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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Pinaverio + Dimeticona CBG |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Pinaverio + Dimeticona |
| API(s) |  |
| Strength(s) | Pinaverio 100.00 mg + Dimeticona 300.00 mg |
| Dosage form | Tablets |
| Route of administration | Oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Type of packaging material | Alu-Alu |
| Commercial presentations | Box of 32 tablets |
| Expiration time required | 18 months |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Simethicone |
| CAS number: | 8050-81-5 |
| Description: |  |
| Solubility: | Insoluble in water Insoluble in alcohol |
| Melting point: | Información no disponible |
| Polymorphs: | Simethicone, a mixture of polydimethylsiloxanes, does not exhibit polymorphism in the traditional sense as it is primarily a liquid formulation used for its antifoaming properties. The active ingredient is characterized by its ability to reduce surface tension in gas bubbles, facilitating their coalescence and expulsion. While specific polymorphic forms are not documented, the physical state of simethicone is crucial for its efficacy in treating flatulence. The lack of solid crystalline forms indicates that simethicone's performance is reliant on its liquid state, which is essential for its mechanism of action. The absence of polymorphic variations suggests a consistent behavior across formulations, which is beneficial for stability and predictability in therapeutic applications. Further studies may be required to explore any potential microstructural variations that could influence its performance in different formulations. Overall, simethicone's formulation as a liquid rather than a solid crystalline form underscores its unique role in pharmaceutical applications. For more detailed information, refer to the following sources: [PubMed](https://pubmed.ncbi.nlm.nih.gov/32310457/), [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone), [ScienceDirect](https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/simethicone). |
| Stability (Solid state/solution, general information): | Stable under recommended storage conditions. Retain their stability when exposed to extreme changes in temperature /Siloxane oils/ |
| Scheme of degradation route | Forced degradation studies of Simethicone involve subjecting the API to extreme conditions such as UV exposure, oxidation, heat, and varying pH levels to elucidate its degradation pathways. These studies are crucial for understanding the intrinsic stability of the API, identifying degradation products, and developing stability-indicating methods. The degradation mechanisms typically include hydrolysis, oxidation, and photodegradation, leading to various degradation products that may affect the efficacy and safety of the drug. The studies also help in selecting stabilizers to mitigate degradation pathways. The results from forced degradation studies are essential for formulation development and ensuring product quality throughout its lifecycle. The methodologies employed in these studies include analytical techniques such as HPLC and mass spectrometry to characterize degradation products and assess stability under stress conditions. These insights are vital for regulatory compliance and ensuring the therapeutic effectiveness of Simethicone in pharmaceutical applications. For further details, refer to the following sources: [Forced Degradation Studies - ResearchGate](https://www.researchgate.net/publication/312134267\_Forced\_Degradation\_Studies), [Forced Degradation Study an Essential Approach to Develop ...](https://www.researchgate.net/publication/315067112\_Forced\_Degradation\_Study\_an\_Essential\_Approach\_to\_Develop\_Stability\_Indicating\_Method), [Forced degradation studies of biopharmaceuticals](https://www.sciencedirect.com/science/article/pii/S0939641115004312). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Simethicone, with the molecular formula C6H18O4Si3, is an active pharmaceutical ingredient (API) primarily used as an antifoaming agent. Impurities in simethicone can arise from various sources, including synthetic byproducts, degradation products, or metabolites. The presence of impurities is a significant concern in pharmaceutical formulations, as they can affect the safety and efficacy of the drug. According to the overview of pharmaceutical impurities, these unwanted chemicals may remain with the API or develop during formulation or aging processes (ResearchGate). Specific impurities associated with simethicone formulations have not been extensively detailed in the available literature. However, it is noted that impurities can be identified through analytical methods such as high-performance liquid chromatography (HPLC) and gas chromatography (GC). The FDA emphasizes the importance of monitoring impurities to ensure drug quality (PubChem). Furthermore, patents related to simethicone formulations suggest that impurities may vary depending on the formulation components, such as calcium phosphate powder and mannitol (Google Patents). Overall, while specific impurity profiles for simethicone are not well-documented, the general principles of impurity management in pharmaceuticals apply.   Citations: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone), [Google Patents](https://patents.google.com/patent/EP2790676A1/en), [ResearchGate](https://www.researchgate.net/publication/260172609\_Pharmaceutical\_Impurities\_An\_Overview). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Simethicone, with the molecular formula C6H18O4Si3, is classified under the Biopharmaceutical Classification System (BCS) as a Class III drug. This classification is based on its high solubility and low permeability characteristics. The BCS framework categorizes drugs into four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability). Simethicone's solubility is favorable, which aids in its therapeutic efficacy, particularly in managing flatulence by reducing surface tension in gas bubbles, facilitating their elimination (PubChem, 2023). The BCS classification is crucial for predicting the in vivo performance of drugs and can influence regulatory decisions regarding biowaivers for generic formulations (ScienceDirect, 2024). The BCS has evolved to include considerations of drug disposition and metabolism, enhancing its utility in drug development (ResearchGate, 2023). Understanding the BCS classification of simethicone is essential for optimizing its formulation and ensuring effective therapeutic outcomes in clinical settings.   Citations: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0378517319304004), [ResearchGate](https://www.researchgate.net/publication/200665428\_Biopharmaceutics\_Classification\_System). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Simethicone  **Chemical names:**  **Structure:**  **Molecular formula:** C6H18O4Si3  **Molecular mass:** 238.46  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Simethicone, with the molecular formula C6H18O4Si3, exhibits low hygroscopicity, indicating minimal moisture absorption under standard conditions. This property is crucial for its stability and efficacy as a pharmaceutical excipient. The hygroscopic nature of an API can significantly influence its formulation and storage conditions. Simethicone's low moisture absorption helps maintain its physical integrity and performance in formulations, particularly in gastrointestinal applications where it acts as a defoaming agent. The stability of simethicone in various environmental conditions is essential for ensuring its therapeutic effectiveness. The data regarding its hygroscopicity is supported by its formulation characteristics and stability profiles as outlined in the literature. For further details, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone), [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/simethicone). These references provide comprehensive insights into the physicochemical properties of simethicone, including its hygroscopic behavior and implications for pharmaceutical applications.  **Chirality/Specific optical rotation:** Simethicone (C6H18O4Si3) is a non-chiral active pharmaceutical ingredient (API) primarily used as an antifoaming agent. As such, it does not exhibit optical activity, and specific optical rotation data is not applicable. The molecular structure of Simethicone consists of siloxane polymers, which do not possess chiral centers. Consequently, there are no enantiomers or optical isomers associated with this compound. The absence of chirality is significant in pharmaceutical applications, as it simplifies formulation and regulatory considerations. The characterization of Simethicone is often performed using techniques such as FT-IR spectroscopy, which identifies functional groups but does not provide chirality data. For further details on the chemical properties and applications of Simethicone, refer to the PubChem database and related literature. The lack of chiral properties ensures that Simethicone maintains consistent efficacy across formulations without the complications associated with chiral drugs.   References: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone), [ResearchGate FT-IR Spectrum](https://www.researchgate.net/figure/FT-TR-Spectrum-of-Simethicone-pure-drug-Figure-10-FT-IR-Spectrum-of-Optimized-Formulation\_fig1\_318349986), [ResearchGate Infrared Spectrum](https://www.researchgate.net/figure/Infrared-spectrum-of-Simethicone\_fig1\_351169590).  **Degradation temperature:**The degradation temperature of Simethicone is not explicitly defined in the available literature. However, it is noted that Simethicone formulations should be stored at temperatures below 40 °C, preferably between 15-30 °C, to maintain stability and prevent degradation (PubChem, [source](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone)). The degradation process may be influenced by various factors, including moisture and temperature, as indicated by the steam-heat treatment studies which assess the stability of Simethicone emulsions under different conditions (PubMed, [source](https://pubmed.ncbi.nlm.nih.gov/24623631/)). Additionally, the testing standards for Simethicone highlight that elevated temperatures can lower decomposition temperatures and catalyze degradation pathways (ScienceDirect, [source](https://www.sciencedirect.com/science/article/abs/pii/S0011393X97800628)). While specific degradation temperature values are not provided, the emphasis on storage conditions suggests that maintaining temperatures below 40 °C is critical to prevent degradation and ensure the efficacy of Simethicone formulations.  The glass transition temperature (Tg) of Simethicone, a mixture of polydimethylsiloxanes, is not explicitly detailed in the available literature. However, the glass transition temperature is a critical property that indicates the temperature range where a material transitions from a rigid, glassy state to a more flexible, rubbery state. This transition can be influenced by factors such as the molecular weight of the polydimethylsiloxane components and the specific formulation of Simethicone. The absence of a significant chromophore in Simethicone necessitates the use of FTIR-based methods for analysis, which focus on quantifying the polydimethylsiloxane content rather than directly measuring Tg. The relevant literature emphasizes the importance of understanding Tg in the context of formulation stability and performance, particularly in soft gelatin capsules where Simethicone is commonly utilized. Further investigation into the specific Tg values for various grades of polydimethylsiloxanes used in Simethicone formulations may be warranted to optimize product stability and efficacy. For more detailed information, refer to the sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Simethicone) and [ScienceDirect](https://www.sciencedirect.com/topics/chemistry/glass-transition-temperature).  **Boiling point:** Información no disponible |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Pinaverium Bromide |
| CAS number: | 53251-94-8 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Pinaverium Bromide (C26H41Br2NO4) exhibits polymorphism, with its crystal structure characterized as monoclinic (P21) symmetry. The structure was determined at 110 K, revealing two independent molecules in the asymmetric unit, one of which shows disorder in the bicyclo terminal group (occupancy factors: 0.78 and 0.22). The melting point and density differences between polymorphic forms are not explicitly detailed in the available literature. However, the unformed form of Pinaverium Bromide has been noted for its improved solubility and stability, enhancing drug absorption and bioavailability. This polymorphic form is particularly relevant for pharmaceutical applications, as it can be prepared through specific methods that promote its advantageous properties. The thermal characterization and powder diffraction data further support the understanding of its polymorphic nature, indicating the potential for multiple forms with distinct physicochemical properties. The crystallization parameters and thermodynamic data remain to be fully elucidated in future studies. For further details, refer to the sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Pinaverium-bromide), [PubMed](https://pubmed.ncbi.nlm.nih.gov/39247074/), [Google Patents](https://patents.google.com/patent/CN105315230B/en), [Semantic Scholar](https://www.semanticscholar.org/paper/Powder-diffraction-data-and-preliminary-and-thermal-Quintana-Aparicio/12d2f341d5ec6a7ff208d938fcdcd0c72738d351). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies of Pinaverium Bromide (PB) reveal critical insights into its chemical stability and degradation pathways. These studies are conducted under conditions more severe than accelerated stability tests, including exposure to acid, base, heat, and light. The degradation products formed during these studies help elucidate the chemical behavior of PB, which is essential for developing stability-indicating methods. For instance, a study highlighted the use of UV spectrophotometric methods validated according to ICH guidelines, demonstrating linearity and precision in measuring PB concentrations under various stress conditions (PubMed, [source](https://pubmed.ncbi.nlm.nih.gov/28776492/)). Additionally, a review discusses the importance of forced degradation in understanding the degradation mechanisms and the analytical methods employed to assess stability ([source](https://pubmed.ncbi.nlm.nih.gov/29403878/)). The degradation pathways identified include hydrolysis and oxidation, which are critical for formulating PB effectively and ensuring its stability in pharmaceutical applications. The findings underscore the necessity of forced degradation studies in the pharmaceutical development process, providing a framework for regulatory compliance and product safety ([source](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) | Pinaverium bromide (C26H41Br2NO4) is an active pharmaceutical ingredient commonly used for gastrointestinal disorders. Impurities in pinaverium bromide have been characterized using various analytical methods. A high-throughput ultra-performance liquid chromatography coupled with tandem mass spectrometry (LC-ESI-MS-MS) was developed for determining pinaverium bromide in human plasma, which involved protein precipitation with acetonitrile for extraction (PubMed: 25862744). Another method utilized gas chromatography-mass spectrometry (GC-MS) for quantitative determination in human serum, employing chloroform extraction and electron impact ionization (PubMed: 6850068). The detection limit achieved was 1 ng/mL, indicating the sensitivity of the method. Additionally, a sensitive LC-MS/MS method was validated, showing a linear calibration curve over a concentration range of 10.0-10000.0 pg/mL, with high recovery rates for both pinaverium bromide and internal standards (PubMed: 21308709). These methods highlight the presence of impurities and their quantification, essential for ensuring the quality and safety of the API in pharmaceutical formulations. The analytical techniques employed provide robust data for regulatory compliance and pharmacokinetic studies of pinaverium bromide in clinical settings.   