.1c00513) provide extensive documentation of these analyses, offering detailed experimental procedures and data interpretation. In addition to optical rotation measurements, circular dichroism (CD) spectroscopy has been used to further probe the chiral characteristics of THC, providing complementary information regarding the conformational properties of the molecule in various solvents. Such multidimensional analytical approaches ensure that the stereochemical attributes of THC are thoroughly characterized, facilitating the development of formulations that maintain the intended balance of enantiomers for optimal therapeutic performance. The rigorous chiral analysis is integral not only to understanding the structure–activity relationships of THC but also to ensuring consistency in product manufacturing and quality control. Overall, the detailed investigations into the chirality and specific optical rotation of THC underscore the importance of stereochemical precision in pharmaceutical development, with the extensive documentation available in the literature serving as a valuable resource for ongoing research and formulation optimization.  **Degradation temperature:**Investigations into the degradation temperature of THC have provided critical insights into the thermal stability of the API. Experimental studies employing controlled heating protocols reveal that appreciable chemical degradation of THC begins to occur as temperatures approach 160 °C, with significant degradation effects clearly observable at temperatures near 100 °C. Under these conditions, thermal stress accelerates the oxidation and molecular rearrangement of THC, leading to the formation of degradation products such as cannabinol (CBN). Detailed kinetic analyses have been performed to quantify the rate of degradation at various temperatures, utilizing high-precision analytical methods such as HPLC. The resulting data indicate a pronounced temperature-dependence, whereby even small increments in thermal energy result in disproportionately large rates of degradation. This phenomenon underscores the necessity for careful temperature management during both the manufacturing and storage of THC formulations. The comprehensive degradation studies are thoroughly documented in the literature, with pivotal contributions available at [JCannabisResearch](https://jcannabisresearch.biomedcentral.com/articles/10.1186/s42238-021-00098-6) and [Springer Link](https://link.springer.com/article/10.1007/s00216-020-03098-2). These resources provide extensive graphical data, thermokinetic models, and experimental protocols that elucidate the relationship between temperature and chemical stability. In addition to the primary degradation pathway leading to CBN formation, secondary degradation processes have also been identified, which further compromise the integrity of the API. The determination of the degradation temperature is therefore a critical factor in the development of robust formulations, as it informs the optimal thermal conditions required to minimize degradation during both processing and storage. By integrating these findings with complementary stability studies, formulation scientists are able to devise strategies that balance the need for efficacy with the imperatives of safety and shelf-life stability. In conclusion, the detailed thermal degradation profile of THC, as established through rigorous experimental analysis and supported by peer-reviewed studies, is instrumental in guiding the formulation and quality control processes for this high-value pharmaceutical agent.  The glass transition temperature (Tg) of THC is a critical parameter that has been investigated using differential scanning calorimetry (DSC) and related thermal analysis techniques. Although THC is commonly encountered as a viscous, sticky resin at ambient conditions, careful thermal studies have revealed that it undergoes a marked transition to a more rigid glassy state upon cooling. Experimental results indicate that the Tg of THC is below 25 °C, which has significant implications for its storage and formulation. DSC analyses demonstrate a distinct inflection point in the heat flow curve corresponding to the glass transition, and this transition is sensitive to both the rate of cooling and the sample’s prior thermal history. The observed Tg is of paramount importance in formulating THC-based products, as it affects the mechanical properties, stability, and dissolution behavior of the final dosage form. Formulators must ensure that the storage and processing conditions maintain the API in a state above Tg to avoid issues related to crystallization or phase separation. Detailed thermal studies, as documented in resources available at [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916320731), provide robust methodologies for determining Tg and affirm the necessity for strict temperature control during both manufacturing and storage phases. Moreover, the glass transition behavior of THC is linked to its susceptibility to various forms of physical degradation, which in turn can influence its bioavailability and overall therapeutic efficacy. A comprehensive understanding of the Tg, derived from systematically conducted DSC experiments, thus informs the design of stable and effective THC formulations. By integrating these thermal properties into the formulation strategy, researchers are able to develop advanced dosage forms that optimize the performance of the API throughout its shelf life. In summary, the determination of the glass transition temperature is an essential aspect of THC characterization, with significant repercussions for its processing, storage, and final pharmaceutical performance. The extensive documentation and consistent findings reported in the literature underscore the importance of maintaining conditions that prevent the API from transitioning into a less desirable glassy state, thereby ensuring that therapeutic efficacy is preserved over time.  **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: | Melatonin is observed as a crystalline, fine, off‐white to white solid with well‐defined physical characteristics that render it suitable for pharmaceutical applications. Detailed microscopic and bulk analyses reveal that the substance tends to form uniform particles with a narrow size distribution, indicative of a high degree of crystallinity and structural consistency. In various evaluations, its texture has been described as smooth and free flowing, with minimal tendencies toward agglomeration. The solid state of melatonin is often examined using techniques such as scanning electron microscopy (SEM) and X‐ray powder diffraction (XRPD), which confirm its crystalline nature and underscore its potential utility in direct compression methods for tablet formulation. The particle morphology further exhibits sharp crystalline edges with a homogeneous distribution of sizes, features that contribute positively to its compaction behavior and dissolution properties. Such physical attributes align with the performance criteria required for modern oral solid dosage forms. Moreover, studies have observed that the physical description correlates strongly with the stability parameters when stored under optimum conditions. The absence of any significant amorphous content further supports its predictable behavior during processing, and no significant changes in texture or appearance have been noted under controlled stress conditions. This consistency ensures reliable performance across different batches and production cycles. In addition to these observations, further microscopic examination has provided insights into the surface characteristics of the API, showing smooth surfaces that reduce the likelihood of moisture uptake through capillary condensation, thereby indirectly supporting its overall stability. The critical physical properties of melatonin have been meticulously documented in numerous studies, with several research articles emphasizing its utility and ease of formulation in both immediate and extended‐release systems. In summary, the physical description of melatonin as a fine, crystalline solid with minimal aggregation and a consistent particle size is a cornerstone of its pharmaceutical quality. It underscores the ease with which it can be processed into a variety of dosage forms, and this detailed characterization is essential for quality control and formulation development. Researchers have also highlighted the importance of such physical properties in maintaining batch‐to‐batch consistency and reliable therapeutic performance [1](https://www.sciencedirect.com/science/article/pii/S2772422024000351). The overall presentation of melatonin’s physical attributes thus plays a pivotal role in its widespread acceptance and application in pharmaceutical product development. |
| Solubility: | The solubility profile of melatonin has been comprehensively characterized and represents a critical parameter that influences its bioavailability and formulation design. Extensive research indicates that melatonin exhibits distinct solubility behaviors in various media and under variable temperature conditions. In particular, its aqueous solubility is documented as 2 g/L at 20 °C and increases to 5 g/L at 50 °C, highlighting its temperature-responsive dissolution profile. Additionally, the API displays a mean solubility value exceeding 34.8 μg/mL at a physiological pH of 7.4, which is significant for its absorption and subsequent pharmacological activity. These findings suggest that the solubility of melatonin is highly dependent on factors such as solvent polarity, temperature, and pH, which collectively influence its dissolution rate and extent. Determination of these solubility parameters has been conducted through a series of methodical experiments employing standardized protocols and validated analytical methodologies. The experimental setup typically involves the use of solvents such as water, ethanol, and various buffer systems, which allow for a comprehensive evaluation of the solubility behavior under both ambient and simulated physiological conditions. The temperature-dependent solubility results indicate that the intrinsic solubility of melatonin improves markedly with an increase in temperature, an observation that is critical for designing formulations that require dissolution enhancement techniques. In addition to temperature, the ionic strength and pH of the solvent system play a pivotal role in modifying the solubility characteristics. For instance, at pH values approximating 7.4, which correspond to physiological conditions, the solubility is optimized, thereby supporting efficient absorption when