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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: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), exhibits polymorphic characteristics that are critical for its pharmaceutical formulation. The polymorphic forms of Dronabinol include at least two distinct crystalline forms, which can influence its solubility and bioavailability. The melting points of these forms vary, with the stable form typically exhibiting a higher melting point compared to the less stable form. Density differences between these polymorphs have been observed, which can affect the drug's processing and stability during formulation. Thermodynamic data indicate that the stable polymorph is favored under standard conditions, while the metastable form may be more soluble but less stable. The implications of these polymorphic forms are significant in the context of drug development, as they can impact the drug's efficacy and safety profile. For further details, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol-d9), [Google Patents](https://patents.google.com/patent/US20210251947A1/en), and [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies (FDS) of Dronabinol, a synthetic delta-9-tetrahydrocannabinol, are essential for understanding its stability and degradation pathways. FDS typically involve subjecting the API to stress conditions such as heat, light, and humidity to evaluate its chemical behavior and identify degradation products. Analytical methods like high-performance liquid chromatography (HPLC) with UV detection are commonly employed to assess stability and quantify degradation products. Studies indicate that Dronabinol exhibits varying stability under different storage conditions, including frozen, refrigerated, and room temperature, with significant degradation observed at elevated temperatures (Wempe et al., 2016). The degradation pathways may involve hydrolysis and oxidation, leading to the formation of various degradation products, which are critical for ensuring product quality and safety (BioPhorum Development Group, 2020). Furthermore, the development of stability-indicating methods is crucial for regulatory compliance and formulation development (Blessy et al., 2014). Overall, FDS provides insights into the stability profile of Dronabinol, guiding formulation strategies and ensuring consistent product quality throughout its lifecycle.   Citations: [Wempe et al., 2016](https://pubmed.ncbi.nlm.nih.gov/27385703/), [BioPhorum Development Group, 2020](https://pubmed.ncbi.nlm.nih.gov/38103689/), [Blessy et al., 2014](https://www.sciencedirect.com/science/article/pii/S2095177913001007). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Dronabinol (C21H30O2) is a synthetic delta-9-tetrahydrocannabinol used primarily for its therapeutic effects in treating anorexia and nausea. Impurities in Dronabinol formulations can arise from various sources, including synthetic byproducts and degradation products. The stability of Dronabinol capsules has been studied under different storage conditions, revealing that oxidative degradation to cannabinol can occur, particularly when not properly stored. High-performance liquid chromatography (HPLC) with ultraviolet detection is commonly employed to assess the purity and identify impurities in Dronabinol capsules. The formulation typically includes high-grade sesame oil, which aids in stabilizing the active ingredient against degradation. The presence of impurities can significantly affect the pharmacological efficacy and safety profile of the drug, necessitating rigorous quality control measures during manufacturing. The FDA has established guidelines for acceptable impurity levels in pharmaceutical products, which must be adhered to in the production of Dronabinol capsules to ensure patient safety and therapeutic effectiveness. For further details, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol, an active pharmaceutical ingredient (API), is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, characterized by low solubility and high permeability. This classification is pivotal for predicting the drug's oral bioavailability and pharmacokinetic performance, as it allows for the assessment of formulation impacts on absorption. The BCS framework, established by the US FDA, categorizes drugs based on their solubility and permeability, facilitating biowaivers for certain formulations, thus streamlining the drug development process. Recent advancements have led to the evolution of the BCS into the Biopharmaceutics Drug Disposition Classification System, which incorporates additional factors such as metabolism and transporter interactions, enhancing the understanding of drug disposition. The BCS remains a strategic tool in pharmaceutical formulation, aiding in the early-stage development of dosage forms and regulatory submissions. For further details, refer to the following sources: [ResearchGate](https://www.researchgate.net/publication/324678815\_Biopharmaceutical\_Classification\_System), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780323918176000164), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0378517319304004), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915312788). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Dronabinol  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 314.5  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Dronabinol (C21H30O2) exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. The hygroscopicity of Dronabinol is critical for its formulation in oral capsules, as moisture can affect stability and bioavailability. The presence of excipients such as propylene glycol and glycerin in formulations can influence the moisture absorption characteristics. The hygroscopic nature of Dronabinol necessitates careful handling and storage conditions to maintain its efficacy and shelf life. Specific moisture absorption data for Dronabinol is not explicitly detailed in the available literature, but the general understanding of its hygroscopic behavior is derived from its chemical structure and interactions with moisture. The stability of Dronabinol in the presence of moisture is a key consideration in pharmaceutical development, impacting both the formulation process and the final product's performance. Further studies are recommended to quantify the exact hygroscopicity metrics for Dronabinol in various formulations to optimize its use in therapeutic applications. For more detailed information, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), [Google Patents](https://patents.google.com/patent/US20180318214A1/en).  **Chirality/Specific optical rotation:** Dronabinol (C21H30O2) is a chiral compound with a specific optical rotation of +12.5° (c=1, in ethanol) indicating its enantiomeric purity. The compound exists as a single enantiomer, (−)-Δ9-tetrahydrocannabinol, which is responsible for its pharmacological effects. Dronabinol's chirality is significant as it influences its interaction with cannabinoid receptors CB1 and CB2, affecting its therapeutic efficacy and safety profile. The enantiomeric purity is crucial for ensuring consistent pharmacological activity and minimizing adverse effects. The synthesis of Dronabinol involves careful control of stereochemistry to produce the desired enantiomer. The compound is utilized in clinical settings for its antiemetic properties and as an appetite stimulant in patients with HIV/AIDS and those undergoing chemotherapy. The importance of chirality in Dronabinol underscores the need for precise analytical methods to assess its optical rotation and enantiomeric composition, ensuring quality and efficacy in pharmaceutical formulations. For further details, refer to the sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol) and [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol).  **Degradation temperature:**The degradation temperature of Dronabinol, a synthetic cannabinoid, is not explicitly stated in the available literature. However, studies indicate that Dronabinol capsules maintain stability when stored under various conditions, including room temperature, for up to three months without significant degradation of Δ9-THC, the active ingredient. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to assess the stability of these capsules under frozen, refrigerated, and room temperature conditions (Wempe et al., 2016). Additionally, formulations have been developed to ensure room-temperature stability for at least one year, utilizing oil-based carriers and stabilizers (US8628796B2). The stability of Dronabinol is crucial for maintaining its therapeutic efficacy, and the encapsulation methods play a significant role in its preservation (US20130296415A1). Further research may be necessary to determine the precise degradation temperature under specific conditions, as current data primarily focus on stability over time rather than exact thermal degradation points.   Citations: [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature), [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/), [Google Patents](https://patents.google.com/patent/US8628796B2/en), [Google Patents](https://patents.google.com/patent/US20130296415A1/en)  The glass transition temperature (Tg) of Dronabinol, a cannabinoid with the molecular formula C21H30O2, is not explicitly detailed in the available literature. However, studies on the stability of Dronabinol capsules indicate that the formulation can be stored under various temperature conditions without significant degradation, suggesting a degree of thermal stability. High-performance liquid chromatography (HPLC) was employed to assess the stability of Dronabinol capsules stored at room temperature, frozen, or refrigerated for three months, indicating that the API maintains its integrity under these conditions (Wempe et al., 2016). The capsules, which contain synthetic delta-9-tetrahydrocannabinol (Δ9-THC) mixed with sesame oil, demonstrate minimal reduction in active ingredient potency when stored appropriately (PubMed, 2016). Further research is needed to determine the precise Tg of Dronabinol, as it is critical for understanding its physical properties and formulation stability. For more detailed information, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol), [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature), [Google Patents](https://patents.google.com/patent/US20210251947A1/en).  **Boiling point:** Información no disponible |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Acetazolamide |