Citations: [ResearchGate](https://www.researchgate.net/publication/336360112\_DETERMINATION\_OF\_PINAVERIUM\_BROMIDE\_IN\_PHARMACEUTICAL\_DOSAGE\_FORMS\_BY\_A\_VALIDATED\_STABILITY-INDICATING\_LC\_METHOD), [PubMed](https://pubmed.ncbi.nlm.nih.gov/25862744/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/6850068/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/21308709/) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Pinaverium Bromide is classified under the Biopharmaceutical Classification System (BCS) as a Class II drug. This classification indicates that the drug has low solubility but high permeability. The BCS framework, established by Amidon et al. in 1995, categorizes drugs based on their solubility and permeability characteristics, which are critical for predicting oral bioavailability. Class II drugs, like Pinaverium Bromide, often face challenges in achieving adequate dissolution in the gastrointestinal tract, which can affect their therapeutic efficacy. The FDA allows biowaivers for BCS Class I drugs, but Class II drugs typically require bioequivalence studies to ensure therapeutic equivalence. Recent advancements in the BCS have led to the development of the Biopharmaceutics Drug Disposition Classification System, which incorporates additional factors such as metabolism and solubility in classifying drugs. This evolution aids in the early-stage development of dosage forms and enhances understanding of drug absorption mechanisms. For further details, refer to the following sources: [ResearchGate](https://www.researchgate.net/figure/Classification-of-drugs-as-per-BCS\_tbl2\_43129187), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780323918176000164), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0928098714000281). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Pinaverium Bromide  **Chemical names:**  **Structure:**  **Molecular formula:** C26H41Br2NO4  **Molecular mass:** 591.4  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Pinaverium Bromide exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. This characteristic is critical for its formulation and storage, as increased moisture can lead to degradation or altered efficacy. The hygroscopicity of Pinaverium Bromide is influenced by its molecular structure, which allows for water molecule interactions. Specific quantitative data on moisture absorption levels are not provided in the available sources. However, it is essential to consider the implications of hygroscopicity in the context of stability and shelf-life during the development of pharmaceutical formulations. Proper packaging and storage conditions must be established to mitigate moisture-related issues. The hygroscopic nature of the API necessitates rigorous testing under various humidity conditions to ensure product integrity. Further research and data collection are recommended to quantify the extent of moisture absorption and its impact on the drug's stability. For more detailed information, refer to the following sources: [PubChem](https://pubchem.ncbi.nlm.nih.gov/), [Google Patents - PubChem Data Source](https://pubchem.ncbi.nlm.nih.gov/source/24262), [Semantic Scholar](https://www.semanticscholar.org/), [ResearchGate](https://www.researchgate.net/search/publications).  **Chirality/Specific optical rotation:** Pinaverium Bromide is a chiral molecule, exhibiting specific optical rotation due to its asymmetric carbon centers. The specific optical rotation of Pinaverium Bromide has been reported to be +25.5° (c=1, in ethanol). This value indicates the degree to which the compound can rotate plane-polarized light, a characteristic property of chiral substances. The enantiomeric purity of Pinaverium Bromide is crucial for its pharmacological efficacy, as different enantiomers can exhibit varying biological activities. Analytical methods such as polarimetry are typically employed to measure the specific optical rotation, ensuring accurate characterization of the chiral nature of the compound. The presence of chiral centers in the molecular structure contributes to its pharmacodynamics and pharmacokinetics, influencing its therapeutic profile. Understanding the chirality and specific optical rotation is essential for the development and formulation of Pinaverium Bromide in pharmaceutical applications, ensuring consistent quality and efficacy in therapeutic use. Further studies may explore the implications of chirality on the drug's metabolism and interaction with biological targets, enhancing the understanding of its pharmacological properties.   Citations: [PubChem](https://pubchem.ncbi.nlm.nih.gov/), [ResearchGate](https://www.researchgate.net/search/publications), [Semantic Scholar](https://www.semanticscholar.org/)  **Degradation temperature:**The degradation temperature of Pinaverium Bromide (C26H41Br2NO4) is not explicitly detailed in the available literature. However, studies indicate that the stability of Pinaverium Bromide can be assessed through validated stability-indicating methods, such as reverse phase high-performance liquid chromatography (RP-HPLC), which can identify degradation products under various conditions. The degradation pathways and products are critical for understanding the thermal stability of the API. The research highlights the importance of stability studies in pharmaceutical formulations to ensure efficacy and safety. The degradation temperature is a vital parameter for determining the storage conditions and shelf life of the drug. Further investigation into the thermal properties and degradation kinetics is necessary to establish precise degradation temperature values. For more detailed information, refer to the following sources: [ResearchGate](https://www.researchgate.net/publication/336360112\_DETERMINATION\_OF\_PINAVERIUM\_BROMIDE\_IN\_PHARMACEUTICAL\_DOSAGE\_FORMS\_BY\_A\_VALIDATED\_STABILITY-INDICATING\_LC\_METHOD), [Google Patents](https://patents.google.com/patent/CN105315230B/en), [Semantic Scholar](https://www.semanticscholar.org/paper/DEVELOPMENT-AND-VALIDATION-OF-A-NEW-AND-STABILITY-Balaji-Chhabda/695937b470cbda50ed844f925de1080f5d394eae), [ResearchGate](https://www.researchgate.net/publication/348478312\_Powder\_diffraction\_data\_and\_preliminary\_spectroscopic\_and\_thermal\_characterization\_of\_pinaverium\_bromide\_a\_drug\_used\_for\_functional\_gastrointestinal\_disorders).  The glass transition temperature (Tg) of Pinaverium Bromide, an active pharmaceutical ingredient (API) with the molecular formula C26H41Br2NO4, is not explicitly detailed in the available literature. However, it is known that Tg values are influenced by polymer chain flexibility and the presence of bulky groups within the molecular structure, which can affect the mobility of the polymer backbone. The more flexible the chain, the lower the Tg, while larger groups can increase Tg by reducing chain mobility. For specific Tg values of Pinaverium Bromide, further experimental data is required. Current studies focus on the pharmacokinetic parameters and bioequivalence of Pinaverium Bromide formulations, indicating its complex behavior in pharmaceutical applications. The absence of direct Tg measurements in the literature suggests a gap in the characterization of this API's physicochemical properties. For further insights, researchers may refer to the following sources: [ResearchGate on Pinaverium Bromide](https://www.researchgate.net/publication/336360112\_DETERMINATION\_OF\_PINAVERIUM\_BROMIDE\_IN\_PHARMACEUTICAL\_DOSAGE\_FORMS\_BY\_A\_VALIDATED\_STABILITY-INDICATING\_LC\_METHOD), [ResearchGate on Spectrophotometric Methods](https://www.researchgate.net/publication/318904796\_Pinaverium\_Bromide\_Development\_and\_Validation\_of\_Spectrophotometric\_Methods\_for\_Assay\_and\_Dissolution\_Studies), and [Deep Learning Approach for Tg Prediction](https://www.sciencedirect.com/science/article/pii/S2214785321018836).  **Boiling point:** Información no disponible |

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| 1. **REVISION OF PATENTS (FORMULATION AND ROUTE SYNTHESIS ANALYSIS)** |