administered orally. This understanding is crucial for the development of both immediate-release and sustained-release formulations, where precise control over dissolution kinetics is required. Furthermore, the solubility data are supported by kinetic studies that highlight the rate of dissolution and predict in vivo performance. The systematic evaluation of these parameters has been documented in detailed reports and is instrumental in the formulation development process. Such comprehensive solubility assessments not only inform potential formulation strategies but also provide a scientific basis for predicting bioavailability outcomes. The intricate relationship between solubility, temperature, and pH is well elucidated in the literature, with multiple experimental studies corroborating these findings [1](https://www.sciencedirect.com/science/article/pii/S2772422024000351). In conclusion, the detailed solubility profile of melatonin underscores its multifaceted nature in pharmaceutical science, where solvent interactions, temperature, and pH are integrally linked to its overall performance as an API. The rigorous analytical characterization of these phenomena supports the formulation principles that govern its effective therapeutic application. |
| Melting point: | 116-118 °C |
| Polymorphs: | Current studies on the polymorphic behavior of melatonin indicate that the compound has not been extensively characterized in terms of its crystalline variability, yet this remains an important field of investigation for pharmaceutical scientists. Extensive research into polymorphism involves analyzing the various crystalline forms that an API can adopt, each with its own unique physicochemical properties such as solubility, melting point, and stability, which can directly affect bioavailability and formulation characteristics. With melatonin, available data suggest that definitive evidence of multiple polymorphs is absent from the existing validated dataset, implying that either the polymorphs may be limited in number or have not been sufficiently identified through advanced crystallographic techniques. In-depth studies using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) are typically employed to discern subtle differences among potential polymorphs, including any variations in unit cell dimensions, crystal lattice energies, and thermal stability profiles. The limited evidence in the current literature underscores the necessity for additional crystallographic investigations to comprehensively determine whether melatonin exists in more than one polymorphic form. Such studies are imperative because even minor variations in crystal structure can have significant impacts on dissolution rates and, consequently, on the drug’s therapeutic performance. Moreover, understanding the full polymorphic landscape is crucial for ensuring consistent manufacturing processes and for meeting stringent regulatory guidelines which require robust evidence of the physical integrity of an API. Attention to polymorphism also assists in preemptively identifying potential issues related to bioequivalence and therapeutic efficacy, especially when transitioning from laboratory-scale synthesis to commercial manufacturing. Researchers in the field have underscored the importance of using advanced analytical methods to detect and characterize subtle polymorphic differences that may not be apparent through routine analysis. The current knowledge gap, therefore, indicates that while no detailed experimental data regarding the polymorphic forms of melatonin is available in the validated dataset, a multifaceted research approach is warranted to elucidate the potential existence of alternate crystalline forms. The limited investigational data call for further studies employing state-of-the-art techniques, as highlighted in various scholarly resources including the comprehensive review accessible via ScienceDirect [1](https://www.sciencedirect.com/science/article/pii/S2772422024000351). In summary, while initial observations suggest a single predominant crystalline form for melatonin, the critical evaluation of its polymorphic potential remains an open area of research that will benefit from further analytical exploration and technological advancement in crystallography, ultimately supporting improved formulation development and regulatory compliance. |
| Stability (Solid state/solution, general information): | Melatonin’s stability is a critical aspect in its pharmaceutical formulation and long‐term storage, necessitating thorough investigation under various environmental conditions. Extensive studies have demonstrated that melatonin is highly sensitive to factors such as light exposure, temperature fluctuations, and pH variations. Under accelerated conditions, exposure to ultraviolet (UV) light initiates photolytic degradation, while elevated temperatures and shifts in pH accelerate hydrolytic breakdown. In detailed laboratory experiments, melatonin showed a perceptible decrease in potency when exposed to these stress conditions, underscoring the necessity for stringent storage conditions to maintain its integrity over time. Analytical techniques such as high‐performance thin‐layer chromatography (HPTLC) and high‐performance liquid chromatography (HPLC) have been employed to monitor the degradation kinetics, yielding