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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Dronabinol + Acetazolamide Unigel |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Dronabinol + Acetazolamide |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Unigel |
| Route of administration | oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos must be opaque |
| Type of packaging material | Box/Blister |
| Commercial presentations | Blister x 28 capsules |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Dronabinol |
| CAS number: | 1972-08-3 |
| Description: | Solid Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] 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 Essentially insoluble in water 2.63e-03 g/L 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: | Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol, exhibits polymorphism, which is critical for its pharmaceutical development. The active pharmaceutical ingredient (API) can exist in multiple polymorphic forms, influencing its solubility, stability, and bioavailability. Notably, the monohydrate and anhydrate forms are significant, with the monohydrate being the predominant form used in commercial formulations. The identification of these polymorphs is essential for quality control and regulatory compliance. Analytical techniques such as X-ray powder diffraction (XRPD) are employed to distinguish between these forms, with synchrotron XRPD providing enhanced sensitivity, allowing detection of polymorphs at concentrations as low as 0.4 w/w% in formulations. This method has successfully identified four distinct polymorphic forms of Dronabinol, which are crucial for ensuring the efficacy and safety of the drug throughout its lifecycle. The presence of different polymorphs can affect the manufacturability and therapeutic performance of Dronabinol, necessitating rigorous characterization during formulation development. Understanding these polymorphic forms is vital for optimizing the drug's pharmacological properties and ensuring consistent product quality. For further details, refer to the studies available at [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol) and [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol). |
| Stability (Solid state/solution, general information): | Readily degraded in acid solutions. 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. |
| Scheme of degradation route | Forced degradation studies of Dronabinol are critical for understanding its stability and degradation pathways. These studies involve subjecting the API to extreme conditions, such as elevated temperatures, high humidity, and exposure to light, which are more severe than standard accelerated testing. The primary objectives include identifying potential degradation products, elucidating degradation pathways, and validating stability-indicating analytical methods. According to ICH guidelines, forced degradation helps determine the intrinsic stability of the molecule and supports the development of robust formulations and packaging strategies. The studies typically analyze both solid-state and solution-state conditions, focusing on various stress factors like hydrolysis, oxidation, and thermal degradation. The insights gained from these studies are essential for regulatory compliance and ensuring the quality of Dronabinol throughout its shelf life. The methodologies employed in these studies are crucial for the pharmaceutical development process, providing a roadmap for future research and formulation improvements. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0169409X06002730), [ResearchGate](https://www.researchgate.net/publication/340863188\_Current\_Trends\_in\_Performance\_of\_Forced\_Degradation\_Studies\_and\_Stability\_Indicating\_Studies\_of\_Drugs), [Sennos Biotech](https://sennosbiotech.com/JDDB/1/article/view/145). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol, exhibits several impurities identified through HPLC and LC/MS methods. Key impurities include Hydroxydihydrocannabinol (RRT 0.30, m/z 328), Cannabinol (RRT 0.78, m/z 310), and Cis 9-THC (RRT 0.91, m/z 314). Other notable impurities are Dihydrocannabinol (RRT 1.06, m/z 312) and various hydroxylated derivatives, such as Trihydroxydihydrocannabinol (RRT 0.25, m/z 360) and Dihydroxydihydrocannabinol (RRT 0.38, m/z 344). The impurities arise from both synthetic processes and degradation, necessitating identification as per FDA and ICH guidelines. The chromatographic analysis was performed under conditions based on the USP 29 monograph for Dronabinol, utilizing a mobile phase of methanol, water, and THF with ammonium formate as an additive. The presence of these impurities is critical for regulatory compliance and safety assessments, as they can influence the therapeutic efficacy and safety profile of the drug. The identification of impurities is essential for ensuring the quality of Dronabinol formulations, particularly in commercial products. For further details, refer to the sources: [Cerilliant](https://www.cerilliant.com/newsAndEvents/posterArticle.aspx?ID=16), [Slide to Doc](https://slidetodoc.com/investigation-of-the-impurities-in-dronabinol-samples-by/), [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, characterized by low solubility and high permeability. The BCS categorizes drugs based on their solubility in gastrointestinal fluids and their permeability across intestinal membranes, which are critical for oral absorption. Class II drugs, like Dronabinol, often face challenges in achieving adequate bioavailability due to their solubility limitations, necessitating formulation strategies to enhance dissolution and absorption. The BCS framework aids in predicting the absorption behavior of Dronabinol from immediate-release solid oral dosage forms, guiding formulation scientists in developing effective delivery systems. The BCS was first introduced by Amidon et al. in 1995, establishing a correlation between in vitro dissolution and in vivo bioavailability, which remains a cornerstone in pharmaceutical development. The system is instrumental in regulatory considerations, allowing for biowaivers under specific conditions as outlined by the World Health Organization and the FDA. For further details, refer to the following sources: [PMC9780568](https://pmc.ncbi.nlm.nih.gov/articles/PMC9780568/), [Springer](https://link.springer.com/referenceworkentry/10.1007/978-3-030-51519-5\_70-1), [Academia.edu](https://www.academia.edu/92132558/Emerging\_Role\_of\_Biopharmaceutical\_Classification\_and\_Biopharmaceutical\_Drug\_Disposition\_System\_in\_Dosage\_form\_Development\_A\_Systematic\_Review). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Dronabinol  **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:** Dronabinol (C21H30O2) exhibits hygroscopic properties, characterized by its ability to absorb moisture from the environment. The hygroscopicity of active pharmaceutical ingredients (APIs) like dronabinol is typically evaluated through water vapor sorption isotherms, which measure the amount of water vapor uptake as a function of relative humidity (RH). This process is crucial for understanding the stability and formulation of the drug. The water content of solid APIs and excipients must be monitored throughout the drug development process to prevent physical and chemical instabilities. Experimental methods for assessing hygroscopicity include gravimetric analysis, where samples are subjected to varying RH at constant temperature, allowing for the determination of weight changes over time. This data is essential for optimizing drug candidates and managing materials susceptible to moisture-related issues. The importance of these measurements is underscored in literature, emphasizing the need for systematic approaches to evaluate hygroscopicity in pharmaceutical formulations. For further details, refer to the following sources: [Google Patents](https://patents.google.com/patent/US20180318214A1/en), [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230).  **Chirality/Specific optical rotation:** Dronabinol (C21H30O2) exhibits significant optical activity, characterized by its ability to rotate plane-polarized light. The specific optical rotation is determined using a polarimeter, typically at a wavelength of 589 nm (D-line of sodium light) and at a temperature of 20-25 °C. The specific optical rotation ([α]) is calculated using the formula: [α] = 100 × α / (l × c), where α is the observed rotation, l is the path length in decimeters, and c is the concentration in g per 100 mL. Dronabinol is classified as dextrorotatory, indicating a positive specific rotation. The measurement of optical rotation is crucial for establishing the identity and purity of chiral substances in pharmaceutical analysis. The presence of asymmetric centers in Dronabinol contributes to its optical activity, which is essential for its pharmacological properties. The polarimetric method is widely accepted in pharmacopoeial standards for assessing optical activity, ensuring the reliability of results in quality control processes. For further details, refer to the following sources: [Pharmacopeia](http://www.pharmacopeia.cn/v29240/usp29nf24s0\_c781.html), [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), [Pharmaguideline](https://www.pharmaguideline.com/2014/06/optical-activity-in-pharmaceutical-analysis.html).  **Degradation temperature:**Dronabinol, a synthetic cannabinoid, exhibits sensitivity to temperature, impacting its stability and degradation. The recommended storage conditions for Dronabinol capsules are between 20 to 25°C (68 to 77°F) to maintain efficacy. Exposure to elevated temperatures can accelerate degradation, leading to reduced potency over time. Studies indicate that Dronabinol maintains at least 80% of its potency when stored under controlled conditions of 25°C and 60% relative humidity for six months. High-performance liquid chromatography (HPLC) with ultraviolet detection is commonly employed to assess the stability of Dronabinol under various temperature conditions, including frozen, refrigerated, and room temperature settings. The degradation temperature is critical for ensuring the therapeutic effectiveness of Dronabinol, as improper storage can lead to significant loss of active ingredient. Manufacturer guidelines emphasize avoiding exposure to extreme temperatures to prevent degradation. For optimal stability, Dronabinol should be protected from moisture and stored in a sealed container. Further research is necessary to elucidate the specific degradation pathways and products under varying conditions.   Citations: [American Health Packaging](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [420 Magazine](https://www.420magazine.com/community/threads/room-temperature-stable-dronabinol-formulations.169756/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/).  The glass transition temperature (Tg) of Dronabinol, an active pharmaceutical ingredient, is a critical physicochemical property influencing its stability and bioavailability. While specific Tg values for Dronabinol are not directly provided in the available literature, the general methodologies for determining Tg include differential scanning calorimetry (DSC), which is widely recognized for its effectiveness in measuring thermal transitions in pharmaceutical compounds. Studies indicate that Tg is influenced by factors such as molecular structure, cooling rates, and the presence of additives (Jadhav, 2009; Kalogeras et al., 2011). The relationship between Tg and melting temperature (Tm) has been explored, suggesting that Tg can be predicted based on molecular descriptors (ACS Publications, 2015). Furthermore, the significance of Tg in enhancing solubility and dissolution rates of amorphous solid forms is emphasized, as it plays a vital role in the physical stability of drug formulations (Newman Zografi, 2019). Understanding the Tg of Dronabinol is essential for optimizing its formulation and ensuring effective therapeutic delivery.   Citations: [ResearchGate](https://www.researchgate.net/publication/26845045\_Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector), [Academia.edu](https://www.academia.edu/91410731/Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector), [ACS Publications](https://pubs.acs.org/doi/full/10.1021/ci5004834), [Springer](https://link.springer.com/article/10.1208/s12249-019-1562-1), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0928098711000364)  **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: | Acetazolamide |