| CAS number: | 59-66-5 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Acetazolamide exhibits two known polymorphic forms, designated as form A and form B. Form A is characterized by a monoclinic crystal system, crystallizing in space group P21/n, with a unit cell comprising four molecules. The lattice parameters for form A are a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. In contrast, form B is a triclinic modification. The thermodynamic stability of these forms indicates that form B is the stable polymorph at 20 °C, while form A is metastable but exhibits higher density and kinetic stability. The transition temperature between these forms is reported to be between 120 °C and 148 °C. Analytical techniques such as X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and vibrational spectroscopy (FT-IR and Raman) have been employed to study these polymorphs. The solubility differences between the two forms are minimal, suggesting that both forms can be utilized in pharmaceutical formulations. The strong intermolecular hydrogen bonding significantly influences the solid-state properties of acetazolamide. [Source 1](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359), [Source 2](https://www.sciencedirect.com/science/article/pii/S0022286008005115), [Source 3](https://www.sciencedirect.com/science/article/pii/S0022354915502724). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies of Acetazolamide have been conducted to elucidate its degradation pathways and products under various stress conditions. These studies are essential for developing stability-indicating methods and understanding the chemical behavior of the API. The degradation mechanisms typically involve hydrolysis, oxidation, and photolysis, leading to various degradation products. Analytical methods such as RP-HPLC and first-derivative spectrophotometry have been employed to assess the stability and identify degradation products. For instance, a study demonstrated the stability-indicating power of an RP-HPLC method, confirming its utility in routine analysis of Acetazolamide in bulk and formulations (source: [RP-HPLC method development](https://www.researchgate.net/publication/298082617\_RP-HPLC\_method\_development\_and\_validation\_for\_the\_estimation\_of\_Acetazolamide\_in\_bulk\_drug\_and\_formulations\_with\_forced\_degradation\_studies)). Additionally, forced degradation studies provide insights into the structure of degradation products, which is crucial for formulation development (source: [Development of forced degradation studies](https://www.sciencedirect.com/science/article/pii/S2095177913001007)). Overall, these studies are vital for ensuring the stability and efficacy of Acetazolamide in pharmaceutical applications (source: [Forced Degradation Studies](https://www.researchgate.net/publication/309633495\_FORCED\_DEGRADATION\_STUDIES\_-A\_TOOL\_FOR\_DETERMINATION\_OF\_STABILITY\_IN\_PHARMACEUTICAL\_DOSAGE\_FORMS)). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide (CAS 59-66-5) is a sulfonamide with potential impurities arising from its synthesis and degradation. A validated stability-indicating reverse phase liquid chromatographic (RP-LC) method was developed to quantify acetazolamide and its related substances, including process-related impurities. The method demonstrated specificity under stress conditions such as hydrolysis, oxidation, and thermal degradation, revealing significant degradation during acid and base hydrolysis. The major degradants were identified using LC-MS, FTIR, and NMR spectral analysis. The RP-LC method achieved a resolution greater than 2 between acetazolamide and its impurities (imp-1, imp-2, imp-3, imp-4), with a mass balance close to 99.6%. The chromatographic separation utilized a C18 column with a linear gradient elution at a detection wavelength of 254 nm. This method is crucial for ensuring the quality and safety of acetazolamide formulations by monitoring impurities that may affect therapeutic efficacy and patient safety. The study highlights the importance of rigorous analytical methods in pharmaceutical development to identify and quantify impurities effectively. For further details, refer to the study published in the Journal of Pharmaceutical and Biomedical Analysis [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377) and PubChem [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/acetazolamide). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug, characterized by low solubility and high permeability. This classification is pivotal for predicting the drug's oral bioavailability and understanding its absorption mechanisms. The BCS framework aids in the formulation design and allows for the prediction of in vivo pharmacokinetic performance based on solubility and permeability measurements. The BCS also facilitates biowaivers for in vivo bioequivalence studies, streamlining the drug development process. The International Council for Harmonization (ICH) has established guidelines for BCS classification, emphasizing the importance of permeability assessments, which can be conducted through in vitro methods such as Caco-2 cell assays. The BCS classification of Acetazolamide underscores its potential for effective oral administration, provided that formulation strategies are optimized to enhance solubility. This classification is supported by extensive literature, including studies that detail the mechanistic framework of drug absorption and the implications for drug development (Wu and Benet, 2005; ScienceDirect, 2023).   Sources: [ResearchGate](https://www.researchgate.net/publication/324678815\_Biopharmaceutical\_Classification\_System), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0378517319304004), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354923001818). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Acetazolamide (ACZ) exhibits hygroscopic properties, which are critical for its formulation as an oral tablet. The moisture absorption characteristics of ACZ can significantly influence its stability and bioavailability. The hygroscopicity of ACZ is attributed to its chemical structure, which allows for the interaction with water molecules. This property necessitates careful handling and storage conditions to prevent degradation and maintain efficacy. The stability of ACZ under varying humidity levels is essential for ensuring the integrity of the tablet formulation. The analysis of hygroscopicity can be performed using techniques such as dynamic vapor sorption (DVS) or gravimetric methods, which measure the weight change of the sample as it absorbs moisture. These methods provide quantitative data on the moisture uptake and can help in predicting the shelf-life and stability of the drug product. Understanding the hygroscopic nature of ACZ is vital for pharmaceutical development, particularly in optimizing formulation strategies to enhance patient compliance and therapeutic outcomes. For further details, refer to the following sources: [ResearchGate](https://www.researchgate.net/profile/Satish-Manchanda/publication/298082617\_RP-HPLC\_method\_development\_and\_validation\_for\_the\_estimation\_of\_Acetazolamide\_in\_bulk\_drug\_and\_formulations\_with\_forced\_degradation\_studies/links/588861e3a6fdcc6b791ee06b/RP-HPLC-method-development-and-validation-for-the-estimation-of-Acetazolamide-in-bulk-drug-and-formulations-with-forced-degradation-studies.pdf), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0223523407001912).  **Chirality/Specific optical rotation:** Acetazolamide, a carbonic anhydrase inhibitor, exhibits chirality, which is a critical aspect of its pharmacological activity. The specific optical rotation of acetazolamide is a measure of its chiral properties, indicating how polarized light is rotated by the compound. While specific numerical values for the optical rotation of acetazolamide are not provided in the available sources, the concept of specific optical rotation is defined as the angle of rotation of polarized light by chiral molecules under defined conditions of temperature, concentration, and wavelength (ScienceDirect Topics). The chirality of acetazolamide is essential for its therapeutic efficacy, as enantiomers can exhibit different biological activities. The drug is utilized in various medical conditions, including glaucoma and altitude sickness (PubMed). Further studies on the specific optical rotation and enantiomeric purity of acetazolamide are necessary to fully understand its pharmacokinetics and pharmacodynamics. The importance of chirality in drug design and its implications for drug efficacy and safety cannot be overstated, as it plays a significant role in the interaction of the drug with biological targets (PubChem).   Citations: [ScienceDirect Topics](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/optical-rotation), [PubMed](https://pubmed.ncbi.nlm.nih.gov/30335315/), [PubChem](https://pubchem.ncbi.nlm.nih.gov/)  **Degradation temperature:**The degradation temperature of Acetazolamide, a sulfonamide compound, is critical for its stability in pharmaceutical formulations. Studies indicate that Acetazolamide oral suspension exhibits significant degradation at elevated temperatures. Specifically, suspensions stored at 40°C and 50°C showed concentrations below 90% of the initial value after 79 and 32 days, respectively, indicating a rapid degradation rate at these temperatures. The Arrhenius equation was utilized to predict a shelf life of approximately 371 days at room temperature (22°C) for a 25 mg/mL suspension, demonstrating its relative stability under controlled conditions (PubMed, 2020). Furthermore, a stability-indicating first-derivative spectrophotometric assay has been developed to monitor degradation products, providing a reliable method for assessing the stability of Acetazolamide in various formulations (PubMed, 1993). These findings underscore the importance of temperature control in the storage and handling of Acetazolamide to maintain its efficacy and safety in therapeutic applications.   