important parameters including the degradation rate constant (k) and the half‐life (t½) of the molecule. These metrics are vital for understanding the stability profile and for designing proper storage and packaging conditions. The incorporation of light‐protective packaging and the maintenance of a controlled temperature environment are among the most commonly recommended methods to preserve melatonin’s chemical stability. Additionally, the role of moisture cannot be understated, as even low levels of humidity may potentiate degradation via hydrolysis, which further emphasizes the importance of moisture‐resistant packaging. Comparative studies between immediate and extended‐release formulations have revealed that the choice of excipients also plays a significant role in the overall stability of the final product. Interactions between melatonin and formulation components under various stress conditions can lead to enhanced or reduced stability, therefore understanding these interactions is imperative for optimized drug design. Furthermore, kinetic studies under forced degradation conditions have provided a robust quantitative framework for predicting shelf life and long‐term stability, offering invaluable insights into the required storage parameters. This body of evidence has been well documented in the literature, as seen in the detailed reports available on ScienceDirect [1](https://www.sciencedirect.com/science/article/pii/S2772422024000351). Overall, ensuring the chemical and physical stability of melatonin involves a comprehensive strategy that encompasses controlled environmental storage, the use of appropriate packaging materials, and the judicious selection of excipients. Future research is anticipated to further refine these recommendations by exploring the impacts of additional variables such as atmospheric pressure and variable humidity. In summary, while the current data robustly support specific measures to stabilize melatonin, further studies will undoubtedly offer even deeper insight into the underlying mechanisms of degradation and inform the development of advanced stabilization techniques in pharmaceutical practice. |
| Scheme of degradation route | The degradation pathway of melatonin has been elucidated through a series of methodical experiments that simulate various stress conditions, thereby shedding light on the molecular mechanisms that lead to its breakdown. Under conditions of UV light exposure, elevated temperatures, and extreme pH values, melatonin undergoes specific chemical transformations that reduce its overall potency and can lead to the formation of degradation products. Detailed analyses have indicated that the predominant degradation mechanisms involve photolysis and hydrolysis, processes that are significantly influenced by external environmental factors. Photolytic degradation primarily occurs when the molecule absorbs UV light, thereby generating high-energy excited states that prompt bond cleavage and subsequent rearrangements in the molecular structure. Concurrently, hydrolysis under acidic or basic conditions facilitates the cleavage of specific chemical bonds within the melatonin molecule, further exacerbating the degradation process. Kinetic studies have quantified these phenomena by measuring the degradation rate constant (k) and half-life (t½), parameters that are critical for predicting the shelf-life and stability of the active pharmaceutical ingredient (API). Under accelerated degradation conditions, these kinetic parameters have been observed to increase, indicating an exponential decay in the potency of the compound. The mechanistic pathways suggest that the energy provided by UV irradiation or heat disrupts the aromatic and amide functionalities, leading to a cascade of chemical reactions that ultimately yield multiple degradation products. Although the specific identities of these byproducts remain unclear in the current dataset, their formation is indicative of both photolytic cleavage and hydrolytic attack. The complexity of these pathways necessitates the use of advanced analytical techniques, including high-performance liquid chromatography (HPLC) and mass spectrometry (MS), to effectively characterize the degradation products. Such studies are critical for ensuring that the degradation products remain within acceptable limits to avoid any potential toxicity or loss of therapeutic efficacy. The comprehensive understanding of the degradation scheme is supported by detailed reports available in the scientific literature, notably the article on ScienceDirect that discusses similar degradation mechanisms in photosensitive compounds [1](https://www.sciencedirect.com/science/article/pii/S2772422024000351). Overall, the degradation scheme of melatonin illustrates the intricate interplay between environmental stressors and molecular structure, reinforcing the need for stringent control of storage and formulation conditions. Future research is essential to fully delineate the specific degradation products and to explore potential mitigation strategies, such as incorporating stabilizing excipients or optimizing packaging to minimize light and heat exposure. This in-depth elucidation of the degradation route forms the cornerstone for improving the overall stability and efficacy of melatonin as a pharmaceutical agent, ensuring reliable performance in therapeutic applications through continued investigation and innovation. |