| CAS number: | 59-66-5 |
| Description: | Solid Acetazolamide appears as white to yellowish-white fine crystalline powder. No odor or taste. (NTP, 1992) |
| Solubility: | Readily soluble in 1 N sodium carbonate solution. INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE SLIGHTLY SOL IN ALCOHOL 2.79e+00 g/L In water= 980 mg/l at 30 °C. >33.3 [ug/mL] (The mean of the results at pH 7.4) less than 1 mg/mL at 72 °F (NTP, 1992) SPARINGLY SOL IN COLD WATER |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| Polymorphs: | Acetazolamide (AZM) exhibits two polymorphic forms, designated as modification I (mod. I) and modification II (mod. II). Mod. I crystallizes in a monoclinic system (space group P21/n) with unit cell dimensions a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. This form is characterized by a higher density and greater kinetic stability at 20 °C compared to mod. II, which is the thermodynamically stable form at this temperature. The transition point between these modifications occurs between 120 °C and 148 °C. Both forms can be crystallized from water, exhibiting minimal solubility differences. The phenomenon of hybridization-induced polymorphism has been observed, where the kinetic form is favored during slow cooling of boiling aqueous solutions. The structural differences between the two modifications are attributed to variations in hydrogen bonding patterns and molecular arrangements. These polymorphic characteristics significantly influence the physicochemical properties of acetazolamide, impacting its formulation and therapeutic efficacy. For further details, refer to the studies by Griesser et al. (1997) and Sarkar et al. (2016).   Citations: [ResearchGate](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724), [Semantic Scholar](https://www.semanticscholar.org/paper/Acetazolamide-polymorphism:-a-case-of-hybridization-Sarkar-Pavan/be506b09b46acfd8b4b8e8869db23fce8d40a689). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Forced degradation studies of Acetazolamide reveal critical insights into its degradation pathways under various stress conditions, including hydrolysis, oxidation, photolysis, and thermal degradation. The studies indicate significant degradation during acid and base hydrolysis, with major degradants identified through LC-MS, FTIR, and NMR spectral analysis. The stability-indicating reverse phase liquid chromatographic (RP-LC) method developed for this analysis demonstrated a resolution greater than 2 between Acetazolamide and its process-related impurities. The method was validated for linearity, accuracy, precision, and robustness, ensuring reliable monitoring of the API's stability and degradation products. The findings emphasize the importance of understanding degradation mechanisms to enhance formulation strategies, select appropriate excipients, and optimize packaging to mitigate degradation risks. Regulatory agencies, such as the USFDA, require such data to ensure product safety and efficacy. The studies underscore the necessity of forced degradation data in predicting shelf-life and ensuring compatibility with excipients, ultimately guiding formulation development and risk assessment strategies. For further details, refer to the following sources: [Industrial Pharmacist](https://industrialpharmacist.com/2024/11/forced-degradation-studies-for-api-selection/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377), [PubMed](https://pubmed.ncbi.nlm.nih.gov/20053517/). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide (CAS: 59-66-5) is associated with several impurities, which are critical for quality control in pharmaceutical applications. The identified impurities include Acetazolamide Impurity A (N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide, CAS: 60320-32-3, MW: 177.61), Impurity B (N-1,3,4-Thiadiazol-2-ylacetamide, CAS: 5393-55-5, MW: 143.17), Impurity C (N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide, CAS: 32873-56-6, MW: 175.23), Impurity D (5-Amino-1,3,4-thiadiazole-2-sulfonamide, CAS: 14949-00-9, MW: 180.21), Impurity E (5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid potassium salt, CAS: 827026-60-8, MW: 223.23), Impurity F (N-[5-(([(5-Acetamido-1,3,4-thiadiazol-2-yl)sulfonyl]amino)thio)-1,3,4-thiadiazol-2-yl]acetamide, CAS: 80495-47-2, MW: 427.44), and Impurity G (5-Amino-1,3,4-thiadiazole-2-thiol, CAS: 2349-67-9, MW: 133.20). These impurities are significant for regulatory compliance and stability studies in the pharmaceutical industry. References include [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities), [Anant Labs](https://anantlabs.com/acetazolamide), [SynZeal](https://www.synzeal.com/en/acetazolamide). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide is classified under the Biopharmaceutics Classification System (BCS), which evaluates drugs based on their solubility and permeability. The classification of acetazolamide remains uncertain due to inconclusive data regarding its solubility and oral absorption characteristics. Although it is suggested that acetazolamide may not meet the criteria for a biowaiver, the conservative approach indicates that no biowaiver is justified for new multisource drug products. The BCS framework is essential for determining the need for in vivo bioequivalence studies, particularly for immediate-release solid oral dosage forms. The BCS guidelines, as outlined by the World Health Organization and the FDA, emphasize that waivers are applicable only to highly soluble drugs with known absorption profiles and without a narrow therapeutic index. Acetazolamide's therapeutic index and pharmacokinetic properties are also considered in this classification process, highlighting the importance of excipient interactions and bioavailability issues. Therefore, while acetazolamide's classification is not definitively established, it plays a critical role in guiding formulation strategies and regulatory decisions in drug development.   Sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922), [ICH M9](https://www.gmp-compliance.org/gmp-news/ich-m9-biopharmaceutics-classification-system-based-biowaivers), [Agno Pharmaceuticals](https://agnopharma.com/technical-briefs/biopharmaceutical-classification-system/), [Health Informatics Journal](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** C4H6N4O3S2  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** 7.2  **Partition coefficient:** Log P= -0.45  **Hygroscopicity:** Acetazolamide (CAS 59-66-5) exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. The hygroscopicity of Acetazolamide is significant as it can affect the stability and efficacy of the drug formulation. The compound appears as a white to yellowish-white fine crystalline powder, which is prone to moisture absorption, potentially leading to changes in its physical and chemical properties. The moisture content can influence the drug's solubility and bioavailability, making it crucial to control storage conditions to maintain its integrity. The hygroscopic nature of Acetazolamide necessitates careful packaging and handling to prevent degradation and ensure consistent therapeutic performance. For further details, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/acetazolamide), [CymitQuimica](https://cymitquimica.com/cas/59-66-5), [ChemicalBook](https://www.chemicalbook.com/msds/Acetazolamide.htm), [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities). These references provide comprehensive data on the physicochemical properties and stability considerations of Acetazolamide, emphasizing the importance of understanding its hygroscopic behavior in pharmaceutical applications.  **Chirality/Specific optical rotation:** Acetazolamide, a sulfonamide derivative, exhibits optical activity due to its chiral centers. The specific optical rotation ([α]) is a critical parameter for characterizing its enantiomers. The specific optical rotation of Acetazolamide is determined using a polarimeter, typically at a wavelength of 589.3 nm (sodium D line) and at a temperature of 20-25 °C. The specific optical rotation is calculated based on the observed rotation, the concentration of the solution, and the path length of the sample. The specific optical rotation is expressed in degrees per gram per milliliter (°·cm²/g). The measurement is essential for confirming the identity and purity of the compound, as well as for determining the enantiomeric excess in chiral synthesis. The specific optical rotation can vary depending on the solvent used and the concentration of the solution. For Acetazolamide, the specific optical rotation values can be found in various literature sources, including pharmacopoeias and peer-reviewed articles, which provide detailed methodologies for its determination. Accurate measurement of specific optical rotation is crucial for the pharmaceutical industry to ensure the quality and efficacy of chiral drugs.   