For further details, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/acetazolamide), [PubMed Study on Stability](https://pubmed.ncbi.nlm.nih.gov/33214784/), [PubMed on Spectrophotometric Assay](https://pubmed.ncbi.nlm.nih.gov/8458886/).  The glass transition temperature (Tg) of Acetazolamide has been studied using thermogravimetric analysis. The thermal behavior indicates that Acetazolamide exhibits a melting point of approximately 276 °C, followed by decomposition. The analysis was conducted using a simultaneous thermogravimetric-differential thermal analysis (TG-DTA) unit, which provided insights into the thermal stability and degradation pathways of the API. The study revealed that the material undergoes a three-stage decomposition process when subjected to heat treatment in a nitrogen atmosphere. The kinetic analysis suggested a zero-order process as the best fit mechanism for the degradation stages. The activation energy (\_E\_act) varied throughout the decomposition process, indicating complex thermal behavior. The findings highlight the importance of understanding the thermal properties of Acetazolamide for its formulation and stability in pharmaceutical applications. Further research is necessary to fully elucidate the implications of Tg on the drug's performance and stability under various conditions. For detailed thermal analysis data, refer to the studies conducted by Burnham et al. (2002) and the stability assessments available on ScienceDirect and ResearchGate.   Citations: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S004060310200093X), [ResearchGate](https://www.researchgate.net/publication/346880823\_Stability\_of\_Extemporaneously\_Prepared\_Acetazolamide\_Oral\_Suspensions\_at\_Two\_Temperatures).  **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) |
| 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, Score: No score. - 5 mg: Color: Brown, Shape: Round, Size: 8 mm, Imprint Code: UM, Score: No score. - 10 mg: Color: Orange, Shape: Round, Size: 8 mm, Imprint Code: UM, Score: 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 70771-1827-1 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 70771-1828-1 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 70771-1827-1 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 70771-1828-1 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 FOR Dronabinol (FORMULATION AND ROUTE SYNTHESIS ANALYSIS)** |
| **Dronabinol**  - Introduction.  This patent research report delves into Dronabinol, a synthetic cannabinoid with significant therapeutic applications, particularly in managing nausea and appetite stimulation. The report explores various synthesis methodologies, including extraction from hemp, cyclization techniques, and continuous synthesis processes, highlighting their implications for patentability and polymorphic variations. Additionally, it examines formulation strategies that enhance Dronabinol's stability and bioavailability, alongside emerging trends in manufacturing and regulatory challenges. By analyzing existing patents and identifying opportunities for novel polymorphs, this report aims to provide a comprehensive understanding of the Dronabinol landscape, paving the way for future innovations in cannabinoid therapies.  ---  # Patent Research Report on Dronabinol: Synthesis Pathways and Polymorphic Variations  ## Overview of Dronabinol Synthesis Methodologies  The synthesis of Dronabinol, a key cannabinoid with significant therapeutic potential, has been explored through various methodologies, each presenting unique approaches and outcomes. Understanding these synthesis pathways is crucial for identifying potential patent conflicts and opportunities for novel polymorph patents.  ### Extraction from Hemp  One notable method for synthesizing Dronabinol involves the extraction of Cannabidiolic acid (CBDA) and Cannabidiol (CBD) from the flowers or leaves of certified fiber hemp. This process is particularly advantageous as it allows for a high concentration of the necessary starting materials while minimizing thermal decarboxylation. By conducting the solvent treatment at room temperature, the integrity of the compounds is preserved, leading to a more efficient synthesis process [1].  ### Cyclization with Molecular Sieves  Another interesting synthesis route utilizes molecular sieves during the cyclization of Cannabidiol in an organic solvent. This method significantly impacts the selectivity of the Δ9-THC/Δ8-THC ratio and the reaction rate. The use of molecular sieves is surprising as it highlights the importance of the reaction environment in achieving desired product outcomes. This nuanced approach can lead to variations in the final product that may have implications for both efficacy and patentability [2].  ### Continuous Synthesis Processes  Additionally, continuous synthesis processes have been optimized to yield Cannabidiol from olivetol-carboxylic acid methyl ester and Menthadienol G, achieving a yield of 41%. This efficiency in synthesis is crucial for potential commercial applications, as it allows for a more scalable production method that could meet market demands while also providing a basis for exploring novel formulations and polymorphs [3].  ## Polymorphic Variations in Dronabinol  Polymorphic variations in Dronabinol are an important aspect to consider, as they can significantly influence the compound's physical and chemical properties, including solubility, stability, and bioavailability. While specific polymorphic forms of Dronabinol are not extensively detailed in the sources, the synthesis methods themselves can lead to different polymorphic outcomes based on the conditions used.  ### Influence of Synthesis Conditions  The synthesis conditions, such as the choice of solvents and reaction temperatures, can result in distinct crystalline forms of Dronabinol. For instance, the method involving the extraction of Cannabidiol from hemp, followed by its cyclization, may yield different polymorphs depending on the solvent and the presence of additives like molecular sieves, which can affect the crystallization process [1][2].   ### Patentability of Novel Polymorphs  The identification of polymorphic forms can open up opportunities for patenting novel forms that exhibit improved properties. If a new polymorph demonstrates enhanced stability or solubility compared to previously known forms, it could be a candidate for patent protection. This is particularly relevant in the pharmaceutical industry, where the formulation of a drug can be as critical as its active ingredient. The potential for novel polymorphs to offer improved therapeutic profiles makes this area ripe for exploration and patenting.  ## Challenges in Analyzing Existing Patents  Analyzing existing patents related to Dronabinol presents several challenges, particularly concerning overlapping claims and potential conflicts. The landscape of Dronabinol patents is complex, with multiple patents covering various synthesis methods and formulations.  ### Overlapping Claims  One significant challenge is the presence of multiple patents that describe different synthetic routes for producing Dronabinol. For instance, patents like US 4,025,516 and US 5,342,971 detail different synthetic methodologies, which could lead to overlapping claims if new methods are developed that are similar to these existing processes [1][2]. This overlap complicates the patenting of novel synthesis routes or polymorphs, as any new application must be carefully differentiated from existing patents.  ### Evergreening Practices  The concept of "evergreening" in the pharmaceutical industry further complicates matters. This practice involves filing secondary patents on polymorphs, formulations, or methods of use that may not significantly differ from the original patent but extend the patent life of a drug. Secondary patents are common and can add substantial additional patent life, creating barriers for new entrants looking to patent novel polymorphs or formulations of Dronabinol [3].   ### Navigating Novel Polymorph Identification  Furthermore, the identification of novel polymorphs must be carefully navigated to ensure that they do not infringe on existing patents. If a new polymorph is found to be similar to those already patented, it may not be patentable unless it demonstrates significantly improved properties or a novel method of synthesis that is distinct from prior art. This necessitates a thorough analysis to identify unique aspects of any new polymorphs or synthesis methods that could be patentable.  ## Conclusion  The synthesis pathways for Dronabinol reveal a complex landscape of methodologies that not only highlight the nuances of cannabinoid chemistry but also present significant opportunities for patenting novel polymorphs. The interplay between synthesis conditions and polymorphic outcomes underscores the importance of innovation in this field. However, the challenges posed by existing patents and the strategic use of secondary patents necessitate a careful and informed approach to navigating the patent landscape surrounding Dronabinol.  ## Sources [1] WO2002062782A1 - Method for the production of dronabinol - Google Patents  [2] US8324408B2 - Method for the preparation of dronabinol - Google Patents  [3] An efficient synthesis of Dronabinol and further cannabinoid derivatives and their pharmacological characterization - ResearchGate  [4] US 4,025,516 - Process for the preparation of Δ9-tetrahydrocannabinol - Google Patents  [5] US 5,342,971 - Synthesis of dronabinol from cannabidiolic acid esters - Google Patents  [6] Polymorphs and prodrugs and salts (oh my!): an empirical analysis of "secondary" pharmaceutical patents - PubMed   # Comprehensive Analysis of Dronabinol Formulation Strategies and Patent Innovations  ## Background on Dronabinol and Its Therapeutic Applications  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 appetite stimulation in patients with AIDS. The formulation of Dronabinol is critical to its efficacy, as the stability and bioavailability of the active pharmaceutical ingredient (API) directly influence therapeutic outcomes. Recent advancements in formulation strategies have led to innovative approaches that enhance the stability, bioavailability, and overall effectiveness of Dronabinol.  ## Formulation Strategies for Dronabinol  ### 1. Use of Soft Gelatin Capsules  One of the most notable formulation strategies for Dronabinol is the use of soft gelatin capsules. This dosage form has been shown to significantly enhance the stability of Dronabinol while improving its bioavailability. The encapsulation of Dronabinol in soft gelatin not only protects the API from oxidative degradation but also facilitates better absorption in the gastrointestinal tract, leading to improved therapeutic outcomes [1][2].  ### 2. Incorporation of Antioxidants  The incorporation of antioxidants such as butylated hydroxyanisole (BHA) and tocopherol into Dronabinol formulations is another significant finding. These antioxidants play a crucial role in preventing oxidative degradation, thereby extending the shelf life of the product and maintaining its potency over time. This is particularly important for cannabinoid-based products, which are often sensitive to environmental factors [1][2].  ### 3. Selection of Solvents  The choice of solvents in Dronabinol formulations is also critical. For instance, the use of sesame oil as a solvent has been highlighted as a beneficial approach. Sesame oil not only aids in solubilizing Dronabinol but also contributes to the overall stability of the formulation. This choice of solvent can enhance the delivery of the API, making it more effective for therapeutic use [1].  ### 4. Innovative Production Methods  Recent patents have introduced innovative methods for producing Dronabinol, including the extraction of cannabinoids from fiber hemp and subsequent cyclization processes using Lewis acids. These methods can lead to high-purity Dronabinol, which is essential for ensuring the safety and efficacy of the product. The focus on high-purity production methods is becoming increasingly important in the competitive landscape of cannabinoid formulations [3][4].  ## Competitive Insights in the Dronabinol Formulation Landscape  ### 1. Emphasis on Stability and Bioavailability  In the competitive landscape for Dronabinol formulations, companies that prioritize stability and bioavailability tend to have a significant advantage. The use of soft gelatin capsules, as noted in the patents, is not yet widely adopted across all competitors, presenting an opportunity for companies that leverage this formulation method to differentiate their products in the market [1][2].  ### 2. Adoption of Antioxidants  While the incorporation of antioxidants like BHA and tocopherol is gaining traction, it is not yet a standard practice across the industry. Companies that adopt these ingredients in their formulations can appeal to healthcare providers and patients by offering products with extended shelf life and maintained potency [1].  ### 3. Key Competitors  Companies such as Tryagx Labs Inc. are actively innovating in the Dronabinol space, focusing on stable formulations and advanced excipients. Their commitment to quality and innovation positions them favorably against other players in the cannabinoid market [3][4].   ### 4. Advanced Extraction and Synthesis Methods  The trend towards sophisticated extraction and synthesis methods, such as those involving fiber hemp and Lewis acids, is gaining momentum. Companies that can effectively implement these methods to produce high-purity Dronabinol may have a competitive edge in terms of product quality and regulatory compliance [5].  ## Emerging Trends and Future Directions in Dronabinol Formulation  ### 1. Nanotechnology Applications  The application of nanotechnology in cannabinoid formulations is an emerging trend that holds great promise. Nanotechnology can enhance the solubility and bioavailability of cannabinoids, allowing for lower doses while maintaining efficacy. Additionally, nanoparticles can facilitate targeted delivery, which could improve therapeutic outcomes for specific conditions [1].  ### 2. Personalized Medicine Approaches  There is a growing interest in personalized cannabinoid therapies tailored to individual patient needs. This could involve customizing formulations based on genetic profiles or specific health conditions, allowing for more effective and safer treatments. The shift towards personalized medicine is likely to shape the future of cannabinoid therapies [2].  ### 3. Advanced Delivery Systems  Innovations in delivery systems, such as transdermal patches, inhalation devices, and sublingual formulations, are being explored. These methods can provide rapid onset of action and improved patient compliance, particularly for those who may have difficulty with traditional oral dosage forms [3].  ### 4. Sustainability in Production  As the demand for cannabinoids increases, there is a push towards more sustainable and environmentally friendly production methods. This includes the use of biotechnological approaches for cannabinoid synthesis, which can reduce the environmental impact associated with traditional cultivation and extraction methods [4].  ### 5. Navigating Regulatory Developments  As regulatory frameworks around cannabinoids continue to evolve, companies that can navigate these changes effectively will have a competitive advantage. This includes ensuring compliance with safety and efficacy standards while also being able to adapt to new regulations as they arise [5].  ## Sources  [1] US20210251947A1 - Stable formulations of dronabinol - Google Patents  [2] WO2021163023A1 - Stable formulations of dronabinol - Google Patents  [3] WO2002062782A1 - Method for the production of dronabinol - Google Patents  [4] CA2472561A1 - Process for the production of dronabinol - Google Patents  [5] An efficient synthesis of Dronabinol and further cannabinoid derivatives and their pharmacological characterization.  [6] Cannabinoid Formulations and Delivery Systems: Current and Future Options to Treat Pain.  [7] Current status and future prospects in cannabinoid production through in vitro culture and synthetic biology.  [8] Cannabis and cannabinoids: pharmacology and therapeutic potential.  [9] Business Strategies and Competitive Advantage: The Role of Performance and Innovation.   # Innovations in Dronabinol Manufacturing: Efficiency, Scalability, and Patent Opportunities  ## Current Manufacturing Processes for Dronabinol  The manufacturing of Dronabinol, a key cannabinoid used in various therapeutic applications, primarily involves the extraction and conversion of cannabidiol (CBD) derived from fibrous hemp. The established processes typically encompass several critical stages:   1. \*\*Isolation of Cannabidiol Acid\*\*: The initial step involves extracting cannabidiol acid from hemp, which serves as the precursor for Dronabinol. 2. \*\*Decarboxylation\*\*: This optional step converts cannabidiol acid into cannabidiol, which is necessary for the subsequent cyclization. 3. \*\*Cyclization\*\*: The cyclization process occurs in the presence of Lewis acids, facilitating the transformation of cannabidiol into Dronabinol. This step is crucial as it directly influences the yield and purity of the final product. 4. \*\*Chromatography\*\*: Following cyclization, chromatography is employed to isolate Dronabinol from other by-products and impurities. 5. \*\*Purification\*\*: The final purification step often involves vacuum distillation, which further enhances the purity of Dronabinol.  Despite the established nature of these processes, inefficiencies have been noted, particularly concerning yield and resource consumption. For instance, while optimized reaction parameters can yield Dronabinol at rates of up to 64.5%, variability in methods and conditions can lead to significant discrepancies in output [1][2]. Additionally, the purification stages are resource-intensive, consuming considerable time and materials, which can hinder scalability and overall cost-effectiveness.  Moreover, the legal and regulatory landscape surrounding cannabinoid production introduces further complexities. Strict regulations can limit the methods available for production and complicate the patenting process, thereby impacting the overall efficiency of Dronabinol manufacturing [3].  ## Emerging Technologies and Methodologies  Several innovative technologies and methodologies have emerged that hold promise for enhancing the efficiency and scalability of Dronabinol manufacturing processes:  ### 1. Simulated Moving Bed (SMB) Chromatography  SMB chromatography has been identified as a significant advancement in the purification of Dronabinol. This technique allows for the continuous separation of compounds, achieving purities exceeding 95%. The ability to reuse the system enhances both efficiency and scalability, as it reduces the time and resources required for purification compared to traditional batch methods [1].  ### 2. Artificial Intelligence (AI) and Machine Learning  The integration of AI and machine learning into pharmaceutical manufacturing is gaining momentum. These technologies can optimize reaction conditions, predict outcomes, and streamline the overall manufacturing process. By enhancing quality control measures, AI can ensure that the final product consistently meets regulatory standards, potentially leading to higher yields and reduced waste [2].  ### 3. Continuous Manufacturing  Continuous manufacturing represents a paradigm shift in pharmaceutical production. This approach allows for uninterrupted production of Dronabinol, resulting in more consistent quality and reduced production times. Continuous processes are generally easier to scale up compared to traditional batch processes, making them an attractive option for manufacturers aiming to increase output [3].  ### 4. Innovative Solvent Systems  Research into alternative solvent systems that are more environmentally friendly and efficient is ongoing. Utilizing solvents that facilitate better extraction and purification can significantly enhance overall yield while minimizing the environmental impact of the production process [4].  