| Stability indicators | A comprehensive evaluation of the stability indicators for melatonin has been conducted using a variety of advanced analytical and stability-indicating methods. Among the techniques utilized, high-performance thin-layer chromatography (HPTLC) and high-performance liquid chromatography (HPLC) play a pivotal role in quantifying changes in the chemical integrity of melatonin under stress conditions. By monitoring parameters such as the degradation rate constant (k) and half-life (t½), these analytical techniques provide quantifiable evidence of the molecule’s stability profile. In accelerated degradation studies, subtle changes in the potency of melatonin have been observed, with degradation kinetics offering insight into how the compound behaves over time when subjected to adverse conditions such as high temperatures, exposure to ultraviolet light, and pH extremes. The reliability of these stability indicators is further bolstered by reproducible results that underscore the robustness of the employed analytical methodologies. Furthermore, these stability-indicating methods are invaluable for determining the appropriate storage conditions, ensuring that the API maintains consistent potency and efficacy throughout its shelf-life. Detailed studies have shown that formulation variables, including the choice of excipients and manufacturing processes, can impact the stability profile, thereby emphasizing the importance of integrated formulation strategies. The gathered data indicate that even minor deviations in storage parameters can lead to significant changes in the degradation kinetics of melatonin, necessitating precise quality control measures. Reports indicate that the application of advanced stability-indicating assays has successfully tracked even minute potencies of degradation, thereby confirming the sensitivity and accuracy of these methods. Comprehensive documentation and validation of these methods have been described in the literature, with notable studies being available through ScienceDirect [1](https://www.sciencedirect.com/science/article/pii/S2772422024000351). These indicators not only help in predicting the shelf-life of the API but also provide essential guidance for formulation improvements and optimized packaging solutions. Overall, the detailed analysis of stability indicators for melatonin encapsulates a critical aspect of pharmaceutical quality assurance, forming the foundation for regulatory submissions and ensuring patient safety. These findings serve as a robust confirmation that systematic and validated analytical protocols are essential for maintaining the therapeutic efficacy of melatonin in both immediate-release and extended-release dosage forms. This methodical assessment underscores the need for continued research to refine these stability-indicating techniques and to further elucidate the complex relationship between formulation, storage conditions, and chemical stability, thereby ensuring that the API meets the highest standards of quality and efficacy. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurity profiling of melatonin is an essential aspect of its pharmaceutical evaluation, with extensive studies dedicated to identifying and quantifying trace impurities that may arise during synthesis or as byproducts of degradation. The analytical techniques employed, such as high-resolution high-performance liquid chromatography (HPLC) coupled with specific detection methods, are in accordance with protocols outlined in the USP Melatonin Monograph. Although the detailed chemical identities—including specific CAS numbers, molecular formulas, and weights—of the impurities are not explicitly provided in the current dataset, the available evidence suggests that the impurities present in melatonin are predominantly synthetic byproducts or degradation products that occur at trace levels. Method development for impurity analysis typically involves the use of specialized columns, such as the XBridge BEH C18 column with a 2.5 μm particle size, which enhances the resolution and sensitivity of impurity detection. In rigorous impurity profiling exercises, the concentration of these unwanted substances is maintained at levels that comply with stringent regulatory standards, ensuring that the overall purity of the API is not compromised. The systematic application of validated analytical techniques allows for the routine monitoring of impurity levels throughout the manufacturing process. Furthermore, advanced techniques such as mass spectrometry (MS) are often implemented in tandem with HPLC to provide structural elucidation of unidentified impurities, thereby offering a deeper insight into the pathway of impurity formation. The critical importance of this impurity profiling has been underscored by studies which demonstrate that even trace levels of impurities can potentially affect both the safety and efficacy of the final pharmaceutical product. The methodologies and findings in impurity profiling are detailed extensively in technical literature, including resources such as the Waters Application Note [2](https://www.waters.com/content/dam/waters/en/app-notes/2023/720007978/720007978-fr.pdf), which provide a framework for best practices in impurity determination. By adhering to these rigorous analytical procedures, manufacturers can ensure that the purity of melatonin remains within the acceptable limits defined by pharmacopeial standards. This comprehensive approach to impurity determination not only supports robust quality control during production but also plays a vital role in the post-market surveillance of the API. In summary, the impurity profile of melatonin, as determined by advanced chromatographic techniques, provides crucial assurance of the product’s safety and therapeutic reliability. Continuous refinement of these analytical methods is essential to adapt to evolving regulatory requirements and to further minimize the presence of any potentially deleterious impurities in the final pharmaceutical formulation. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Biopharmaceutical classification of melatonin has been an extensively studied aspect, with research focusing on its absorption, solubility, and permeability characteristics under various physiological conditions. Data derived from pharmacokinetic studies in healthy volunteers indicate that melatonin is rapidly absorbed following oral administration, with immediate-release formulations demonstrating a higher peak concentration (Cmax) and a shorter time to reach maximum plasma concentration (Tmax) compared to prolonged-release formulations. The high aqueous solubility, as shown by its solubility values of 2 g/L at 20 °C and 5 g/L at 50 °C, combined with a moderately favorable lipophilicity profile (logP of 1.18 at 28 °C), suggests that melatonin possesses a balance between solubility and permeability. These characteristics are essential in determining its classification under the Biopharmaceutical Classification System (BCS). Although there is some debate regarding whether melatonin may fall under Class I (high solubility and high permeability) or Class II (low solubility but high permeability), the preponderance of the evidence points towards high permeability. Nevertheless, establishing an unequivocal classification requires in vitro permeability data in addition to the in vivo pharmacokinetic parameters that have already been documented. In-depth research studies have outlined that the formulation matrix and the nature of the excipients used can significantly influence the biopharmaceutical performance of the dosage form. The kinetic profile of absorption, bioavailability data, and dissolution studies collectively contribute to a more detailed understanding of the absorption mechanisms. Such comprehensive assessments are critical in designing both immediate-release and modified-release formulations that align with therapeutic goals. The scientific community has placed considerable emphasis on the importance of this classification, as it has direct implications for the regulatory approval process and the design of bioequivalence studies. Detailed reports published on repositories such as NCBI provide further insight into these pharmacokinetic parameters [3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11456059/). Overall, the biopharmaceutical classification of melatonin is a multifaceted topic that requires an integration of in vitro and in vivo data to fully discern its permeability and solubility potential. Continuous research is warranted to refine these classifications further, taking into account the latest advancements in experimental modeling and simulation techniques. This approach ensures that the therapeutic efficacy and safety of melatonin are maintained, while also providing a robust framework for the development of improved dosage forms that cater to a wide range of clinical needs. |
| 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; -0.69  **Partition coefficient:** 1.18 at 28 °C  **Hygroscopicity:** The hygroscopic properties of melatonin remain an area that necessitates further detailed examination, as current data on moisture uptake under various environmental conditions are sparse. In the realm of pharmaceutical development, understanding the hygroscopicity of an API is essential because it directly influences the stability, flow characteristics, and overall quality of the final dosage form. Hygroscopicity describes the capacity of a material to absorb moisture from its surroundings, and even minor moisture uptake can have profound effects on the chemical stability, physical state, and efficacy of the compound. While melatonin is primarily characterized as a solid with minimal reported moisture sensitivity, the absence of comprehensive quantitative data on its hygroscopic behavior leaves a gap in understanding its performance under conditions of variable relative humidity and temperature. In practice, hygroscopicity testing typically involves exposing the API to controlled environments at specified relative humidities, often ranging from 30% to 90%, and then monitoring changes in weight and physical appearance over time. Such experiments enable researchers to determine the threshold at which moisture absorption becomes significant and to predict the impact this might have on the stability of the formulation. For melatonin, preliminary observations suggest that its crystalline nature may inherently limit moisture uptake compared to more amorphous compounds; however, conclusive evidence requires a systematic approach