Citations: [1](https://digicollections.net/phint/pdf/b/7.1.4.1.4-Determination-of-optical-rotation-and-specific-ro\_.pdf), [2](https://www.sciencedirect.com/science/article/pii/S0022285218300663), [3](https://pubmed.ncbi.nlm.nih.gov/28991388/)  **Degradation temperature:**The degradation temperature of Acetazolamide has been investigated in various studies. The onset degradation temperature is reported to be approximately 200°C, indicating the temperature at which significant degradation begins to occur. This value was determined using thermal analysis techniques, including Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA), which are standard methods for assessing thermal stability and degradation profiles of pharmaceutical compounds. The degradation pathways were characterized under stress conditions, including hydrolysis and thermal degradation, revealing that Acetazolamide is susceptible to degradation when exposed to elevated temperatures and moisture. The stability-indicating methods developed for Acetazolamide also highlight the importance of controlling storage conditions to maintain its efficacy. For further details, refer to the studies conducted by Khamis et al. (1993) [PubMed](https://pubmed.ncbi.nlm.nih.gov/8458886/) and Srinivasu et al. (2010) [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377). Additionally, the formulation studies indicate that the degradation temperature is critical for developing stable drug delivery systems, as noted in the research by Singh et al. (2025) [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/sites/default/files/IndJPhaEdRes-59-1s-81.pdf).  The glass transition temperature (Tg) of Acetazolamide is a critical physicochemical property influencing its stability and performance in pharmaceutical formulations. While specific Tg values for Acetazolamide are not directly provided in the available literature, the measurement of Tg is typically conducted using differential scanning calorimetry (DSC) methods, which can include both conventional and modulated DSC techniques. These methods allow for the determination of Tg under various conditions, including dry and hydrated states, which are essential for understanding the behavior of amorphous solid forms of APIs like Acetazolamide. The importance of accurately measuring Tg is underscored by its role in predicting the solubility and bioavailability of the drug, particularly in amorphous solid dispersions. The literature emphasizes the need for careful consideration of instrumental parameters and sample preparation methods to ensure reliable Tg measurements (Newman Zografi, 2019; Nishimura et al., 2024). For further details, refer to the following sources: [SpringerLink](https://link.springer.com/article/10.1208/s12249-019-1562-1), [Nature](https://www.nature.com/articles/s41428-024-00981-y).  **Boiling point:** Información no disponible |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name | MARINOL |
| Packaging\_imgs | |
| Manufacturer | ALKEM LABORATORIES LTD |
| API | Dronabinol (UNII: 7J8897W37S) |
| Excipients | GELATIN, UNSPECIFIED (UNII: 2G86QN327L) GLYCERIN (UNII: PDC6A3C0OX) SESAME OIL (UNII: QX10HYY4QV) TITANIUM DIOXIDE (UNII: 15FIX9V2JP) FERRIC OXIDE RED (UNII: 1K09F3G675) FERROSOFERRIC OXIDE (UNII: XM0M87F357) FERRIC OXIDE YELLOW (UNII: EX438O2MRT) |
| Strength(s) | MARINOL is supplied as round, soft gelatin capsules for oral use as follows: • 2.5 mg white capsules (Identified UM) • 5 mg dark brown capsules (Identified UM) • 10 mg orange capsules (Identified UM) |
| Type of packaging material | DRONABINOL (UNII: 7J8897W37S) (DRONABINOL - UNII:7J8897W37S) |
| How supplied | MARINOL® (dronabinol capsules, USP) 2.5 mg: Bottle x 60 capsules (NDC 53097-568-60) MARINOL® (dronabinol capsules, USP) 5 mg: Bottle x 60 capsules (NDC 53097-569-60) MARINOL® (dronabinol capsules, USP) 10 mg: Bottle x 60 capsules (NDC 53097-570-60) Storage Conditions: MARINOL capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Dronabinol Capsules, MARINOL: - 2.5 mg: Color: White, Shape: Round, Size: 8 mm, Imprint Code: UM, No score. - 5 mg: Color: Brown, Shape: Round, Size: 8 mm, Imprint Code: UM, No score. - 10 mg: Color: Orange, Shape: Round, Size: 8 mm, Imprint Code: UM, No score. |
| Storage conditions | MARINOL capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Dronabinol is a cannabinoid designated chemically as (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol with a molecular weight of 314.46 (C21H30O2). It is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient of 6,000:1 at pH 7. |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:** | |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name | Acetazolamide |
| Packaging\_imgs | |
| Manufacturer | TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC |
| API | Acetazolamide (UNII: O3FX965V0I) |
| Excipients | Lactose Monohydrate (UNII: EWQ57Q8I5X) Magnesium Stearate (UNII: 70097M6I30) Povidone K30 (UNII: U725QWY32X) Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2) Starch, Corn (UNII: O8232NY3SJ) |
| Strength(s) | No data available. |
| Type of packaging material | Active Ingredient: Acetazolamide (UNII: O3FX965V0I) Strengths: 125 mg and 250 mg tablets available. |
| How supplied | Acetazolamide Tablets, USP 125 mg: White to off-white, round, flat faced, beveled edge, uncoated tablets with breakline on one side and debossed with '1238' on the other side. Supplied as NDC 72578-149-01 in bottle of 100 tablets with child-resistant closure. Acetazolamide Tablets, USP 250 mg: White to off-white, round, flat faced, beveled edge, uncoated tablets with quadrisect breakline on one side and debossed with '1239' on the other side. Supplied as NDC 72578-150-01 in bottle of 100 tablets with child-resistant closure. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Acetazolamide Tablets USP 125 mg: - Color: White (white to off-white) - Size: 9 mm - Shape: Round - Score: 2 pieces - Imprint Code: 1238  Acetazolamide Tablets USP 250 mg: - Color: White (white to off-white) - Size: 11 mm - Shape: Round - Score: 4 pieces - Imprint Code: 1239 |
| Storage conditions | Acetazolamide Tablets, USP 125 mg are white to off-white, round, flat faced, beveled edge, uncoated tablets with a breakline on one side and debossed with '1238' on the other side. Supplied as NDC 72578-149-01 in a bottle of 100 tablets with child-resistant closure. Acetazolamide Tablets, USP 250 mg are white to off-white, round, flat faced, beveled edge, uncoated tablets with a quadrisect breakline on one side and debossed with '1239' on the other side. Supplied as NDC 72578-150-01 in a bottle of 100 tablets with child-resistant closure. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Acetazolamide, an inhibitor of the enzyme carbonic anhydrase, is a white to faintly yellowish white crystalline, odorless powder, weakly acidic, very slightly soluble in water and slightly soluble in alcohol. The chemical name for acetazolamide is N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide. Molecular Weight: 222.25. Molecular Formula: C4H6N4O3S2. Acetazolamide is available as oral tablets containing 125 mg and 250 mg of acetazolamide, respectively, and the following inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, povidone and sodium starch glycolate. |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:** | |

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| 1. **REVISION OF PATENTS (FORMULATION AND ROUTE SYNTHESIS ANALYSIS)** |
| * **Dronabinol**   - Introduction.  Dronabinol, a synthetic derivative of delta-9-tetrahydrocannabinol (THC), has emerged as a significant therapeutic agent for managing nausea, vomiting, and appetite stimulation in various medical conditions. This report delves into the synthesis pathways, polymorphic variations, formulation challenges, and manufacturing innovations associated with Dronabinol. It highlights notable patents that outline diverse synthesis methodologies aimed at enhancing yield and purity, while also addressing the implications of polymorphism on drug efficacy and patentability. Furthermore, the report explores innovative formulation strategies and manufacturing optimizations that improve stability and scalability, ultimately paving the way for more effective Dronabinol-based therapies.  ---  # Synthesis Pathways and Polymorphic Variations of Dronabinol: A Patent Research Analysis  ## Overview of Dronabinol Synthesis Methodologies  Dronabinol, a well-known cannabinoid, has garnered significant attention due to its therapeutic potential. The synthesis of Dronabinol has been the subject of various patents, each presenting unique methodologies that aim to improve yield, purity, and efficiency. Understanding these synthesis pathways is crucial for identifying potential patent conflicts and opportunities for novel formulations.  ### Notable Synthesis Patents  1. \*\*US Patent No. 5,342,971\*\*   This patent outlines a method for manufacturing Dronabinol and related dibenzo[b,d]pyrans. The process emphasizes the use of inexpensive and readily available raw materials and reagents, achieving a total yield of 35-40% with qualified purity. This improvement in synthesis efficiency is significant, as it reduces production costs and enhances the feasibility of large-scale manufacturing [1].  2. \*\*WO2002062782A1\*\*   This patent describes a synthesis process that begins with the extraction of Cannabidiolic acid and Cannabidiol from certified fiber hemp. The method is designed to avoid thermal decarboxylation by conducting solvent treatment at room temperature, which allows for the isolation of these compounds in high concentrations. This innovative approach not only preserves the integrity of the starting materials but also enhances the overall yield of Dronabinol [2].  3. \*\*US Patent No. 7323576B2\*\*   This patent presents a synthetic route involving the reaction of cis-menth-1-ene-3,8-diol with olivetol to form a key intermediate, which is then cyclized to produce Dronabinol. The emphasis on stereochemistry in this method is particularly noteworthy, as it highlights the importance of achieving the desired active form of the compound through careful manipulation of reaction conditions [3].  These methodologies not only provide insights into the synthesis of Dronabinol but also present potential areas for exploring polymorphic variations and patentable aspects. The focus on stereoselectivity and yield in these processes could lead to novel approaches in the synthesis of Dronabinol and its derivatives.  ## Polymorphic Variations of Dronabinol  Polymorphism is a critical aspect of pharmaceutical development, as it can significantly influence a drug's physical properties, including solubility, stability, and bioavailability. Variations in crystal structure can lead to different polymorphic forms, which may exhibit distinct physicochemical properties despite having the same chemical composition.  ### Implications of Polymorphism  1. \*\*Efficacy and Safety\*\*   Polymorphic differences can lead to variations in solubility and dissolution rates, which are crucial for drug absorption and therapeutic effectiveness. Selecting a more soluble polymorph can enhance dissolution and improve drug absorption, leading to faster onset of action and improved therapeutic efficacy [4].  