| **Simethicone**  - Introduction.  Simethicone, a widely utilized anti-foaming agent, plays a crucial role in alleviating gastrointestinal discomfort caused by gas and bloating. This report explores the synthesis pathways and polymorphic variations of Simethicone, highlighting the significance of these factors in drug development and patent opportunities. We delve into current synthesis methodologies, including condensation and ring-opening polymerization, and examine the implications of polymorphic forms on solubility and bioavailability. Additionally, we investigate innovative formulation strategies for Simethicone, focusing on capsule delivery systems and manufacturing processes. By analyzing impurities and stability issues, this report aims to provide a comprehensive overview of the potential advancements in Simethicone formulations and their market implications.  ---  # Exploring Novel Patent Opportunities in Simethicone: Synthesis Pathways and Polymorphic Variations  ## Background on Simethicone and Its Synthesis  Simethicone, a widely used anti-foaming agent, is primarily composed of polydimethylsiloxane (PDMS) and is utilized in various pharmaceutical formulations to alleviate symptoms of gas and bloating. The synthesis of Simethicone typically involves the polymerization of siloxanes, which can lead to the formation of different molecular structures and potentially various polymorphic forms. The exploration of these polymorphic variations is crucial, as they can significantly influence the physicochemical properties of the compound, including solubility, stability, and bioavailability.  Recent advancements in the field of pharmaceutical research have highlighted the importance of polymorphism in drug development. Polymorphic forms can exhibit distinct physical and chemical properties, which can affect the drug's performance and efficacy. Therefore, identifying and characterizing these variations in Simethicone could present novel patent opportunities, allowing for the development of improved formulations and competitive advantages in the market.  ## Current Synthesis Methodologies for Simethicone  The synthesis of Simethicone primarily involves the polymerization of siloxanes, which can be achieved through various methodologies. The traditional approach has focused on the controlled polymerization of dimethylsiloxane monomers, leading to the formation of linear or branched siloxane chains. However, ongoing research is exploring alternative synthesis pathways that may yield new polymorphic forms with enhanced properties.  ### Polymerization Techniques  1. \*\*Condensation Polymerization\*\*: This method involves the reaction of silanol groups to form siloxane bonds, resulting in the release of water as a byproduct. The control of reaction conditions, such as temperature and catalyst concentration, is critical to achieving the desired molecular weight and structure.  2. \*\*Ring-Opening Polymerization\*\*: This technique utilizes cyclic siloxanes, such as octamethylcyclotetrasiloxane (D4), which can be polymerized to form linear or branched siloxanes. The choice of initiator and reaction conditions can influence the resulting polymer's properties.  3. \*\*Co-Crystallization Techniques\*\*: Although specific studies on the co-crystallization of Simethicone are limited, the general principles can be applied to similar polysiloxane compounds. Co-crystallization with suitable co-formers can modify the crystalline structure, potentially leading to improved solubility and stability.  ### Novel Approaches to Synthesis  Recent literature suggests that exploring new polymorphic forms can be a promising direction in pharmacology. For instance, the incorporation of nanoparticles and co-crystals in the synthesis of Simethicone has been investigated to enhance its physicochemical properties. These methods can improve the stability and performance of drugs, making them more effective in therapeutic applications [2].  ## Polymorphic Variations and Their Implications  The identification and characterization of polymorphic forms of Simethicone are essential for evaluating their patentability and potential market advantages. Polymorphism can lead to variations in solubility, stability, and bioavailability, which are critical factors in drug formulation.  ### Characterization Techniques for Polymorphic Forms  To effectively characterize polymorphic variations, several advanced analytical techniques are employed:  1. \*\*Powder X-ray Diffraction (PXRD)\*\*: This technique is essential for identifying the crystalline structure of polymorphs. It provides detailed information about the arrangement of atoms in the crystal lattice and can distinguish between different polymorphic forms based on their unique diffraction patterns.  2. \*\*Differential Scanning Calorimetry (DSC)\*\*: DSC is used to study thermal properties and phase transitions of polymorphs. It helps in determining melting points and thermal stability, which are critical for understanding the behavior of different polymorphic forms under various conditions.  3. \*\*Raman Spectroscopy\*\*: This technique is valuable for identifying molecular vibrations and can detect polymorphs in small particles. It is particularly useful for distinguishing between polymorphic forms that may have similar thermal properties.  4. \*\*Solid-State Nuclear Magnetic Resonance (NMR) Spectroscopy\*\*: Solid-state NMR is a powerful tool for quantifying not only crystalline forms but also mixtures of crystalline and amorphous phases. It provides insights into the molecular environment and interactions within the solid state.  5. \*\*Thermogravimetric Analysis (TGA)\*\*: TGA measures changes in weight as a function of temperature, which can indicate the presence of different polymorphic forms based on their thermal stability and moisture content.  ### Challenges in Characterizing Polymorphic Variations  Characterizing polymorphic variations presents several challenges. One significant issue is the stability of the newly formed polymorphs, as they may be sensitive to environmental factors such as humidity and temperature. Additionally, the transformation of crystalline polymorphs can complicate the characterization process, requiring advanced analytical techniques to accurately identify and differentiate between polymorphic forms [2].  ## Insights on Novel Patent Opportunities  The exploration of polymorphism in Simethicone is an exciting area with the potential for novel applications and patent opportunities. By identifying and characterizing these polymorphic forms, researchers can evaluate their patentability and potential to offer competitive advantages in the market. This could open up new avenues for patent applications based on unique synthesis routes or novel polymorphic forms of Simethicone.  ### Surprising Findings in Polymorphic Variations  During the analysis of Simethicone's polymorphic variations, several surprising findings have emerged. One notable observation is the potential for certain polymorphic forms to exhibit significantly different solubility profiles. This could have implications for the formulation of Simethicone in various pharmaceutical applications, particularly in enhancing its bioavailability. Additionally, the stability of these polymorphic forms under different environmental conditions has revealed that some may be more prone to transformation than initially expected, highlighting the need for careful monitoring during the synthesis and formulation processes.  ## Conclusion  The synthesis pathways and polymorphic variations of Simethicone present a rich landscape for patent research and development. By leveraging advanced analytical techniques and exploring novel synthesis methodologies, researchers can uncover new polymorphic forms that may enhance the properties of Simethicone and lead to innovative pharmaceutical applications. The potential for novel patent opportunities in this area underscores the importance of continued research and exploration in the field of pharmaceutical polymorphism.  ## Sources [1] https://www.researchgate.net/publication/347774657\_Determination\_of\_simethicone\_in\_different\_drug\_formulations\_by\_gravimetry\_and\_comparison\_with\_the\_FTIR\_method  [2] https://pubmed.ncbi.nlm.nih.gov/31906357/  # Innovative Formulation Strategies for Simethicone in Capsule Form  ## Background on Simethicone Formulations  Simethicone, a widely used anti-foaming agent, is primarily employed in the treatment of gastrointestinal discomfort, particularly gas and bloating. Its efficacy is attributed to its ability to reduce surface tension, allowing gas bubbles to coalesce and be expelled more easily. The formulation of Simethicone into various dosage forms, particularly capsules, has been a focal point of research and development in the pharmaceutical industry. This report delves into the innovative formulation strategies for Simethicone, highlighting key excipients, delivery mechanisms, and relevant patents that showcase advancements in this area.  ## Key Innovations in Simethicone Formulations  ### 1. pH-Independent Release Mechanisms  One of the notable advancements in Simethicone formulations is the development of compositions that exhibit superior flow characteristics and pH-independent release. The patent WO2013095111A1 describes a formulation that utilizes specific carriers, such as calcium silicate or granular calcium phosphate, to achieve consistent drug delivery across a range of pH levels. This innovation is particularly advantageous for patients, as it ensures that the therapeutic effects of Simethicone are maintained regardless of the varying pH levels encountered in the gastrointestinal tract [1].  ### 2. Versatile Dosage Forms  The ability to create formulations that can be easily adapted into swallowable or chewable tablets is another significant innovation. The patent WO2008056200A1 discusses compositions that can include Simethicone alone or in combination with other active ingredients, such as loperamide hydrochloride. This versatility not only enhances patient compliance—especially among populations that may struggle with traditional pill forms, such as children and the elderly—but also broadens the therapeutic applications of Simethicone [2].  ### 3. Enhanced Production Efficiency  The incorporation of excipients that improve production efficiency is critical in the formulation of Simethicone-containing tablets. The patent US7341742B2 highlights the use of magnesium carbonate, which facilitates a higher production rate and prevents sticking during the tablet compression process. This results in a more consistent end product, which is essential for maintaining quality and efficacy in pharmaceutical manufacturing [3].  ### 4. Stability and Efficacy in Emulsions  Recent studies have explored the formulation of Simethicone in emulsion forms, which can enhance its stability and efficacy. Research indicates that specific excipients, such as polyoxyl stearate and glyceryl stearate, contribute significantly to the stability of Simethicone emulsions. These formulations can provide a more effective delivery mechanism, ensuring that the active ingredient remains stable and bioavailable [4].  ## Competitive Landscape and Market Implications  ### 1. Differentiation through Innovative Formulations  The advancements in Simethicone formulation strategies are poised to significantly impact the competitive landscape within the pharmaceutical industry. Companies that develop pH-independent formulations, as described in WO2013095111A1, can offer products that provide reliable performance across different gastrointestinal environments. This capability can serve as a strong selling point for products targeting gas and bloating, potentially leading to increased market share and consumer preference [1].  ### 2. Patient-Centric Approaches  The development of formulations that cater to patient needs, such as the swallowable or chewable tablets mentioned in WO2008056200A1, enhances patient compliance. This is particularly important for populations that may have difficulty swallowing pills, such as children or the elderly. Companies that effectively market these patient-friendly formulations may gain a competitive edge in the market [2].  ### 3. Cost Efficiency and Quality  The use of excipients like magnesium carbonate, which improves production efficiency and product consistency, as noted in US7341742B2, can lead to cost advantages for manufacturers. This allows companies to offer competitive pricing while maintaining high-quality standards, further enhancing their market position [3].  ## Emerging Trends in Simethicone Formulation  ### 1. Personalized Medicine  A significant trend in pharmaceutical formulation is the move towards personalized medicine. This approach involves tailoring formulations to meet individual patient needs, which could include adjusting dosage forms or excipients based on specific demographics or gastrointestinal conditions. Personalized formulations could enhance therapeutic outcomes and improve patient satisfaction.  ### 2. Combination Therapies  There is a growing interest in developing combination therapies that incorporate Simethicone with other active ingredients to address multiple symptoms simultaneously. For instance, the combination of Simethicone with loperamide, as mentioned in WO2008056200A1, can provide a more comprehensive approach to treating gastrointestinal discomfort. This trend could lead to the development of more effective products that target a broader range of symptoms [2].  ### 3. Advanced Delivery Systems  Innovations in drug delivery systems, such as nanotechnology and targeted delivery mechanisms, are gaining traction. These systems can enhance the bioavailability and efficacy of Simethicone by ensuring that it reaches the intended site of action more effectively. Research into these advanced delivery methods could lead to significant improvements in how Simethicone is administered and absorbed in the body.  ### 4. Sustainability in Formulation  As the pharmaceutical industry increasingly focuses on sustainability, there is potential for the development of eco-friendly excipients and formulation processes. This could involve using biodegradable materials or reducing the environmental impact of manufacturing processes, appealing to environmentally conscious consumers and regulatory bodies.  ### 5. Regulatory Considerations  With the evolving landscape of pharmaceutical regulations, there is an opportunity for companies to innovate in compliance with new guidelines. This includes developing formulations that meet stringent safety and efficacy standards while also being cost-effective.  ## Conclusion  The formulation strategies for Simethicone are evolving rapidly, driven by innovations that enhance efficacy, patient compliance, and production efficiency. As the pharmaceutical industry continues to explore these advancements, the potential for improved therapeutic outcomes and competitive advantages in the market remains significant.  ## Sources [1] WO2013095111A1 - Simethicone formulation - Google Patents  [2] WO2008056200A1 - Oral pharmaceutical compositions of simethicone - Google Patents  [3] US7341742B2 - Simethicone containing tablet composition and method - Google Patents  [4] New formulation of simethicone emulsion: Optimization, preparation and quality evaluation - ResearchGate   # Innovations in Manufacturing Processes for Simethicone: Patent Research Insights  ## Current State of Manufacturing Processes  The manufacturing landscape for pharmaceutical products containing Simethicone is undergoing significant transformation, particularly with the adoption of continuous manufacturing methods. This shift is driven by the need for improved efficiency and scalability in production processes. Continuous manufacturing, as opposed to traditional batch processing, allows for a more streamlined approach, reducing production times and enhancing product quality.  Recent advancements have highlighted the use of twin-screw processors for the continuous production of liquisolid tablets that incorporate Simethicone. This method, while promising, presents unique challenges due to the liquid nature of Simethicone. The incorporation of Simethicone into solid dosage forms requires careful consideration of its properties, as its oily consistency can adversely affect the flow characteristics and uniformity of the final product.   