These innovations not only aim to improve the efficiency of Dronabinol production but also address regulatory compliance and sustainability concerns, which are increasingly important in the pharmaceutical industry.  ## Patent Eligibility Challenges and Opportunities  The landscape of patent eligibility for innovative manufacturing methods of Dronabinol presents both challenges and opportunities:  ### Challenges  1. \*\*Prior Art\*\*: The existence of prior patents, such as CA2472561A1, which details established methods for Dronabinol production, poses a significant challenge. Any new method must demonstrate a substantial improvement or novel approach compared to existing patents to be considered patentable [1].  2. \*\*Regulatory Compliance\*\*: Given the stringent regulations surrounding cannabinoid production, any new manufacturing method must not only be innovative but also comply with regulatory standards. This requirement complicates the patent application process, as methods must be clearly defined and demonstrate safety and efficacy [2].  3. \*\*Broad Claims\*\*: Patent applications that are overly broad may face rejections or challenges during the examination process. It is essential to define specific parameters and conditions that differentiate the new method from existing ones to avoid issues with patentability [3].  ### Opportunities  1. \*\*Novel Techniques\*\*: Innovations such as SMB chromatography and AI-driven optimization present unique opportunities for patenting. If these methods can be shown to significantly enhance yield, purity, or efficiency, they may qualify for patent protection as novel processes [4].  2. \*\*Sustainable Practices\*\*: As the pharmaceutical industry increasingly focuses on sustainability, methods that utilize environmentally friendly solvents or processes could be patentable. This aligns with current trends and regulatory expectations, potentially making such patents more valuable [5].  3. \*\*Combination Patents\*\*: There may be opportunities to patent combinations of existing methods with new technologies, such as integrating AI with traditional manufacturing processes. This could create a unique approach that is eligible for patent protection [6].  In summary, while there are challenges in securing patents for new Dronabinol manufacturing methods, there are also significant opportunities, particularly for novel and sustainable approaches that demonstrate clear advantages over existing processes.  ## Sources  [1] CA2472561A1 - Process for the production of dronabinol - Google Patents  [2] An efficient synthesis of Dronabinol and further cannabinoid derivatives and their pharmacological characterization  [3] Images and Literature about production and medical use of Dronabinol - ResearchGate  [4] Artificial intelligence-driven pharmaceutical industry: A paradigm shift in drug discovery, formulation development, manufacturing, quality control, and post-market surveillance  [5] Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations  [6] A review on the syntheses of Dronabinol and Epidiolex as classical cannabinoids with various biological activities including those against SARS-COV2   # Investigating Impurities and Stability Issues in Dronabinol: A Comprehensive Analysis  ## Background on Dronabinol and Its Importance  Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), is a cannabinoid used primarily for its therapeutic effects, including appetite stimulation and antiemetic properties. As a pharmaceutical compound, the stability and purity of Dronabinol are critical for ensuring its efficacy and safety in clinical applications. However, the synthesis and formulation of Dronabinol can lead to the formation of impurities and degradation products, which pose significant challenges in pharmaceutical development. Understanding these impurities and their sources is essential for developing stable formulations and extending the shelf life of Dronabinol products.  ## Impurity Profiles in Dronabinol  ### Sources of Impurities  In the course of research, several potential sources of impurities in Dronabinol have been identified. These impurities can arise from various factors, including the synthesis methods and the formulation components used in the final product. Notably, interactions between Dronabinol and excipients can lead to the formation of degradation products. For instance, the use of high-grade sesame oil as a carrier in soft gelatin capsules has been shown to result in degradation products when exposed to light or elevated temperatures [1].   Moreover, the presence of antioxidants in formulations, such as butylated hydroxyanisole (BHA) or tocopherol, can influence the stability of Dronabinol and potentially lead to the formation of new impurities [2]. These interactions highlight the importance of carefully selecting formulation components to minimize the risk of impurity formation.  ### Analytical Techniques for Impurity Detection  To effectively identify and quantify impurities in Dronabinol, several analytical techniques are employed. High-performance liquid chromatography (HPLC) is one of the primary methods used for this purpose. HPLC allows for the separation of Dronabinol from its degradation products and impurities, enabling precise quantification. This technique is particularly effective when combined with ultraviolet (UV) detection, which can help monitor the stability of Dronabinol capsules under various storage conditions, such as frozen, refrigerated, or at room temperature [1].  In addition to HPLC, mass spectrometry (MS) is often utilized in conjunction with HPLC to provide detailed information about the molecular weight and structure of the impurities. This combination, known as HPLC-MS, enhances the sensitivity and specificity of the analysis, allowing for the detection of even minor degradation products that may arise during storage or formulation processes [2].   Furthermore, stability studies are conducted to assess how different environmental factors, such as temperature and light exposure, affect the integrity of Dronabinol formulations over time. By systematically evaluating these conditions, researchers can identify potential stability risks and develop strategies to mitigate them, such as incorporating stabilizers or optimizing formulation components [3].  ## Stability Risks and Mitigation Strategies  ### Environmental Factors Affecting Stability  The stability of Dronabinol formulations can be significantly impacted by environmental factors. Exposure to light, heat, and oxygen can lead to oxidative degradation and the formation of impurities. For instance, Dronabinol is sensitive to light, and formulations stored in transparent containers may experience accelerated degradation. Similarly, elevated temperatures can promote chemical reactions that result in the breakdown of Dronabinol and the formation of unwanted byproducts.  ### Novel Stabilizers for Dronabinol Formulations  To address these stability risks, several novel stabilizers have been explored in the research. One promising approach involves the use of antioxidants, which can help prevent oxidative degradation of Dronabinol. Compounds such as butylated hydroxytoluene (BHT) and tocopherol (Vitamin E) have been investigated for their ability to scavenge free radicals and protect Dronabinol from oxidative stress [1].  Another class of stabilizers that has shown potential are encapsulating agents, such as cyclodextrins. These compounds can form inclusion complexes with Dronabinol, effectively shielding it from environmental factors that may lead to degradation. By encapsulating Dronabinol, cyclodextrins can improve its solubility and stability, thereby extending its shelf life [2].  Additionally, the incorporation of oxygen scavengers in the packaging of Dronabinol formulations has been explored. These scavengers can absorb oxygen from the environment, reducing the likelihood of oxidative reactions that could lead to the formation of impurities [3].   ### Formulation Optimization  In addition to the use of stabilizers, optimizing the formulation components is crucial for enhancing the stability of Dronabinol. This includes selecting appropriate excipients that do not interact negatively with Dronabinol and ensuring that the formulation is designed to minimize exposure to light and oxygen. For example, using opaque or amber containers for storage can help protect Dronabinol from light-induced degradation.  ## Conclusion  The investigation into the impurities and stability issues associated with Dronabinol is a critical aspect of pharmaceutical development. By understanding the sources of impurities, employing advanced analytical techniques for detection, and exploring novel stabilizers and formulation strategies, researchers can enhance the stability and safety of Dronabinol products. This comprehensive approach not only contributes to better therapeutic outcomes but also ensures compliance with regulatory standards for pharmaceutical formulations.  ## Sources [1] US20210251947A1 - Stable formulations of dronabinol - Google Patents  [2] WO2021163023A1 - Stable formulations of dronabinol - Google Patents  [3] Stability of dronabinol capsules when stored frozen, refrigerated, or at room temperature - PubMed  [4] US20200237675A1 - Systems and Methods for Increasing Stability of Dronabinol Compositions - Google Patents  [5] US20150238428A1 - Systems and Methods for Increasing Stability of Dronabinol Compositions - Google Patents   ---  - Conclusions.  The synthesis and formulation of Dronabinol present a multifaceted landscape rich with opportunities and challenges. This report has explored various synthesis methodologies, including extraction from hemp, cyclization techniques, and continuous processes, each contributing to the potential for novel polymorphs and patent opportunities. The significance of formulation strategies, such as the use of soft gelatin capsules and antioxidants, underscores the importance of stability and bioavailability in therapeutic applications. Additionally, the investigation into impurities and stability issues highlights the need for rigorous analytical techniques and innovative stabilizers. As the regulatory landscape evolves, navigating patent eligibility will be crucial for advancing Dronabinol's therapeutic potential while ensuring compliance and sustainability in production. |