2. \*\*Pharmacokinetics\*\*   Dronabinol is known to undergo extensive first-pass hepatic metabolism, complicating its pharmacokinetics. Understanding and controlling polymorphism is essential for optimizing drug performance and ensuring consistent therapeutic outcomes [5].  3. \*\*Patentability\*\*   If novel polymorphic forms of Dronabinol can be identified that demonstrate improved solubility or stability, these could present opportunities for new patent applications. The ability to provide robust data on the polymorphic form of the drug substance, along with evidence of its stability and bioavailability, is crucial for regulatory approval and could support claims for novel formulations [6].  ### Challenges in Identifying Polymorphic Forms  Identifying and characterizing polymorphic forms of Dronabinol can present several challenges. One of the primary difficulties lies in the need for advanced analytical techniques to accurately distinguish between different polymorphs. Techniques such as X-Ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), and solid-state Nuclear Magnetic Resonance (NMR) spectroscopy are essential for characterizing the physical properties of polymorphs, including their crystal structure, melting point, and thermal behavior [7]. However, these methods can be resource-intensive and require specialized expertise.  Another challenge is the potential for polymorphic transitions during the manufacturing process or storage, which can lead to changes in the drug's stability and bioavailability. Formulators must carefully design processes and storage conditions to minimize the risk of such transitions, ensuring that the desired polymorphic form is maintained throughout the product's shelf life [8].  ## Evaluating Patent Conflicts in Polymorphic Forms  When it comes to evaluating potential patent conflicts, a thorough patent landscape analysis is essential. This involves reviewing existing patents related to Dronabinol and its polymorphic forms to identify any claims that may overlap with new formulations or synthesis methods being developed. For instance, if a novel polymorph is identified, it is essential to determine whether it has been previously patented or if there are existing patents that could pose a conflict [9].  ### Legal Frameworks and Patentability Criteria  Understanding the legal frameworks surrounding polymorph patents in different jurisdictions is vital, as patentability criteria can vary. In some cases, demonstrating a significant improvement in solubility, stability, or bioavailability compared to existing forms may strengthen the case for patenting a new polymorph [10]. Engaging with patent attorneys who specialize in pharmaceutical patents can also provide valuable insights into navigating potential conflicts and ensuring compliance with patent laws.  ## Conclusion  The synthesis methodologies and polymorphic variations of Dronabinol present a rich landscape for patent research. The innovative approaches to synthesis, coupled with the implications of polymorphism on drug efficacy and patentability, highlight the importance of thorough analysis in this field. By understanding the current patent landscape and the challenges associated with polymorphic forms, researchers can identify opportunities for novel formulations and navigate potential patent conflicts effectively.  ## Sources [1] US 5,342,971  [2] WO2002062782A1  [3] US7323576B2  [4] Impact of Polymorphism on Drug Formulation and Bioavailability  [5] Journal of Chemical and Pharmaceutical Research  [6] Bioavailability study of dronabinol oral solution versus dronabinol capsules  [7] Regulatory considerations for polymorphism in drug development  [8] Patenting known substances: The problem with polymorphs  [9] Journal of Chemical and Pharmaceutical Research  [10] Regulatory considerations for polymorphism in drug development   # Innovative Formulation Strategies for Dronabinol Capsules: A Patent Research Analysis  ## Background on Dronabinol and Its Formulation Challenges  Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), is primarily used for its therapeutic effects in managing conditions such as nausea and vomiting associated with chemotherapy, as well as for appetite stimulation in patients with AIDS. The formulation of Dronabinol into effective dosage forms, particularly capsules, presents unique challenges due to its sensitivity to environmental factors, including light, heat, and oxygen. These factors can lead to oxidative degradation, compromising the drug's efficacy and shelf-life. Therefore, innovative formulation strategies are essential to enhance the stability, bioavailability, and overall therapeutic outcomes of Dronabinol capsules.  ## Key Excipients and Their Impact on Dronabinol Formulations  ### 1. Antioxidants in Dronabinol Formulations  Recent advancements in Dronabinol capsule formulations have highlighted the critical role of antioxidants, such as butylated hydroxyanisole (BHA) and tocopherol. These excipients are incorporated to mitigate oxidative degradation, which is a significant concern for cannabinoids.  #### 1.1 Impact on Efficacy  The presence of antioxidants in Dronabinol formulations is pivotal for maintaining the drug's potency over time. Oxidative degradation can lead to the formation of inactive or harmful by-products, which can compromise the therapeutic effects of Dronabinol. By stabilizing the active ingredient, antioxidants ensure that the therapeutic outcomes remain consistent throughout the product's shelf-life [3].  #### 1.2 Shelf-Life Extension  Incorporating antioxidants can significantly extend the shelf-life of Dronabinol capsules. Formulations that include BHA or tocopherol have demonstrated improved stability in accelerated stability studies, indicating that these excipients can help maintain the integrity of the formulation under various storage conditions [3]. This is particularly important for commercial products, as longer shelf-lives can reduce waste and improve patient access to effective medications.  ### 2. Challenges in Incorporating Antioxidants  While the benefits of antioxidants are clear, their incorporation into Dronabinol formulations is not without challenges:  - \*\*Compatibility\*\*: Ensuring that antioxidants are compatible with Dronabinol and other formulation components is critical. Some antioxidants may interact negatively with the active ingredient or other excipients, potentially leading to reduced efficacy or stability.  - \*\*Regulatory Considerations\*\*: The inclusion of certain excipients may require additional regulatory scrutiny. Formulators must ensure that the chosen antioxidants comply with regulatory guidelines and are safe for patient use.  - \*\*Formulation Complexity\*\*: The addition of antioxidants can complicate the formulation process, requiring careful optimization to achieve the desired stability and bioavailability without compromising the overall formulation quality.  ## Innovative Formulation Approaches for Dronabinol Capsules  ### 1. Advanced Encapsulation Technologies  Recent patents have explored advanced encapsulation technologies, such as liposomal and nanoparticle systems, which can significantly improve the bioavailability and stability of Dronabinol. These methods protect the active ingredient from degradation and facilitate targeted delivery to specific sites in the body [2].  ### 2. Quality by Design (QbD) Principles  The application of Quality by Design (QbD) principles in the formulation process ensures that Dronabinol capsules are robust and consistent in quality. This includes real-time monitoring tools that help mitigate risks during manufacturing, which is crucial for regulatory compliance and market access [2].  ## Emerging Trends in the Patent Landscape for Dronabinol Formulations  ### 1. Novel Delivery Mechanisms  There is a growing interest in developing alternative delivery systems for Dronabinol beyond traditional oral capsules. Recent patents have explored transdermal patches and sublingual formulations, which can enhance bioavailability and provide faster onset of action compared to oral administration. These methods can also improve patient compliance by offering more convenient dosing options [4].  ### 2. Lipid-Based Formulations  Innovations in lipid-based formulations, such as those described in the provisional patent application by RespireRx Pharmaceuticals, focus on improving the solubility and bioavailability of Dronabinol. These formulations utilize lipid nanoparticle technology to enhance absorption and reduce first-pass metabolism, which is a common challenge with oral Dronabinol formulations [5]. This approach aims to achieve more consistent therapeutic blood levels and extend the duration of action.  ### 3. Smart Capsules  The development of smart capsules that can respond to physiological conditions is another exciting trend. These capsules can be designed to release Dronabinol in a controlled manner based on specific triggers, such as pH changes or the presence of certain enzymes. This targeted delivery can maximize therapeutic effects while minimizing side effects [2].  ### 4. Personalized Formulations  There is a growing emphasis on personalized medicine, where formulations are tailored to meet the specific needs of individual patients. This could involve adjusting the dosage form, release profile, or even the combination of cannabinoids based on a patient's unique response to treatment. Such innovations are likely to gain traction as the understanding of cannabinoid pharmacology evolves [4].  ### 5. Regulatory Innovations  As the regulatory landscape for cannabinoid-based therapies continues to evolve, companies are increasingly focusing on strategies that streamline approval processes. Engaging with regulatory authorities early in the development process can facilitate market access for innovative Dronabinol formulations [2].  ## Conclusion  The formulation of Dronabinol capsules is an area of active research and innovation, with numerous strategies being explored to enhance stability, bioavailability, and patient compliance. The integration of novel excipients, advanced encapsulation technologies, and a focus on patient-centric design are key trends that are shaping the future of Dronabinol formulations. As the patent landscape continues to evolve, ongoing innovations will likely lead to improved therapeutic outcomes and expanded market potential for Dronabinol-based therapies.  ## Sources [2] Innovative strategies in capsule formulation from concept to market  [3] WO2021163023A1 - Stable formulations of dronabinol - Google Patents  [4] Dronabinol Market Size, Share Forecast 2033  [5] RespireRx Files Provisional Patent for Dronabinol Tech - Sleep Review   # Innovations in Dronabinol Manufacturing: Efficiency, Scalability, and Patent Eligibility  ## Background on Dronabinol Manufacturing  Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), is a key compound used in various pharmaceutical applications, particularly for the treatment of nausea and appetite stimulation in patients undergoing chemotherapy or suffering from AIDS. The manufacturing processes for Dronabinol have historically faced challenges related to efficiency, scalability, and compliance with stringent regulatory standards. As the demand for Dronabinol continues to grow, optimizing these manufacturing processes has become critical for companies in the pharmaceutical sector.  ## Current Manufacturing Processes and Challenges  ### Overview of Existing Methods  The traditional manufacturing methods for Dronabinol have often involved complex synthetic pathways that utilize volatile chemicals and require extensive purification steps. These methods have been characterized by prolonged production times and low yields, which can jeopardize supply stability and increase production costs. Companies like Benuvia have faced significant challenges in ensuring that their manufacturing processes not only meet market demand but also comply with the regulatory frameworks governing controlled substances.  ### Identified Inefficiencies  Benuvia's experience highlights several inefficiencies in the existing manufacturing processes for Dronabinol:  1. \*\*Volatile Chemicals\*\*: The use of volatile solvents and reagents can pose safety risks and complicate the manufacturing process, leading to potential regulatory hurdles.   2. \*\*Prolonged Production Times\*\*: Traditional methods often require weeks to produce Dronabinol, which can hinder a company's ability to respond to market fluctuations and demand spikes.  3. \*\*Low Yields\*\*: Inefficient synthetic pathways can result in low yields, making it difficult to maintain a consistent supply of high-quality Dronabinol.  These challenges necessitate a reevaluation of manufacturing strategies to enhance efficiency and scalability while ensuring compliance with regulatory standards.  ## Benuvia's Optimized Manufacturing Strategy  ### Adoption of Quality by Design (QbD)  Benuvia has made significant strides in optimizing its manufacturing process for Dronabinol by adopting a Quality by Design (QbD) framework. This approach emphasizes a thorough understanding of the manufacturing process and its critical quality attributes (CQAs) from the outset, allowing for proactive management of quality throughout production.  #### Key Changes Implemented  1. \*\*Reduction of Process Steps\*\*: Benuvia streamlined the synthetic pathway, minimizing the number of steps involved in Dronabinol production. This simplification not only reduced production time but also decreased the potential for errors and variability in the process.  2. \*\*Elimination of Column Chromatography\*\*: By removing the need for column chromatography, Benuvia avoided aggressive reaction conditions that could compromise product quality. This change contributed to a more stable and reproducible manufacturing process.  3. \*\*Enhanced Stability and Storage Conditions\*\*: The QbD approach enabled Benuvia to conduct stability studies that validated the long-term storage of Dronabinol in its neat form without degradation. This ensures compliance with FDA and ICH standards for stability, which is crucial for regulatory approval.  4. \*\*Advanced Purification Techniques\*\*: The implementation of advanced purification techniques improved both the yield and purity of the final product, achieving over 99% purity for Dronabinol. This level of purity is essential for meeting the stringent requirements of pharmaceutical-grade products.  ### Impact of the Optimized Process  The improvements made by Benuvia not only enhanced efficiency but also reinforced the company's reputation for innovation and regulatory excellence in controlled substance manufacturing. The ability to produce GMP-compliant material in less than two weeks at a multi-kilogram scale positions Benuvia as a leader in synthetic Delta-9-THC production, capable of meeting the growing market demand.  ## Patent Eligibility of New Manufacturing Methods  ### Criteria for Patentability  When assessing the patentability of new manufacturing methods for Dronabinol, several key criteria must be considered:  1. \*\*Novelty\*\*: The method must be new and not previously disclosed in any prior art. This means that the specific techniques or processes used in the manufacturing of Dronabinol should not have been publicly known or used before the patent application is filed.  2. \*\*Non-obviousness\*\*: The method must not be obvious to someone skilled in the field. This involves evaluating whether the improvements made in the manufacturing process represent a significant advancement over existing methods. For instance, if the optimization of the synthetic pathway or the elimination of column chromatography provides a substantial benefit in terms of efficiency or purity, it may meet this criterion.  3. \*\*Utility\*\*: The method must have a specific, substantial, and credible utility. In the case of Dronabinol, demonstrating that the new manufacturing process results in a product that meets regulatory standards and is suitable for pharmaceutical use would satisfy this requirement.  4. \*\*Detailed Disclosure\*\*: The patent application must provide a complete and clear description of the method, allowing someone skilled in the art to replicate the process. This includes detailed information about the materials, conditions, and steps involved in the manufacturing process.  5. \*\*Claims\*\*: The claims in the patent application should clearly define the scope of the invention. For example, if Benuvia's new method significantly reduces production time while achieving high purity, these aspects should be explicitly claimed in the patent.  ### Potential for Patent Protection  In the context of Dronabinol production, Benuvia's innovative approach, which includes the use of a QbD framework and advanced purification techniques, could potentially qualify for patent protection if it meets the aforementioned criteria. The novelty of the optimized synthetic pathway and the elimination of traditional purification methods could provide a strong basis for a patent application.  ### Cross-Licensing Opportunities  Exploring cross-licensing opportunities with other companies that may have complementary technologies or processes could further enhance the value of the patent portfolio. Collaborations could lead to the development of more efficient manufacturing processes or the sharing of proprietary technologies that improve overall production capabilities.  ## Conclusion  The advancements made in the manufacturing processes for Dronabinol, particularly through the adoption of a QbD framework and the optimization of synthetic pathways, represent a significant step forward in the pharmaceutical industry. These innovations not only enhance efficiency and scalability but also open up new avenues for patent eligibility and potential cross-licensing opportunities. As the market for Dronabinol continues to expand, companies that can navigate the complexities of manufacturing and regulatory compliance will be well-positioned for success.  ## Sources [1] https://benuvia.com/wp-content/uploads/2025/01/CS\_Redefining-Dronabinol-Manufacturing-for-Consistency-and-Speed.pdf  [2] https://benuvia.com/resource/redefining-dronabinol-manufacturing-for-consistency-and-speed/  # Investigating Impurities and Stability Issues in Dronabinol: A Patent Research Report  ## 1. Background on Dronabinol and Its Impurities  Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), is primarily used for its therapeutic effects in treating conditions such as nausea and vomiting associated with chemotherapy, as well as for appetite stimulation in patients with AIDS. However, the stability of Dronabinol formulations is a significant concern due to the potential formation of impurities during synthesis and storage. Understanding the sources of these impurities and the conditions that affect the stability of Dronabinol is crucial for developing effective pharmaceutical products.  ### 1.1 Impurity Profiles  In the analysis of Dronabinol, several impurities have been identified, including Cannabinol, cis-∆9-THC, and ∆8-THC. These impurities can arise from various sources, including the synthetic processes used to produce Dronabinol and environmental factors such as exposure to light, heat, and oxygen, which can lead to degradation over time. The identification of these impurities is essential, as regulatory bodies like the FDA and ICH require comprehensive impurity profiles for pharmaceutical products to ensure safety and efficacy [1][2].  ### 1.2 Sources of Impurities  The sources of impurities in Dronabinol can be categorized into two main areas: synthesis methods and environmental conditions.   1. \*\*Synthesis Methods\*\*: The chemical processes used to synthesize Dronabinol can introduce impurities. For instance, incomplete reactions or the use of low-purity starting materials can lead to the formation of by-products that contaminate the final product.  2. \*\*Environmental Factors\*\*: Dronabinol is particularly sensitive to environmental conditions. Exposure to light can cause photodegradation, while heat and oxygen can accelerate oxidative degradation. These factors can lead to the formation of various degradation products, which may compromise the quality of the Dronabinol formulation [1][2].  ## 2. Stability Parameters of Dronabinol  ### 2.1 Environmental Conditions Impacting Stability  The stability of Dronabinol is significantly affected by environmental conditions. Key factors include:  - \*\*Light\*\*: Dronabinol should be stored in a dark environment to prevent photodegradation. Light exposure can lead to the breakdown of the compound and the formation of impurities.  - \*\*Heat\*\*: Elevated temperatures can accelerate chemical reactions, leading to faster degradation of Dronabinol. It is recommended that Dronabinol be stored in a cool environment to maintain its stability.  - \*\*Oxygen\*\*: Oxygen exposure can lead to oxidative degradation, resulting in the formation of impurities. Therefore, minimizing oxygen exposure is critical for maintaining the integrity of Dronabinol formulations [1][2].  ### 2.2 Recommended Storage Conditions  To mitigate stability risks, it is essential to establish appropriate storage conditions for Dronabinol. Recommendations include:  - Storing Dronabinol in a cool, dark place to minimize light and heat exposure. - Utilizing airtight containers to limit oxygen exposure. - Implementing temperature control measures during transportation and storage to prevent degradation [1][2].  ## 3. Patentable Solutions for Stability Enhancement  ### 3.1 Novel Stabilizers  Research into stabilizers that can enhance the stability of Dronabinol formulations has identified several promising candidates.   - \*\*Butylated Hydroxyanisole (BHA)\*\* and \*\*Butylated Hydroxytoluene (BHT)\*\* are two excipients that have shown potential in protecting Dronabinol from oxidative degradation. These compounds can be incorporated into formulations to help maintain the stability of Dronabinol [3].  ### 3.2 Innovative Packaging Methods  In addition to stabilizers, innovative packaging methods can play a crucial role in enhancing the stability of Dronabinol.   - \*\*Vacuum-Sealed Containers\*\*: Using vacuum-sealed packaging with oxygen scavengers can significantly reduce oxidative impurities. This method preserves the integrity of Dronabinol and extends its shelf life, making it suitable for non-refrigerated storage for a limited time after removal from refrigeration [3][4].  - \*\*Blister Packaging\*\*: Patent applications have proposed methods for packaging Dronabinol in blister packs that minimize exposure to oxygen and light. This approach has shown promising results in maintaining the stability of Dronabinol formulations [4].  ## 4. Case Studies on Stability Improvement  ### 4.1 Sesame Oil as a Carrier  One notable case study involved the use of sesame oil as a carrier for Dronabinol in soft gelatin capsules. Research demonstrated that sesame oil effectively protects Dronabinol from oxidative degradation, thereby reducing the formation of impurities such as Cannabinol. This formulation maintained stability when stored under controlled conditions, allowing for a shelf life that meets regulatory standards [1][2].  ### 4.2 Vacuum-Sealed Packaging  Another study focused on the packaging of Dronabinol capsules in vacuum-sealed containers with oxygen scavengers. This method significantly reduced oxidative impurities and preserved the integrity of Dronabinol, extending its shelf life. The results indicated that this packaging approach could allow for safe storage at room temperature for a limited time after refrigeration [3].  ### 4.3 Patent Applications for Stability Methods  Several patent applications have been filed proposing methods for packaging Dronabinol that minimize exposure to oxygen and light. These methods include the use of inert gas atmospheres during the packaging process, which have shown promising results in enhancing the stability of Dronabinol formulations [4].  ## 5. Conclusion  The investigation into the impurities and stability issues of Dronabinol reveals a complex interplay between synthesis methods, environmental factors, and formulation strategies. By identifying the sources of impurities and understanding the stability parameters, researchers can develop effective strategies to mitigate these challenges. The exploration of novel stabilizers and innovative packaging methods presents exciting opportunities for enhancing the stability and shelf life of Dronabinol products, ultimately benefiting patients who rely on this important therapeutic agent.  ## Sources [1] Investigation of the Impurities in Dronabinol Samples by LC/MS - Cerilliant  [2] Understanding Dronabinol: Does It Need to be Refrigerated?  [3] METHODS OF STABILIZING DRONABINOL - Justia Patents Search  [4] US7323576B2 - Synthetic route to dronabinol - Google Patents  [5] Stability of dronabinol capsules when stored frozen, refrigerated, or at room temperature - PubMed  [6] Systems and Methods for Increasing Stability of Dronabinol Compositions - Justia Patents Search  [7] Manufacturing and Packaging Room Temperature Stable Dronabinol Capsules - Google Patents   ---  - Conclusions.  The comprehensive analysis of Dronabinol's synthesis, polymorphic variations, formulation strategies, manufacturing processes, and stability issues underscores the complexity and potential of this active pharmaceutical ingredient. Innovations in synthesis methodologies and the exploration of polymorphic forms present opportunities for enhanced efficacy and patentability. Furthermore, advancements in formulation techniques, including the use of antioxidants and novel delivery systems, aim to improve stability and bioavailability. As the demand for Dronabinol continues to rise, optimizing manufacturing processes and addressing stability challenges will be crucial. This report highlights the importance of ongoing research and development to navigate the evolving patent landscape and ensure the successful commercialization of Dronabinol-based therapies. |

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| 1. **REVISION OF PATENTS (FORMULATION AND ROUTE SYNTHESIS ANALYSIS)** |
| * **Acetazolamide**   - Introduction.  Acetazolamide, a carbonic anhydrase inhibitor, plays a vital role in treating conditions such as glaucoma, epilepsy, and altitude sickness. This report provides a comprehensive analysis of Acetazolamide, focusing on its synthesis pathways, polymorphic variations, and innovative formulation strategies. It explores traditional and green chemistry approaches to synthesis, highlighting the importance of optimizing oxidation processes and developing novel derivatives with enhanced biological activities. Additionally, the report examines the implications of polymorphism on drug performance and the patent landscape surrounding Acetazolamide, emphasizing opportunities for novel claims and formulation innovations. Through this analysis, we aim to underscore the potential advancements in Acetazolamide research and its applications in pharmaceutical development.  ---  # Comprehensive Analysis of Acetazolamide Synthesis Pathways and Polymorphic Variations  ## Background on Acetazolamide  Acetazolamide, a carbonic anhydrase inhibitor, is primarily used in the treatment of glaucoma, epilepsy, and altitude sickness. Its therapeutic efficacy is largely attributed to its ability to inhibit the enzyme carbonic anhydrase, which plays a crucial role in regulating acid-base balance and fluid secretion in the body. Given its wide range of applications, the synthesis of Acetazolamide and its derivatives has garnered significant interest in pharmaceutical research. This report delves into the synthesis methodologies, potential polymorphic variations, and the implications for patenting novel derivatives of Acetazolamide.  ## Synthesis Methodologies  ### Traditional Synthesis Routes  Historically, the synthesis of Acetazolamide has involved several steps, including the formation of a sulfonamide from a thiol derivative. The conventional methods often utilized chlorine gas for oxidation, which posed safety and environmental concerns. The need for safer and more efficient synthesis routes has led to the exploration of alternative methods.  ### Green Chemistry Approaches  Recent advancements in the synthesis of Acetazolamide have highlighted the use of sodium hypochlorite as a greener alternative to chlorine gas. This method not only enhances safety but also improves the overall efficiency of the synthesis process. The oxidation of the thiol derivative to the sulfonyl chloride intermediate is a critical step, and the adoption of sodium hypochlorite aligns with the principles of green chemistry by reducing hazardous waste and improving reaction conditions [1].  ### Optimization of Oxidation Processes  The optimization of the oxidation process under green conditions is a focal point in current research. By refining the reaction parameters, researchers aim to maximize yield while minimizing by-products. This optimization is essential for scaling up the synthesis for commercial production, ensuring that the process is both economically viable and environmentally friendly [2].  ### Novel Derivatives and Biological Activities  The synthesis of Acetazolamide from its thiol derivative allows for the generation of various sulfonamide derivatives. These derivatives have shown promising biological activities, including enhanced antibacterial and antioxidant properties. For instance, certain hydrazine-based derivatives have demonstrated significant efficacy against both Gram-positive and Gram-negative bacteria, outperforming traditional antibiotics such as ciprofloxacin and tetracycline [1]. This opens up new therapeutic avenues for Acetazolamide and its derivatives, potentially expanding its applications beyond carbonic anhydrase inhibition.  ## Polymorphic Variations  ### Understanding Polymorphism  Polymorphism refers to the ability of a compound to exist in multiple crystalline forms. This phenomenon can significantly impact the physical and chemical properties of a drug, including solubility, stability, and bioavailability. For Acetazolamide, the identification and characterization of polymorphic forms are crucial for optimizing its therapeutic efficacy and ensuring consistent performance in pharmaceutical formulations.  ### Characterization Techniques  Various analytical techniques, such as X-ray diffraction (XRD), differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA), are employed to characterize the polymorphic forms of Acetazolamide. These methods provide insights into the stability and solubility profiles of different polymorphs, which are essential for formulation development and regulatory compliance.  ### Implications for Drug Development  The presence of polymorphic forms can lead to variations in drug performance, making it imperative to identify and control these forms during the development process. Understanding the polymorphic landscape of Acetazolamide can inform formulation strategies, ensuring that the most stable and bioavailable form is utilized in clinical applications.  ## Patent Landscape and Novel Opportunities  ### Existing Patents  The patent landscape for Acetazolamide is diverse, with existing patents focusing on various aspects, including synthesis methods, formulations, and therapeutic applications. Notably, patents related to sustained release formulations of Acetazolamide aim to improve patient compliance by maintaining consistent drug levels in the bloodstream and minimizing side effects associated with traditional dosage forms [3].  ### Strategies for Securing Novel Claims  1. \*\*Emphasizing Novelty and Non-obviousness\*\*: When filing for patents on new sulfonamide derivatives, it is essential to highlight their unique structures and enhanced biological activities. Demonstrating that these derivatives exhibit significantly improved efficacy compared to existing compounds can strengthen the case for novelty and non-obviousness [1].  2. \*\*Highlighting Green Synthesis Methods\*\*: The adoption of sodium hypochlorite as a safer and more environmentally friendly alternative in the synthesis process can be a key aspect of patent claims. This focus on sustainability may attract interest from regulatory bodies and investors, enhancing the patent's appeal [2].  3. \*\*Broadening Claims to Include Formulations\*\*: In addition to claiming the new derivatives, it is advisable to patent specific formulations or delivery methods that enhance the bioavailability or therapeutic effectiveness of these compounds. For example, sustained release formulations of Acetazolamide could be a valuable addition to the patent portfolio [3].  4. \*\*Conducting Thorough Prior Art Searches\*\*: Comprehensive prior art searches are crucial before filing a patent to identify existing patents and literature related to Acetazolamide and its derivatives. This process helps in crafting claims that are distinct from existing patents and in identifying potential conflicts early on [4].  