using gravimetric analysis and advanced moisture analysis techniques such as dynamic vapor sorption (DVS). In addition, the role of excipients in modulating the hygroscopicity of a final formulation should be considered, as some excipients can either exacerbate or mitigate the effects of moisture. The importance of establishing a comprehensive hygroscopic profile is underlined by the need for appropriate packaging solutions—such as the use of desiccants or moisture-barrier materials—to preserve the integrity and therapeutic efficacy of the API during storage and transportation. Although the current literature does not provide a dedicated URL reference for hygroscopicity data on melatonin, the significance of this parameter is widely recognized in pharmaceutical research. Future studies aimed at elucidating the moisture uptake characteristics of melatonin under varying environmental conditions will be invaluable in optimizing formulation strategies and ensuring product stability. Such investigations will benefit from standardized testing protocols and advanced analytical instrumentation. As a result, a more complete understanding of the hygroscopicity of melatonin will directly contribute to improved manufacturing processes and quality control measures in pharmaceutical development. At this juncture, while the quantitative data remain limited, the qualitative implications of hygroscopicity for melatonin are acknowledged as critical for the advancement of formulation science.  **Chirality/Specific optical rotation:** Melatonin is a molecule that is characterized by the absence of chiral centers, rendering it inherently achiral and therefore not associated with specific optical rotation values. Despite the general importance of chirality in determining the pharmacodynamic and pharmacokinetic properties of many active pharmaceutical ingredients, melatonin’s molecular structure does not give rise to stereochemical complexity. Detailed analytical assessments, including polarimetric studies, have consistently indicated that melatonin displays no measurable optical activity, a feature that simplifies its synthesis and quality control processes. In pharmaceutical research, the determination of chirality or specific optical rotation typically involves sophisticated techniques such as polarimetry or chiral chromatography aimed at discerning the presence of enantiomeric forms within an active compound. However, in the case of melatonin, these methods have confirmed that the compound exists as a single, achiral entity, thereby eliminating concerns related to enantiomeric purity or the potential for stereoselective interactions in vivo. The lack of chirality in melatonin is significant as it reduces the complexity of its pharmacological behavior and simplifies both the manufacturing and regulatory processes. This characteristic is particularly advantageous in ensuring batch-to-batch consistency and in minimizing the risk of variability in therapeutic outcomes. Although the methodologies for optical rotation analysis have been extensively developed and applied to chiral compounds, the application of these techniques to melatonin has essentially confirmed its achiral nature. The scientific literature, including publications available on PubMed [4](https://pubmed.ncbi.nlm.nih.gov/11284025/), provides detailed discussions on the optical properties of structurally complex molecules; however, in the context of melatonin, they serve to underscore the molecule’s structural simplicity. Furthermore, the absence of chiral centers in melatonin obviates the necessity for chiral resolution steps during its synthesis, thus streamlining the manufacturing process and reducing costs associated with stereochemical analyses. This has direct implications for regulatory submissions where rigorous demonstration of enantiomeric purity is often required for chiral drugs. In conclusion, the absence of chirality or measurable specific optical rotation in melatonin is a defining characteristic that contributes to its favorable profile as a pharmaceutical agent. While related studies have provided extensive methodologies for chirality assessment, the findings for melatonin remain unequivocal—its achiral nature simplifies both its clinical application and its production, ensuring consistent performance without the complications associated with stereochemical variability. With continued research and development, the established achirality of melatonin continues to support its widespread use in therapeutic applications, ensuring predictable and reproducible clinical outcomes.  **Degradation temperature:**The degradation temperature of melatonin is an essential thermal parameter that reflects the point at which the API undergoes significant chemical decomposition. Although specific numerical thresholds for degradation are not explicitly detailed in the available dataset, the collective experimental observations indicate that melatonin is susceptible to thermal degradation when subjected to elevated temperatures, especially in environments where pH conditions may further exacerbate the process. Under controlled laboratory conditions, studies have demonstrated that melatonin undergoes thermal degradation through pathways that are intensified by both heat and pH-driven mechanisms. Such degradation typically involves the breakdown of sensitive moieties within the melatonin molecule, leading to the formation of various by-products whose identities require further elucidation. Detailed kinetic studies have revealed that as the temperature increases, the rate constant for degradation rises, indicating a more rapid decline in the intact API concentration. The intersection of thermal energy and pH effects suggests a complex degradation scenario where even minor variations in storage or processing temperatures can trigger significant chemical changes. Analytical techniques such as thermogravimetric analysis (TGA) and DSC are employed to monitor these thermal events, providing researchers with insights into the onset of degradation as well as the overall thermal stability profile. Although definitive temperature thresholds are challenging to establish without additional data, the experimental evidence underscores the importance of maintaining melatonin at temperatures well below the point of rapid degradation to ensure its stability and therapeutic efficacy. This concept is further supported by studies that draw correlations between accelerated stability testing and degradation behavior under forced conditions. Researchers have consistently emphasized the need for careful control of processing and storage conditions, recommending that melatonin be formulated in a way that minimizes exposure to high temperatures and adverse pH environments. Published resources, including reports available on PubMed, further detail such degradation phenomena and highlight the critical interplay between thermal conditions and chemical stability [6](https://pubmed.ncbi.nlm.nih.gov/32258489/). In practical terms, the determination of an operational degradation temperature is pivotal for setting safe manufacturing, storage, and transportation parameters. By extrapolating from the observed degradation kinetics, pharmaceutical scientists can design stability protocols that preclude the API from reaching temperatures that would compromise its integrity. Although a precise numerical value for the degradation temperature is not provided in the current dataset, the overarching consensus is that the integrity of melatonin can be preserved through stringent thermal management strategies. Ongoing research into the thermal degradation pathways of melatonin is expected to yield more precise temperature thresholds, thereby enhancing the formulation and shelf-life predictions for this therapeutic agent.  The determination of the glass transition temperature (Tg) for melatonin is a critical parameter in understanding its physical stability, particularly in its amorphous or semi-crystalline forms. Differential Scanning Calorimetry (DSC) studies have revealed that melatonin exhibits a glass transition temperature in the vicinity of 284.2 K (approximately 11 °C). This thermal transition point is indicative of the molecular mobility within the amorphous phase of the compound, which in turn impacts its stability, solubility, and processing characteristics. The DSC analyses performed on melatonin, and on its deuterated analogues, have shown remarkably similar Tg values (with deuterated forms registering a Tg of approximately 283.7 K), thereby affirming the consistency of its thermal behavior across different isotopic compositions. The glass transition temperature represents a boundary where the material transitions from a brittle, glassy state to a more rubbery, viscous state, a transformation that has significant implications for the storage and handling of the API. For melatonin, maintaining temperatures below the Tg is generally considered favorable to ensure that the molecular structure remains in a relatively less mobile state, minimizing the risk of crystallization or other phase transitions that could compromise its therapeutic efficacy. Detailed thermal studies comprehensively document the conditions under which the Tg was determined; such studies typically employ controlled heating rates and inert atmospheres to prevent oxidative degradation during the measurement process. The understanding of Tg is pivotal for formulating dosage forms, as it influences not only the selection of excipients but also the design of processing protocols, such as milling, granulation, and compression. The correlation between the Tg and other physical parameters, such as melting point and crystallinity, is also critical for predicting long-term stability and the robustness of the final product under various storage conditions. Literature sources, including recent articles published in Nature, provide in-depth analyses of glass transition phenomena in pharmaceutical compounds and describe the intricate relationship between molecular mobility and thermal properties [5](https://www.nature.com/articles/s41598-022-18478-0). In summary, the DSC-determined glass transition temperature for melatonin offers a fundamental insight into its physical behavior, guiding formulation scientists in the design of stable and efficacious drug products. Continued research using advanced thermal analysis techniques is anticipated to refine these observations further, thereby enhancing the applicability of Tg as a predictive tool for the performance of melatonin-based formulations.  **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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