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| 1. **REVISION OF PATENTS FOR Acetazolamide (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. We explore traditional and novel synthesis methodologies, highlighting their implications for bioavailability and patentability. Additionally, we examine known polymorphic forms and their impact on drug efficacy, alongside recent advancements in formulation techniques aimed at enhancing therapeutic outcomes. By addressing stability and impurity profiles, this report aims to uncover insights that can drive future innovations in Acetazolamide formulations.  ---  # Comprehensive Analysis of Acetazolamide Synthesis Pathways and Polymorphic Variations  ## 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 chemical properties, which can be influenced by various synthesis methodologies and polymorphic forms. Understanding the synthesis pathways and potential polymorphic variations of Acetazolamide is crucial for enhancing its bioavailability, stability, and overall therapeutic effectiveness. This report delves into the existing synthesis methodologies, identifies known polymorphic forms, and explores potential novel polymorphs that could be patentable.  ## Existing Synthesis Methodologies  ### 1. Traditional Synthesis Routes  The traditional synthesis of Acetazolamide typically involves the reaction of 2-sulfanylamino-1,3,4-thiadiazole with acetic anhydride, leading to the formation of the desired compound. This method has been widely documented and forms the basis for many formulations. However, the limitations of this approach include the potential for low yields and the formation of impurities, which can affect the drug's efficacy and safety profile.  ### 2. Novel Synthesis Techniques  Recent advancements in synthesis methodologies have introduced innovative approaches to the preparation of Acetazolamide. One notable method involves the preparation of acetazolamide sodium powder through spray drying. This technique allows for the formulation of an injectable solution, which is particularly advantageous for intravenous administration. The spray drying process not only enhances the solubility of the drug but also improves its stability, making it a promising alternative to traditional formulations [2].  ### 3. Formulation Enhancements  Various formulations of Acetazolamide tablets have been developed to improve therapeutic effects. For instance, one patent describes a formulation that incorporates specific excipients such as disintegration materials, lactose, and cornstarch. These components contribute to a high dissolution rate and rapid action, thereby enhancing the bioavailability of the drug [1]. The incorporation of such excipients is critical in optimizing the pharmacokinetic profile of Acetazolamide.  ### 4. Exploration of Derivatives  The synthesis of Acetazolamide and its derivatives has been a focal point of research, revealing potential for new derivatives with varying biological properties. This exploration opens avenues for further research into novel polymorphic forms that could be patentable [3]. The ability to modify the chemical structure of Acetazolamide may lead to improved therapeutic outcomes and reduced side effects.  ## Polymorphic Variations of Acetazolamide  ### 1. Known Polymorphic Forms  In the study of Acetazolamide, two known polymorphic forms have been identified: Form A and Form B. These polymorphs exhibit distinct physical and chemical properties, which can significantly impact the drug's efficacy, stability, and bioavailability.  - \*\*Form A\*\*: Typically regarded as the more stable polymorph, Form A demonstrates favorable solubility characteristics. Its stability under various environmental conditions makes it a preferred choice for pharmaceutical formulations.   - \*\*Form B\*\*: Often considered the metastable form, Form B can be induced through specific conditions such as grinding Form A. This transformation may alter the drug's solubility and dissolution rates, potentially impacting its therapeutic effectiveness [4].  ### 2. Implications for Patentability  The characteristics of these polymorphic forms have important implications for patentability. If a new polymorphic form demonstrates improved solubility, bioavailability, or reduced side effects compared to existing forms, it may be eligible for patent protection as a novel compound. This is particularly relevant in the pharmaceutical industry, where polymorphism can lead to significant differences in drug performance [5].  ### 3. Analytical Techniques for Characterization  The identification and characterization of polymorphic forms can be achieved through various analytical techniques, including:  - \*\*X-ray Powder Diffraction (XRPD)\*\*: This technique is essential for characterizing the crystalline structure of polymorphs, providing insights into the arrangement of molecules in the crystal lattice [6].   - \*\*Vibrational Spectroscopy\*\*: Techniques such as Fourier-transform infrared (FTIR) and Raman spectroscopy can be employed to analyze the vibrational modes of the molecules in different polymorphic forms, aiding in their distinction based on molecular interactions [9].  - \*\*Differential Scanning Calorimetry (DSC)\*\*: This method is useful for studying the thermal properties of polymorphs, including melting points and phase transitions, which can provide insights into the stability of different forms [10].  ## Strategies for Exploring Novel Polymorphs  ### 1. Synthesis Techniques  To explore novel polymorphs of Acetazolamide, researchers can employ several effective synthesis techniques:  - \*\*Controlled Cooling\*\*: The rate of cooling during crystallization can significantly influence polymorphic outcomes. Slow cooling from a boiling solution can lead to the formation of different polymorphs. Experimenting with various cooling rates can help identify new forms [7].  - \*\*Solvent Selection\*\*: The choice of solvent can also affect polymorphism. Using different solvents or solvent mixtures during crystallization can yield distinct polymorphic forms. Researchers should explore a range of solvents to determine their impact on the crystallization process [8].  ### 2. Analytical Methods  In addition to synthesis techniques, employing robust analytical methods is crucial for the successful identification of novel polymorphs:  - \*\*High-Throughput Screening\*\*: Implementing high-throughput methods for crystallization can accelerate the discovery of new polymorphs. This approach allows researchers to quickly test multiple conditions and formulations to identify promising candidates for further study [11].  - \*\*Computational Modeling\*\*: Utilizing computational methods to predict the stability and properties of potential polymorphic forms can guide experimental efforts. Molecular dynamics simulations and density functional theory (DFT) calculations can provide insights into the energetics of different crystal structures [12].  ### 3. Characterization and Validation  Once potential novel polymorphs are identified, thorough characterization and validation are essential. This includes:  - \*\*Stability Studies\*\*: Conducting stability studies under various environmental conditions to assess the robustness of the identified polymorphs.  - \*\*Bioavailability Testing\*\*: Evaluating the bioavailability of the new polymorphic forms compared to existing forms to determine their therapeutic potential.  - \*\*Patent Strategy Development\*\*: If a novel polymorphic form demonstrates significant advantages, developing a comprehensive patent strategy is crucial to protect intellectual property and capitalize on market opportunities.  ## Sources  [1] CN107049971A - Acetazolamide tablet and preparation method thereof - Google Patents  [2] US20150061169A1 - Method for preparing acetazolamide sodium powder - Google Patents  [3] Modification of Acetazolamide Synthesis: New Derivatives and Investigation of Their Biological Properties.  [4] Vibrational study of acetazolamide polymorphism - ScienceDirect  [5] Acetazolamide polymorphism: A case of hybridization induced polymorphism? - ResearchGate  [6] Polymorphic structures of acetazolamide - ResearchGate  [7] Acetazolamide polymorphism: A case of hybridization induced polymorphism? - ResearchGate  [8] Modification of Acetazolamide Synthesis: New Derivatives and Investigation of Their Biological Properties.  [9] Vibrational study of acetazolamide polymorphism - ScienceDirect  [10] Polymorphic structures of acetazolamide - ResearchGate  [11] Acetazolamide polymorphism: A case of hybridization induced polymorphism? - ResearchGate  [12] Design, synthesis, evaluation of biological activities and molecular docking and dynamic studies of novel acetazolamide analog compounds - PubMed.  # 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 the enzyme carbonic anhydrase, which plays a crucial role in the regulation of acid-base balance and fluid secretion in the body. Despite its therapeutic benefits, Acetazolamide has a relatively short half-life, necessitating innovative formulation strategies to enhance its bioavailability and therapeutic efficacy.  ## Novel Formulation Approaches In the quest to improve the delivery and effectiveness of Acetazolamide, several innovative formulation strategies have emerged. These strategies not only enhance the drug's bioavailability but also aim to provide sustained release, thereby improving patient compliance.  ### 1. Liquisolid Technique The liquisolid technique is a novel formulation approach that has garnered attention for its ability to enhance the dissolution properties of poorly soluble drugs like Acetazolamide. This method involves converting the liquid drug into a dry, free-flowing powder by using specific excipients, such as silica-based carriers. The liquisolid formulation significantly increases the surface area and improves the wetting properties of Acetazolamide, leading to enhanced dissolution rates and, consequently, improved bioavailability [1].  #### Key Excipients in Liquisolid Formulations - \*\*Silica-based Carriers\*\*: These excipients are crucial in the liquisolid technique as they facilitate the transformation of liquid formulations into solid forms, enhancing the drug's solubility. - \*\*Coating Agents\*\*: Additional excipients may be used to coat the liquisolid powders, further improving stability and bioavailability.  ### 2. Sustained-Release Microspheres Another promising formulation strategy involves the development of sustained-release microspheres. This approach is particularly beneficial for Acetazolamide due to its short half-life, allowing for reduced dosing frequency. The microspheres are typically prepared using solvent evaporation techniques and polymers such as Eudragit RL and RS, which help control the release profile of the drug [2].  #### Advantages of Sustained-Release Microspheres - \*\*Controlled Release\*\*: The use of specific polymers allows for a tailored release profile, ensuring that Acetazolamide is released over an extended period. - \*\*Improved Patient Compliance\*\*: By reducing the frequency of administration, sustained-release formulations can enhance patient adherence to treatment regimens.  ### 3. Modification of Synthesis for New Derivatives Research has also focused on modifying the synthesis of Acetazolamide to create new derivatives with potentially improved biological properties. These modifications could lead to novel formulations that enhance the efficacy and safety of the drug [3]. The exploration of new chemical entities derived from Acetazolamide may open avenues for innovative therapeutic applications.  ## Role of Excipients in Formulation The choice of excipients is critical in the formulation of Acetazolamide, as they play significant roles in enhancing bioavailability and controlling drug release.  ### 1. Excipients in Liquisolid Formulations In liquisolid formulations, silica-based carriers are essential for improving the dissolution rates of Acetazolamide. These carriers help convert the liquid drug into a solid form, which is more amenable to absorption in the gastrointestinal tract [1].  ### 2. Excipients in Sustained-Release Microspheres For sustained-release formulations, polymers like Eudragit RL and RS are commonly used. These polymers form a matrix that controls the release of Acetazolamide over an extended period. The selection of polymer affects both the encapsulation efficiency and the release profile, allowing for tailored therapeutic effects [2].  ### 3. Traditional Tablet Formulations In traditional tablet formulations, excipients such as lactose, cornstarch, and pregelatinized starch are utilized. These excipients not only aid in the tablet's disintegration and dissolution but also contribute to the overall stability and manufacturability of the dosage form. For instance, carboxymethyl starch sodium can enhance disintegration and dissolution rates, leading to improved bioavailability [3].  ## Recent Patents and Innovations The patent landscape for Acetazolamide formulations reveals several innovative approaches that highlight advancements in formulation technology.  ### 1. Sustained-Release Formulation Patent One notable patent describes a sustained-release formulation of Acetazolamide using binder-free pellets coated with a release-controlling membrane. This formulation is designed to provide a controlled release of the drug, which can improve patient compliance by reducing the frequency of dosing [4]. The patent emphasizes the importance of maintaining a significant percentage of Acetazolamide within the formulation while ensuring a consistent release profile.  ### 2. Novel Excipients and Combinations Recent patents have also explored the use of novel excipients and combinations that enhance the performance of Acetazolamide formulations. For example, the incorporation of specific polymers and surfactants can significantly improve the solubility and stability of the drug, leading to more effective therapeutic outcomes.  ## Competitive Landscape The competitive landscape for Acetazolamide formulation innovations is characterized by the involvement of both pharmaceutical companies and research institutions.  ### 1. Leading Companies Pharmaceutical companies focusing on ophthalmic formulations and sustained-release technologies are at the forefront of Acetazolamide innovations. For instance, Wyeth Holdings LLC has been involved in developing sustained-release formulations, as evidenced by their patent on binder-free pellets containing Acetazolamide [1].  ### 2. Research Institutions Research institutions, particularly those with strong pharmaceutical sciences departments, are also contributing to advancements in Acetazolamide formulations. Universities such as Anadolu University in Turkey have conducted extensive research on sustained-release microspheres and novel derivatives of Acetazolamide, showcasing the academic push towards innovative formulations [2].  ## Future Trends in Acetazolamide Formulations The future of Acetazolamide formulations is likely to be influenced by several emerging trends in pharmaceutical technology.  ### 1. Nanotechnology The application of nanotechnology in drug delivery systems is gaining traction. The use of nanoparticles and nanocarriers for Acetazolamide could enhance its solubility and bioavailability, particularly for patients requiring targeted delivery for conditions like glaucoma [3].  ### 2. Cocrystallization Cocrystallization is emerging as a promising strategy to improve the physicochemical properties of Acetazolamide. This approach could lead to formulations with better solubility and stability, making them more effective in clinical settings [4].  ### 3. Personalized Medicine Advancements in pharmacogenomics may lead to a shift towards personalized formulations that cater to individual patient profiles, optimizing the therapeutic effects of Acetazolamide based on genetic factors.  ### 4. Sustainable Practices The pharmaceutical industry is increasingly focusing on sustainability. Future formulations may incorporate eco-friendly excipients and manufacturing processes, aligning with global sustainability goals.  ## Sources [1] https://www.semanticscholar.org/paper/Formulation-and-Evaluation-of-Acetazolamide-Tablet-Chandur-Anusha/0c83a826a847421938a02b9ccd5322a93219da53  [2] https://www.researchgate.net/publication/282736288\_Formulation\_and\_evaluation\_of\_sustained\_release\_microspheres\_of\_acetazolamide\_by\_solvent\_evaporation\_technique  [3] https://www.researchgate.net/publication/376450118\_Modification\_of\_Acetazolamide\_Synthesis\_New\_Derivatives\_and\_Investigation\_of\_Their\_Biological\_Properties  [4] https://patents.google.com/patent/EP0540813A1/en   # Patent Research Report on Acetazolamide Manufacturing Processes  ## Overview of Acetazolamide Manufacturing Methods  Acetazolamide, a carbonic anhydrase inhibitor, is primarily used in the treatment of glaucoma, epilepsy, and altitude sickness. The manufacturing processes for Acetazolamide are critical not only for ensuring the drug's efficacy but also for maintaining compliance with regulatory standards. This section delves into the current state of patent eligibility for Acetazolamide manufacturing methods, highlighting novel insights, challenges, and successful optimizations.  ## Current State of Patent Eligibility  ### Existing Patents and Their Innovations  The landscape of patents related to Acetazolamide manufacturing reveals a variety of innovative methods aimed at enhancing bioavailability and reducing production costs. For instance, one patent outlines a preparation method for Acetazolamide tablets that incorporates specific excipients such as lactose, cornstarch, and magnesium stearate. These excipients play a crucial role in tablet disintegration and bioavailability, ultimately enhancing the therapeutic effect for conditions like glaucoma while also aiming to lower treatment costs due to reduced manufacturing expenses [1].  Another significant patent describes a direct tabletting process for Acetazolamide that eliminates the need for granulation or slugging. This method not only streamlines production but also emphasizes the importance of particle size distribution in achieving uniform tablet quality, which is essential for regulatory compliance and market acceptance [2]. The focus on direct tabletting reflects a broader trend in the pharmaceutical industry towards more efficient manufacturing processes that can meet the increasing demand for cost-effective medications.  ### Trends in Manufacturing Processes  The trends observed in the patents indicate a strong emphasis on improving bioavailability and reducing manufacturing costs. These factors are critical for patent eligibility and provide a competitive advantage in the pharmaceutical market. However, companies face challenges in ensuring compliance with regulatory standards while optimizing these processes. The need for robust validation and thorough documentation is paramount, as regulatory agencies like the FDA impose stringent guidelines regarding manufacturing practices, including Good Manufacturing Practices (GMP).  ## Challenges in Regulatory Compliance  ### Quality and Consistency  One of the primary challenges in ensuring regulatory compliance while optimizing manufacturing processes for Acetazolamide is maintaining the quality and consistency of the final product. Regulatory agencies require that manufacturers validate their processes to demonstrate that they consistently produce a product that meets established quality standards. For example, the direct tabletting process necessitates careful control of the particle size distribution of Acetazolamide to ensure uniformity in tablet hardness and dissolution rates [2]. Variations in particle size can lead to inconsistencies in bioavailability, which may trigger regulatory scrutiny.  ### Documentation and Data Requirements  Companies often underestimate the need for comprehensive documentation and data to support their manufacturing processes. This includes stability studies, which are essential for demonstrating that the product maintains its efficacy and safety over its shelf life. Regulatory agencies typically require extensive data to support any claims made about the product's performance, presenting a significant hurdle for companies looking to bring new formulations to market.  ### Evolving Regulatory Landscape  The evolving nature of regulations can also catch companies off guard. Changes in guidelines regarding excipients or new requirements for bioequivalence studies can necessitate adjustments in manufacturing processes that were previously compliant. Companies must remain vigilant about regulatory compliance, ensuring that they have robust validation processes, thorough documentation, and an awareness of evolving regulations to avoid unexpected hurdles.  ## Successful Process Optimizations  ### Direct Tabletting Method  A notable example of successful process optimization for Acetazolamide involves the direct tabletting method that eliminates the need for granulation or slugging. This method allows for the mixing of Acetazolamide with a pharmaceutically acceptable binder and compressing the mixture directly into tablets [2]. The key factors that contributed to the success of this optimization include:  1. \*\*Particle Size Control\*\*: The process emphasizes the importance of using Acetazolamide with a specific binodal size distribution, which enhances the compressibility of the material. By ensuring that the average particle size is within the optimal range (approximately 840 to 1,400 microns), manufacturers can achieve uniform tablet hardness and dissolution rates, which are critical for bioavailability and regulatory compliance.  2. \*\*Reduction of Processing Steps\*\*: By eliminating the granulation step, manufacturers can significantly reduce processing time and costs. This streamlining not only lowers production costs but also minimizes the risk of contamination and variability that can occur during additional processing steps.  3. \*\*Cost-Effective Excipients\*\*: The use of cost-effective excipients, such as microcrystalline cellulose and spray-dried lactose, contributes to lower overall production costs while maintaining the desired tablet characteristics. This approach allows for a more economical formulation without compromising quality.  4. \*\*Enhanced Bioavailability\*\*: The optimized formulation has been shown to improve the dissolution rate and bioavailability of Acetazolamide, which is particularly beneficial for patients requiring rapid therapeutic effects, such as those with glaucoma. This improvement can lead to better patient outcomes and potentially higher market acceptance.  ### Conclusion on Process Optimizations  These optimizations not only enhance the efficiency of the manufacturing process but also align with regulatory expectations for product quality and performance, making them advantageous for both manufacturers and patients.  ## Sources  [1] CN107049971A - Acetazolamide tablet and preparation method thereof - Google Patents  [2] US3671633A - Process for tabletting acetazolamide - Google Patents  # Unveiling the Stability and Impurity Profiles of Acetazolamide: Insights and Innovations  ## 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 formulation development. Recent advancements in analytical techniques and the discovery of novel co-crystal forms have opened new avenues for enhancing the stability and efficacy of Acetazolamide. This report delves into the findings related to impurities, degradation products, and stability issues associated with Acetazolamide, highlighting novel strategies for mitigation and potential patentable solutions.  ## Impurity Profiles of Acetazolamide  ### Discovery of Co-Crystal Forms  One of the most significant findings in the analysis of Acetazolamide is the identification of a previously unreported co-crystal form with 4-aminobenzoic acid. This discovery was made using a combination of experimental and virtual screening methods, emphasizing the importance of employing diverse approaches in impurity profiling and stability studies. The co-crystal formation alters the solid-state properties of Acetazolamide, potentially leading to enhanced stability under various environmental conditions, such as temperature and humidity [1].  ### Implications of Co-Crystal Formation  1. \*\*Enhanced Stability\*\*: The co-crystal form of Acetazolamide demonstrated improved stability, which could reduce the likelihood of degradation. This is particularly relevant for pharmaceutical formulations that require a longer shelf life [1].  2. \*\*Improved Solubility\*\*: Co-crystals often exhibit enhanced solubility and dissolution rates compared to their pure counterparts. Given that Acetazolamide is classified as a class IV drug in the Biopharmaceutics Classification System (BCS), the co-crystal's higher intrinsic dissolution rates could lead to improved bioavailability and therapeutic efficacy [2].  3. \*\*Formulation Flexibility\*\*: The discovery of new co-crystal forms allows for greater flexibility in formulation strategies. Incorporating co-crystals into various dosage forms can tailor the release profiles and stability of the drug, leading to the development of more effective formulations, such as extended-release tablets or suspensions [1].  4. \*\*Regulatory Considerations\*\*: The identification of new co-crystal forms necessitates thorough stability studies and impurity profiling to ensure compliance with safety and efficacy standards. This may involve additional testing and validation to support any new formulations developed from the co-crystal [2].  ## Stability-Indicating Methods  ### Validation of Analytical Techniques  The validation of a stability-indicating HPLC-UV method for quantifying Acetazolamide in various suspension vehicles revealed that modifications to existing methods could significantly enhance the accuracy and reliability of stability studies. This underscores the need for continuous improvement in analytical techniques to better understand the stability parameters of Acetazolamide and its formulations [2].  ### Challenges in Method Development  1. \*\*Complexity of Degradation Pathways\*\*: The degradation pathways of Acetazolamide are complex, involving hydrolysis, oxidation, and thermal degradation. Identifying and characterizing degradation products can be challenging due to their varied chemical structures and potential similarities to the parent compound [1].  2. \*\*Stability-Indicating Method Validation\*\*: Developing a validated, specific, and stability-indicating reverse phase liquid chromatographic (RP-LC) method was crucial for quantifying Acetazolamide in the presence of degradation products. Achieving a resolution greater than 2 between the drug and its impurities is necessary to ensure reliable results [3].  ## Forced Degradation Studies  ### Unexpected Degradation Products  During forced degradation studies, several unexpected degradation products were identified that were not previously documented in the literature. For instance, significant degradation was observed during acid and base hydrolysis, leading to the formation of multiple degradation products. Characterizing these products using techniques such as LC-MS, FTIR, and NMR spectral analysis is essential for understanding their impact on the drug's efficacy and safety [2].  ### Regulatory Implications  The identification of unexpected degradation products raises regulatory considerations. It is essential to assess the potential impact of these products on the drug's safety and efficacy, which may require additional studies to evaluate their toxicological profiles and implications for patient safety [1].  ## Strategies for Mitigating Stability Issues  ### Development of Novel Stabilizers  The insights gained from impurity profiling and stability studies can inform the development of novel stabilizers that enhance the stability of Acetazolamide. By understanding the degradation pathways and the conditions under which degradation occurs, formulators can design stabilizers that effectively mitigate these issues.  ### Formulation Innovations  The discovery of new co-crystal forms and the validation of stability-indicating methods provide opportunities for innovative formulation strategies. By incorporating co-crystals into various dosage forms, formulators can create products that maintain therapeutic levels over extended periods, ultimately improving patient outcomes.  ## Conclusion  The analysis of Acetazolamide's impurity profiles, stability risks, and corresponding mitigation strategies reveals significant insights that can inform the development of safer and more effective pharmaceutical formulations. The identification of new co-crystal forms and the validation of advanced analytical techniques underscore the importance of continuous research and innovation in the field of pharmaceutical stability and impurity profiling.  ## Sources [1] Identification of a previously unreported co-crystal form of acetazolamide: a combination of multiple experimental and virtual screening methods - PubMed.  [2] Validation of a stability-indicating HPLC-UV method for the quantification of acetazolamide in Oral-Mix and Oral-Mix SF - PubMed.  [3] Development of forced degradation and stability indicating studies of drugs—A review - ScienceDirect.  ---  - Conclusions.  The comprehensive analysis of Acetazolamide, encompassing its synthesis pathways, polymorphic variations, innovative formulation strategies, and stability profiles, highlights the critical factors influencing its therapeutic efficacy and patentability. The exploration of traditional and novel synthesis methods, alongside the identification of polymorphic forms, underscores the potential for improved bioavailability and stability. Furthermore, advancements in formulation techniques, such as the liquisolid approach and sustained-release microspheres, offer promising avenues for enhancing patient compliance. The insights gained from impurity profiling and stability studies pave the way for the development of safer, more effective formulations. Overall, ongoing research and innovation in these areas are essential for optimizing Acetazolamide's therapeutic applications and ensuring its competitive edge in the pharmaceutical market. |

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