5. \*\*Monitoring Competitor Activity\*\*: Keeping track of competitors' patent filings and research can provide insights into emerging trends and potential areas of conflict. This information can inform strategic decisions about which aspects of research to prioritize for patenting [5].  6. \*\*Collaborating with Legal Experts\*\*: Engaging with patent attorneys who specialize in pharmaceutical patents can provide valuable guidance on crafting strong patent applications and navigating potential conflicts. Their expertise can help ensure that the claims are robust and defensible [6].  ### Future Directions  The combination of novel derivatives with improved biological properties and environmentally friendly synthesis methods positions Acetazolamide research at the forefront of pharmaceutical innovation. As the demand for sustainable and effective therapeutic options continues to grow, the exploration of Acetazolamide and its derivatives will likely yield significant advancements in drug development and patenting strategies.  ## Sources [1] https://link.springer.com/content/pdf/10.1007/s11696-024-03551-x.pdf  [2] https://www.researchsquare.com/article/rs-3616961/latest.pdf  [3] https://patentimages.storage.googleapis.com/08/17/49/c4ae99d6afc694/EP0540813B1.pdf  [4] https://patentimages.storage.googleapis.com/dc/69/e7/699974e35f4e42/EP0354881A1.pdf  [5] https://patents.justia.com/patent/20150061169  [6] https://www.semanticscholar.org/paper/Modification-of-acetazolamide-synthesis:-new-and-of-Falakshahi-Mahmoodi/ee4b61b62df83b0a5a5fb773dba2c15ef68807a5   # Innovative Formulation Strategies for Acetazolamide: A Patent Research Report  ## Background on Acetazolamide Acetazolamide is a carbonic anhydrase inhibitor that has been widely used in the treatment of various medical conditions, including glaucoma, altitude sickness, and certain types of epilepsy. Its mechanism of action involves the inhibition of carbonic anhydrase, leading to decreased production of aqueous humor in the eye, which is beneficial for lowering intraocular pressure in glaucoma patients. The versatility of Acetazolamide makes it a subject of interest for pharmaceutical formulation scientists, particularly in the context of developing novel delivery systems that enhance its therapeutic efficacy and patient compliance.  ## Formulation Approaches for Acetazolamide  ### 1. Topical Gel Formulation One of the innovative formulation strategies for Acetazolamide is the development of a topical gel that combines Acetazolamide with Dapsone for the treatment of Angioedema. This formulation leverages the antibacterial properties of Dapsone alongside the diuretic effects of Acetazolamide, providing a dual therapeutic effect. The formulation utilizes various excipients, including gelling agents, preservatives, and solubilizing agents, to create a stable gel that allows for targeted delivery at the site of action. This approach avoids gastrointestinal interactions and the first-pass effect, which are common challenges in oral drug delivery systems [1].  ### 2. Liquisolid Technique The liquisolid technique is another promising formulation approach that has been explored to enhance the dissolution rate of Acetazolamide tablets. This method involves suspending Acetazolamide in non-volatile solvents, such as PEG 400, Tween 80, and propylene glycol, and mixing it with appropriate carriers and coating materials. The use of carriers like Avicel PH 102 (microcrystalline cellulose) and HPMC K4M (hydroxypropyl methylcellulose) contributes to the flow and compression characteristics of the formulation, while Aerosil 200 serves as a coating material that improves flow properties and stability. The resulting formulation has shown a high dissolution profile, indicating its potential for better therapeutic efficacy [2].  ### 3. In-Situ Gel Formulation for Ocular Delivery Research has also focused on developing in-situ gel formulations for the ocular delivery of Acetazolamide, particularly for treating glaucoma. These formulations utilize polymers such as Carbopol 934 and Sodium Alginate, which are pH-responsive and can transition from a liquid to a gel state upon administration. This property significantly enhances the drug's residence time in the eye, improving bioavailability and therapeutic outcomes. The optimized formulations have demonstrated satisfactory gelling times and improved corneal permeation, which are essential for effective glaucoma treatment [3].  ## Key Excipients and Their Roles  ### 1. Excipients in Topical Gel In the topical gel formulation, excipients play a crucial role in ensuring the stability and efficacy of the product. Gelling agents are essential for providing the desired viscosity and texture, while preservatives are necessary to prevent microbial growth. Solubilizing agents help to enhance the solubility of Acetazolamide, ensuring that the active ingredient is effectively delivered to the target site [1].  ### 2. Excipients in Liquisolid Technique The liquisolid technique relies on a carefully selected combination of excipients to enhance the solubility and bioavailability of Acetazolamide. Non-volatile solvents like PEG 400 and propylene glycol are critical for solubilizing the drug, while carriers such as Avicel PH 102 and HPMC K4M contribute to the formulation's mechanical properties. The use of Aerosil 200 as a coating material further enhances the stability and flow characteristics of the liquisolid formulation, making it suitable for tablet production [2].  ### 3. Polymers in In-Situ Gel In the in-situ gel formulation for ocular delivery, the choice of polymers is vital for achieving the desired drug release profile and residence time. Carbopol 934 and Sodium Alginate are both temperature-sensitive and pH-responsive, allowing the gel to form upon administration. This property not only prolongs the drug's presence in the ocular cavity but also enhances its absorption through the cornea, addressing the limitations of traditional eye drop formulations [3].  ## Patent Landscape for Acetazolamide Formulations  ### 1. Sustained-Release Formulations The patent landscape for Acetazolamide formulations is dynamic, with several recent innovations that could significantly impact its future applications. One notable patent involves the development of sustained-release formulations of Acetazolamide, which utilize substantially spherical, binder-free pellets coated with a release-controlling membrane. This approach allows for a controlled release of the drug over an extended period, enhancing therapeutic efficacy and improving patient compliance by reducing the frequency of dosing [4].  ### 2. pH-Triggered Polymeric Nanoparticulate In-Situ Gels Another interesting patent focuses on the use of pH-triggered polymeric nanoparticulate in situ gels for ocular delivery of Acetazolamide. This formulation aims to enhance conjunctival permeation and prolong the precorneal residence time of the drug, addressing the challenges associated with traditional eye drops. The incorporation of nanoparticles represents a novel approach to improving the bioavailability of Acetazolamide in treating glaucoma [5].  ### 3. Innovative Gelling Agents and Excipients Additionally, there are patents related to the use of innovative gelling agents and excipients that enhance the stability and effectiveness of Acetazolamide formulations. These innovations often focus on optimizing the interaction between the drug and the excipients to improve solubility, stability, and release profiles, which are critical for achieving the desired therapeutic outcomes [6].  ## Conclusion The exploration of innovative formulation strategies for Acetazolamide highlights the importance of formulation science in developing effective therapeutic options. The combination of novel excipients, advanced delivery mechanisms, and recent patent developments underscores the potential for improved patient outcomes and the ongoing evolution of Acetazolamide formulations.  ## Sources [1] Kerle, V., et al. (2022). Formulation and evaluation of topical gel containing combination of dapsone and acetazolamide. International Journal of Health Sciences.  [2] Chandur, V. K., et al. Formulation and Evaluation of Acetazolamide Tablet by Liquisolid Technique. RGUHS Journal of Pharmaceutical Sciences.  [3] Ali, F., et al. Formulation and evaluation of acetazolamide loaded in-situ gel for the treatment of Glaucoma. Journal of Research in Pharmacy.  [4] EP0540813A1 - Sustained release formulations of acetazolamide - Google Patents.  [5] Development of acetazolamide-loaded, pH-triggered polymeric nanoparticulate in situ gel for sustained ocular delivery - PubMed.  [6] Advanced Formulation Approaches for Ocular Drug Delivery: State-Of-The-Art and Recent Patents - PubMed.  # Optimizing Manufacturing Processes for Acetazolamide: A Patent Research Perspective  ## Current Manufacturing Processes for Acetazolamide  The manufacturing of Acetazolamide, a carbonic anhydrase inhibitor used primarily in the treatment of glaucoma and other conditions, involves several critical chemical reactions. The primary method for synthesizing Acetazolamide begins with the reaction between hydrazine hydrate and ammonium thiocyanate, which produces 5-amino-2-mercapto-1,3,4-thiadiazole as an intermediate. This step is foundational, as it sets the stage for subsequent reactions that lead to the final product [1].  ### Inefficiencies in Traditional Methods  Despite the established processes, there are notable inefficiencies that can hinder the overall yield and purity of Acetazolamide. One such inefficiency is highlighted in the direct tabletting process described in US3671633A, which allows for the production of tablets without the need for granulation or slugging. While this method can save time and reduce costs, it requires precise control over the particle size distribution of acetazolamide crystals. This requirement can complicate scaling up the process for larger production volumes, as maintaining the desired particle size becomes increasingly challenging [2].  Moreover, the oxidation processes used in synthesizing Acetazolamide derivatives present additional opportunities for improvement. Recent studies suggest that substituting chlorine gas with sodium hypochlorite for oxidation not only enhances safety and environmental conditions but also improves the efficiency of the synthesis [3]. This shift could lead to a more streamlined manufacturing process that aligns with modern safety standards.  ## Regulatory Compliance and Good Manufacturing Practices (GMP)  Regulatory compliance, particularly concerning Good Manufacturing Practices (GMP), is a critical aspect of the manufacturing process for Acetazolamide. The FDA's GMP regulations establish minimum standards for the manufacturing, processing, packing, or holding of drug products to ensure their safety, quality, and efficacy [4].  ### Challenges in Adhering to GMP  Manufacturers face several challenges in adhering to GMP, primarily due to the need for rigorous in-process controls and testing. The FDA's recent guidance emphasizes the importance of defining and justifying the timing and nature of in-process controls to monitor critical quality attributes. This requirement can complicate the manufacturing process, necessitating additional testing and documentation, which can slow down production and increase costs.  The integration of advanced manufacturing technologies, while beneficial for enhancing product quality and scaling up production, also requires manufacturers to adapt their processes to meet GMP standards. This includes ensuring that new technologies are validated and that staff are adequately trained to operate them [5]. The transition to these advanced methods can be resource-intensive and may lead to temporary disruptions in production.  Furthermore, manufacturers must navigate the complexities of global supply chains and varying regulatory environments, which can further complicate compliance efforts. Different regions may have specific requirements that necessitate adjustments in manufacturing practices, impacting overall efficiency [6].  ## Patent Eligibility and Cross-Licensing Opportunities  When evaluating the patent landscape for Acetazolamide manufacturing processes, several key factors must be considered to determine patent eligibility and potential cross-licensing opportunities.  ### Key Factors for Patent Eligibility  1. \*\*Novelty and Non-obviousness\*\*: The core criteria for patent eligibility are that the manufacturing process must be novel and non-obvious. Innovations in the synthesis of Acetazolamide, such as the use of alternative reagents or innovative techniques that enhance yield or purity, could be patentable. For instance, the substitution of chlorine gas with sodium hypochlorite in oxidation processes represents a potential area for patenting due to its safety and efficiency improvements [3].  2. \*\*Existing Patents\*\*: A thorough analysis of existing patents is crucial. For Acetazolamide, several patents related to its synthesis and formulation exist, such as US3671633A, which outlines a direct tabletting process without granulation [2]. Understanding the scope and claims of these patents helps identify potential freedom-to-operate issues and areas where new patents could be filed.  3. \*\*Cross-licensing Opportunities\*\*: Given the competitive nature of the pharmaceutical industry, cross-licensing can be a strategic move. Companies may seek to collaborate on specific technologies or processes that complement their existing patents. For example, if one company holds a patent on a novel synthesis route while another has a patent on a unique formulation, they could explore cross-licensing agreements to enhance their product offerings and market reach.  ### Trends in Patent Filings  An interesting trend observed in the patent landscape for Acetazolamide is the increasing focus on derivatives and related compounds. As research continues to explore new therapeutic applications for Acetazolamide and its derivatives, there is a growing number of patent filings in this area. This trend indicates a potential shift towards developing new formulations or combinations that could expand the market for Acetazolamide [6].  ### Regulatory Considerations in Patent Strategy  The evolving regulatory landscape, particularly regarding GMP and advanced manufacturing technologies, can also influence patent strategies. Innovations that align with regulatory trends may be more attractive for patenting, as they can provide a competitive edge in compliance and marketability.  ## Sources  [1] https://www.procurementresource.com/production-cost-report-store/acetazolamide  [2] https://patents.google.com/patent/US3671633A/en  [3] https://link.springer.com/article/10.1007/s11696-024-03551-x  [4] https://www.arnoldporter.com/en/perspectives/advisories/2025/01/fda-guidance-good-manufacturing-practices-for-drugs  [5] https://qualia-bio.com/blog/pharmaceutical-engineering-gmp-standards-guide-2025/  [6] https://jafconsulting.com/blog/top-gmp-guidelines-and-best-practices-for-2025/  [6] https://synapse.patsnap.com/drug/79bb4244ab47435c93308f3fda1ddfed   # Comprehensive Analysis of Impurities and Stability Issues in Acetazolamide: Patent Research Insights  ## Background on Acetazolamide Acetazolamide is a carbonic anhydrase inhibitor primarily used in the treatment of glaucoma, epilepsy, and altitude sickness. Its therapeutic efficacy is closely linked to its stability and purity, making the understanding of its degradation pathways and impurity profiles critical for pharmaceutical development. The stability of Acetazolamide can be significantly affected by various factors, including environmental conditions, synthesis methods, and formulation components. This report delves into the findings related to the impurities and stability of Acetazolamide, highlighting novel insights and potential patentable solutions.  ## Impurity Profiling and Stability Analysis ### Degradation Pathways In the analysis of Acetazolamide, significant degradation was observed under stress conditions, particularly during acid and base hydrolysis. The degradation studies revealed the formation of major degradants, which were characterized using advanced analytical techniques such as Liquid Chromatography-Mass Spectrometry (LC-MS), Fourier Transform Infrared Spectroscopy (FTIR), and Nuclear Magnetic Resonance (NMR) spectral analysis. The validated stability-indicating LC method developed for this analysis demonstrated a resolution greater than 2 between Acetazolamide and its process-related impurities, which included several identified impurities (imp-1, imp-2, imp-3, imp-4) and degradation products [1].  The mass balance of the stress samples was found to be close to 99.6%, indicating that the method is effective for quantitative determination in the presence of impurities and degradation products. This high mass balance is crucial for regulatory compliance and ensures the reliability of the results in a pharmaceutical context [1][2].  ### Stress Conditions and Their Impact The most significant degradation of Acetazolamide was observed under stress conditions that included hydrolysis (both acidic and basic), oxidation, photolysis, and thermal degradation. These conditions were applied as per the International Conference on Harmonization (ICH) guidelines to assess the stability-indicating power of the developed method [1].   During forced degradation studies, it was noted that Acetazolamide was particularly susceptible to degradation in acidic and basic environments. The major degradant formed under these conditions was identified through various analytical techniques, underscoring the importance of considering pH levels in both synthesis methods and formulation components, as they can significantly impact the stability of the drug [1][2].  ### Role of Formulation Components The formulation components, such as excipients used in the dosage forms, can also influence the stability of Acetazolamide. Certain excipients may promote hydrolysis or oxidation, leading to increased levels of impurities. Therefore, careful selection of formulation components is essential to mitigate these stability issues and ensure the integrity of the final product. The interaction between Acetazolamide and excipients must be thoroughly evaluated to prevent adverse effects on stability [1][2].  ## Strategies for Mitigating Stability Issues ### Use of Novel Stabilizers Several strategies have been identified to mitigate stability issues and reduce impurity levels in Acetazolamide formulations. One effective approach is the use of novel stabilizers that can enhance the stability of the drug under various conditions. For instance, incorporating specific antioxidants can help prevent oxidative degradation, while pH stabilizers can be used to maintain the drug's integrity in formulations that may otherwise promote hydrolysis [1].  ### Controlled-Release Formulations The formulation of Acetazolamide in a controlled-release matrix is another viable strategy. This approach not only helps in maintaining the drug's stability but also improves its bioavailability and therapeutic efficacy. By controlling the release rate, the exposure of Acetazolamide to potentially degrading conditions can be minimized, thereby extending its shelf life and ensuring consistent therapeutic effects [2].  ### Patentable Solutions The development of a unique formulation that combines Acetazolamide with specific stabilizers or excipients that have shown to significantly enhance stability could be a strong candidate for patent protection. This could include formulations that utilize novel polymeric carriers or encapsulation techniques that protect the drug from environmental factors leading to degradation. Such innovations not only aim to extend the shelf life of Acetazolamide but also ensure that the drug remains effective and safe for patient use [1][2].  ## Conclusion The analysis of impurities and stability issues in Acetazolamide reveals critical insights into the degradation pathways and the impact of formulation components. The identification of specific degradation products and the development of validated stability-indicating methods are essential for ensuring the safety and efficacy of Acetazolamide. Furthermore, the exploration of novel stabilizers and controlled-release formulations presents exciting opportunities for patentable solutions that can enhance the stability and therapeutic potential of this important pharmaceutical compound.  ## Sources [1] A validated stability-indicating LC method for acetazolamide in the presence of degradation products and its process-related impurities - ScienceDirect  [2] Reverse-phase LC method development and validation for the quantification of acetazolamide and its specified and unspecified degradation products in hard gelatin capsule formulations.  ---  - Conclusions.  The comprehensive analysis of Acetazolamide underscores its significance as a versatile therapeutic agent, particularly in treating glaucoma, epilepsy, and altitude sickness. This report highlights innovative synthesis methodologies, including green chemistry approaches that enhance safety and efficiency. The exploration of polymorphic variations and their implications for drug performance emphasizes the need for careful characterization in formulation development. Additionally, the patent landscape reveals opportunities for novel derivatives and formulations, including sustained-release and in-situ gel systems. Addressing stability and impurity challenges through advanced formulation strategies further positions Acetazolamide for future pharmaceutical advancements, ensuring its continued relevance in clinical applications. |

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