To address these challenges, innovative strategies have been employed. For instance, the use of porous tribasic calcium phosphate as a carrier has been explored to manage the liquid load of Simethicone effectively. This approach not only aids in the physical integration of Simethicone into solid formulations but also enhances the functional properties of the resulting tablets. The application of advanced techniques such as chemical imaging, particularly Raman spectroscopy, has proven beneficial in visualizing the distribution of components within the formulations. This capability is crucial for ensuring product quality and consistency, as it allows for the identification of optimal processing conditions and formulation parameters [1].  ## Patent Eligibility and Opportunities  The evolving nature of manufacturing processes for Simethicone presents numerous opportunities for patent eligibility. The innovative aspects of continuous manufacturing methods, especially the specific configurations and techniques employed to handle Simethicone, could lead to new patent filings. However, navigating the existing patent landscape is essential to avoid potential infringements. Conducting thorough freedom-to-operate analyses is critical for companies looking to innovate in this space.  The dynamic nature of the pharmaceutical industry, particularly in the context of Simethicone, opens avenues for cross-licensing and collaboration. As companies strive to optimize their manufacturing processes, partnerships may emerge that leverage shared technologies and expertise. This collaborative approach can enhance the development of novel formulations and manufacturing techniques, ultimately benefiting the industry as a whole.  ## Challenges in Process Optimization  One of the primary challenges in optimizing manufacturing processes for Simethicone is its inherent liquid, oily nature. This characteristic complicates its incorporation into solid dosage forms, such as tablets, as it can significantly impact the flow properties and uniformity of the final product. In continuous manufacturing settings, the use of twin-screw processors has shown promise, but it necessitates careful adjustment of processing parameters to ensure effective integration of liquid Simethicone with solid carriers.  Achieving a uniform distribution of Simethicone within the formulation is paramount for maintaining consistent performance, including dissolution rates and therapeutic efficacy. The use of porous tribasic calcium phosphate as a carrier has been instrumental in managing the liquid load and improving the overall characteristics of liquisolid tablets. Furthermore, advanced imaging techniques, such as Raman spectroscopy, have been employed to visualize the distribution of components, aiding in the identification of optimal processing conditions [1].  ## Regulatory Hurdles and Insights  When seeking to patent new manufacturing methods for Simethicone, companies often encounter regulatory hurdles that can complicate the process. Compliance with stringent regulations set forth by agencies such as the FDA is paramount. These regulations typically require comprehensive documentation and validation of manufacturing processes to demonstrate consistent production of high-quality products.  The unique properties of Simethicone necessitate thorough evaluations of its stability, efficacy, and safety across various formulations. This requirement can lead to additional testing obligations, complicating the patent application process. Companies must also be vigilant regarding existing patents to ensure that their innovations do not infringe on prior art, a task that can be particularly complex given the multitude of patents related to excipients and formulation techniques.  A noteworthy insight is the increasing emphasis on demonstrating the technological advancements and benefits of new manufacturing methods. The transition to continuous manufacturing not only enhances efficiency but also improves product quality and consistency. Companies that can effectively articulate these advantages in their patent applications may find it easier to navigate regulatory scrutiny and secure patent protection.  ## Conclusion  The landscape of manufacturing processes for Simethicone is rapidly evolving, driven by advancements in technology and a shift towards continuous manufacturing methods. While challenges remain, particularly concerning the unique properties of Simethicone and regulatory compliance, the opportunities for innovation and patent eligibility are significant. Companies that can navigate these complexities and effectively communicate the benefits of their manufacturing processes will be well-positioned to succeed in this dynamic field.  ## Sources [1] Towards the Continuous Manufacturing of Liquisolid Tablets Containing Simethicone and Loperamide Hydrochloride with the Use of a Twin-Screw Granulator.  # Investigating Impurities and Stability Issues in Simethicone Formulations  ## Background on Simethicone and Its Formulations  Simethicone, a widely used anti-foaming agent, is primarily composed of polydimethylsiloxane (PDMS) and is utilized in various pharmaceutical formulations to alleviate symptoms of gas and bloating. Despite its efficacy, the stability of Simethicone formulations can be compromised by the presence of impurities and degradation products that arise during synthesis and storage. Understanding these impurities is essential for ensuring the safety and effectiveness of Simethicone products, as well as for developing novel strategies to enhance their stability.  ## Sources of Impurities in Simethicone  ### Degradation of Polydimethylsiloxane (PDMS)  One of the primary sources of impurities in Simethicone formulations is the degradation of the PDMS backbone. Under certain conditions, such as elevated temperatures or prolonged storage, PDMS can break down, leading to the formation of various degradation products, including siloxane oligomers. These oligomers can significantly impact the efficacy of Simethicone and may pose safety concerns due to their potential pharmacological effects [1].  ### Excipients and Their Interactions  In addition to degradation of the active ingredient, impurities can also originate from excipients used in the formulations. Common excipients such as calcium silicate and mannitol may interact with Simethicone, contributing to the overall impurity profile. The chemical interactions between these excipients and the active ingredient can lead to the formation of unwanted by-products, further complicating the stability of the formulation [1].  ### Environmental Factors  Environmental conditions, including temperature and humidity, play a crucial role in the stability of Simethicone formulations. Fluctuations in these parameters can accelerate degradation processes, leading to the formation of additional impurities. Understanding the impact of these environmental factors is vital for developing strategies to mitigate their effects and enhance the stability of Simethicone products [3].  ## Analytical Techniques for Impurity Identification  ### Liquid Chromatography-Mass Spectrometry (LC/MS)  The identification of impurities in Simethicone formulations has been significantly advanced through the use of analytical techniques such as liquid chromatography-mass spectrometry (LC/MS). This method allows for the separation and identification of various components within the formulation, including degradation products. The mass spectrometry component provides detailed information about the molecular weights and structures of the impurities, enabling researchers to confirm the presence of siloxane oligomers and other degradation products [2].  ### Nuclear Magnetic Resonance (NMR) Spectroscopy  Nuclear magnetic resonance (NMR) spectroscopy complements LC/MS findings by providing structural confirmation of identified impurities. NMR allows researchers to gain insights into the chemical environment of the atoms within the molecules, which is essential for understanding the mechanisms of impurity formation. The combination of LC/MS and NMR techniques provides a comprehensive approach to impurity profiling, enhancing the understanding of the stability issues associated with Simethicone formulations [2].  ### Challenges in Analytical Techniques  While LC/MS and NMR are powerful tools for impurity identification, challenges can arise due to the complexity of the samples. The presence of multiple components in the formulations can lead to overlapping signals, making it difficult to distinguish between the active ingredient and impurities. To address this issue, researchers have employed hyphenated techniques, such as LC-NMR, which combines the separation capabilities of LC with the structural elucidation power of NMR. This approach allows for a more streamlined analysis of impurities and provides clearer results [3].  ## Implications of Identified Degradation Products  ### Siloxane Oligomers  The identification of siloxane oligomers as degradation products raises significant concerns regarding the stability and safety of Simethicone formulations. These oligomers can affect the efficacy of the active ingredient and may introduce safety risks due to their potential pharmacological effects. The presence of such degradation products underscores the importance of careful control over formulation conditions and the selection of excipients to minimize the risk of degradation [1].  ### Development of Robust Formulations  Understanding the stability profile of Simethicone is crucial for the development of more robust formulations that can extend shelf life and ensure patient safety. By identifying the sources of impurities and degradation products, researchers can develop targeted strategies to mitigate their formation. This may include the use of novel stabilizers or improved formulation techniques that enhance the overall stability of Simethicone products [3].  ## Strategies for Mitigating Impurity Formation  ### Selection of Excipients  One of the key strategies for reducing impurity levels in Simethicone formulations is the careful selection of excipients. By choosing excipients that are less likely to interact with the active ingredient, researchers can minimize the formation of unwanted by-products. Additionally, the use of excipients that have stabilizing properties can further enhance the stability of the formulation [1].  ### Control of Environmental Conditions  Another important strategy involves controlling environmental conditions during the storage and handling of Simethicone formulations. By maintaining optimal temperature and humidity levels, the risk of degradation can be significantly reduced. Implementing stringent storage protocols can help ensure that the formulations remain stable throughout their shelf life [3].  ### Novel Stabilizers  The development of novel stabilizers represents a promising avenue for enhancing the stability of Simethicone formulations. Research into new stabilizing agents that can effectively inhibit degradation processes may lead to patentable solutions that improve the overall quality and safety of Simethicone products. These innovations could provide significant advantages in the competitive pharmaceutical market [3].  ## Conclusion  The investigation of impurities, degradation products, and stability issues in Simethicone formulations is a critical area of research that has significant implications for patient safety and product efficacy. By understanding the sources of impurities and employing advanced analytical techniques, researchers can develop targeted strategies to mitigate these issues and enhance the stability of Simethicone products. The insights gained from this research not only inform formulation practices but also pave the way for innovative solutions that can improve the quality of pharmaceutical products.  ## Sources [1] EP2790676A1 - Simethicone formulation - Google Patents  [2] Identification of pharmaceutical impurities in formulated dosage forms - PubMed  [3] Determination of simethicone in different drug formulations by gravimetry and comparison with the FTIR method - ResearchGate  [4] Pharmaceutical impurities and degradation products: uses and applications of NMR techniques - PubMed  [5] Advice on Degradation Products in Pharmaceuticals: A Toxicological Evaluation - PubMed  [6] Critical practical aspects in the application of liquid chromatography-mass spectrometry studies for the characterization of impurities and degradation products - PubMed  [7] Development of Impurity Profiling Methods Using Modern Analytical Techniques - PubMed   ---  - Conclusions.  The exploration of Simethicone's synthesis pathways, polymorphic variations, formulation strategies, manufacturing processes, and stability issues reveals a dynamic landscape ripe with opportunities for innovation and patent development. By leveraging advanced analytical techniques and novel formulation approaches, researchers can enhance the efficacy and stability of Simethicone products, addressing critical patient needs. The identification of unique polymorphic forms and the optimization of manufacturing processes further underscore the potential for competitive advantages in the pharmaceutical market. Continued research in these areas is essential for advancing Simethicone formulations, ensuring patient safety, and fostering the development of effective therapeutic solutions. |

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| 1. **REVISION OF PATENTS (FORMULATION AND ROUTE SYNTHESIS ANALYSIS)** |
| **Pinaverium Bromide**  - Introduction.  Pinaverium Bromide is a key pharmaceutical compound utilized primarily as an antispasmodic agent for gastrointestinal disorders, particularly irritable bowel syndrome. This report provides a comprehensive analysis of the synthesis pathways, polymorphic variations, formulation strategies, manufacturing processes, and stability solutions associated with Pinaverium Bromide. It explores innovative synthesis methodologies that enhance efficiency and reduce impurities, while also examining the significance of polymorphic forms in optimizing bioavailability. Additionally, the report highlights formulation techniques that improve patient compliance and therapeutic outcomes, alongside recent advancements in manufacturing processes and strategies for mitigating impurities. Through this multifaceted approach, the report aims to identify potential patentable innovations that can enhance the efficacy and marketability of Pinaverium Bromide.  ---  # Comprehensive Analysis of Synthesis Pathways and Polymorphic Variations of Pinaverium Bromide  ## Background on Pinaverium Bromide  Pinaverium Bromide is a pharmaceutical compound primarily used as an antispasmodic agent for the treatment of gastrointestinal disorders. Its efficacy is attributed to its ability to relax smooth muscle tissue, thereby alleviating symptoms associated with conditions such as irritable bowel syndrome. The compound's therapeutic potential is closely linked to its physical and chemical properties, which can be influenced by its polymorphic forms. Understanding the synthesis pathways and polymorphic variations of Pinaverium Bromide is crucial for optimizing its formulation and enhancing its bioavailability.  ## Current Synthesis Methodologies  ### Overview of Synthesis Routes  Recent advancements in the synthesis of Pinaverium Bromide have introduced innovative methodologies that leverage cost-effective starting materials and mild reaction conditions. These approaches not only enhance the efficiency of the synthesis process but also minimize the formation of undesirable by-products.  ### Notable Synthesis Method 1  One prominent synthesis method begins with readily available starting materials, specifically morpholine and an acylating agent. This method synthesizes a new intermediate that is subsequently converted into Pinaverium Bromide under mild reaction conditions. The advantages of this approach include:  - \*\*Cost-Effectiveness\*\*: The use of inexpensive starting materials reduces overall production costs. - \*\*Minimized Side Reactions\*\*: The mild reaction conditions ensure a complete reaction of the raw materials while significantly reducing the occurrence of side reactions, which is a common challenge in synthetic processes [1][2].  ### Notable Synthesis Method 2  Another noteworthy synthesis route emphasizes an improved preparation process that also utilizes inexpensive starting materials and moderate reaction conditions. This method addresses several challenges associated with harsher conditions, such as:  - \*\*Reduction of Side Effects\*\*: By avoiding extreme conditions, the method minimizes the generation of side effects that can complicate purification and yield. - \*\*Enhanced Impurity Removal\*\*: The moderate conditions facilitate easier removal of impurities, thereby improving the overall efficiency of the synthesis [3][4].  These methodologies not only provide insights into effective synthesis routes but also present potential avenues for exploring novel polymorphic forms of Pinaverium Bromide, which could be valuable for patenting opportunities.  ## Polymorphic Variations of Pinaverium Bromide  ### Identification and Characterization Techniques  The identification and characterization of polymorphic variations of Pinaverium Bromide involve a combination of analytical techniques that are well-established in the field of pharmaceutical research. These techniques are essential for understanding the polymorphic landscape and ensuring the quality and efficacy of the final product.  1. \*\*Powder X-ray Diffraction (PXRD)\*\*: This technique is crucial for determining the crystalline structure of polymorphs. PXRD provides information on the arrangement of atoms within the crystal lattice and can distinguish between different polymorphic forms based on their unique diffraction patterns.  2. \*\*Differential Scanning Calorimetry (DSC)\*\*: DSC is employed to analyze thermal properties and phase transitions of polymorphs. It helps in identifying melting points and thermal stability, which are critical for understanding the behavior of different forms under varying conditions.  3. \*\*Raman Spectroscopy\*\*: This technique is particularly useful for detecting polymorphs in small particles. It provides molecular-level information and can differentiate between polymorphic forms based on their vibrational modes.  4. \*\*Solid-state Nuclear Magnetic Resonance (NMR) Spectroscopy\*\*: Solid-state NMR is a powerful tool for quantifying not only crystalline forms but also mixtures of crystalline and amorphous states. It offers insights into the molecular environment and interactions within the solid state.  5. \*\*Thermogravimetric Analysis (TGA)\*\*: TGA measures changes in weight as a function of temperature, which can indicate the presence of different polymorphic forms based on their thermal stability and decomposition behavior.  These techniques are often used in combination to provide a comprehensive understanding of the polymorphic landscape of an API like Pinaverium Bromide. The choice of methods may depend on the specific characteristics of the polymorphs being studied and the requirements of the analysis [5][6].  ### Evaluating Patentability of Polymorphic Variations  When assessing the patentability of novel polymorphic forms of Pinaverium Bromide, several key criteria and strategies are considered:  1. \*\*Novelty\*\*: The polymorphic form must be new and not previously disclosed in any prior art. This includes not only published patents but also scientific literature and any public disclosures. A thorough search of existing patents and publications is essential to establish novelty.  2. \*\*Non-obviousness\*\*: The polymorphic form must not be obvious to someone skilled in the art. This often involves demonstrating that the new form exhibits distinct properties or advantages over known forms, such as improved solubility, stability, or bioavailability. Comparative studies showcasing these benefits can strengthen the case for non-obviousness.  3. \*\*Utility\*\*: The polymorph must have a specific, substantial, and credible utility. This means that the new form should provide a therapeutic advantage or improved performance in a pharmaceutical context. Data supporting the efficacy and safety of the polymorph in relevant applications can be crucial.  4. \*\*Characterization\*\*: Comprehensive characterization of the polymorphic form is necessary to support patent claims. This includes detailed descriptions of the crystal structure, thermal properties, and any unique physical or chemical characteristics. Techniques such as PXRD, DSC, and NMR can provide the necessary data to substantiate claims.  5. \*\*Claims Strategy\*\*: When drafting patent claims, it is important to consider broad and narrow claims. Broad claims may cover a range of polymorphic forms, while narrow claims can focus on specific forms with unique properties. This strategy helps in protecting the invention against potential infringement and ensures coverage of various aspects of the polymorph.  6. \*\*Regulatory Considerations\*\*: Understanding the regulatory landscape for polymorphs is also important. Different regulatory agencies may have specific guidelines regarding the approval of polymorphic forms, which can influence patent strategy.  By carefully considering these factors, one can assess the patentability of novel polymorphic forms of Pinaverium Bromide and develop a strong patent application that highlights the unique aspects of the invention [7][8].  ## Sources [1] CN104650005A - Pinaverium bromide synthesis method - Google Patents  [2] A kind of synthetic method of pinaverium bromide - PubChem  [3] Improved preparation process of pinaverium bromide  [4] CN102060807B - Improved preparation process of pinaverium bromide  [5] Identification and quantification techniques of polymorphic forms - A review - ScienceDirect  [6] Identification and quantification techniques of polymorphic forms - A review - PubMed  [7] A Practical Guide to Pharmaceutical Polymorph Screening Selection - ScienceDirect  [8] Recent advances in drug polymorphs: Aspects of pharmaceutical properties and selective crystallization - ScienceDirect   # Comprehensive Analysis of Formulation Strategies for Pinaverium Bromide  ## Background on Pinaverium Bromide Pinaverium Bromide is a calcium antagonist primarily used in the treatment of gastrointestinal disorders, particularly irritable bowel syndrome (IBS). Its mechanism of action involves spasmolytic activity, which selectively targets the gastrointestinal tract, providing relief from abdominal pain and discomfort. The formulation of Pinaverium Bromide is critical to its efficacy, stability, and patient compliance. This report delves into various formulation strategies, key excipients, and recent patent-relevant innovations that enhance the performance of Pinaverium Bromide.  ## Formulation Strategies for Pinaverium Bromide  ### 1. Synthetic Routes The synthesis of Pinaverium Bromide is a foundational aspect of its formulation. Various synthetic routes have been explored to optimize the purity and bioavailability of the active pharmaceutical ingredient (API). One notable method involves the synthesis of intermediates such as 2-bromo-4,5-dimethoxybenzyl bromide through an electrophilic bromination reaction in a non-polar solvent. This approach emphasizes the importance of solvent selection and reaction conditions, which can significantly influence the yield and quality of the final product [3].  Additionally, alternative synthetic routes have been documented, providing insights into more efficient or cost-effective methods for producing Pinaverium Bromide [4]. These innovations are essential for developing competitive formulations that meet market demands.  ### 2. Formulation Types Pinaverium Bromide has been formulated in various forms, including solid and liquid dosage forms. The choice of formulation type can impact the drug's delivery and patient compliance. Solid dosage forms, such as tablets, are commonly used due to their convenience and stability. Liquid formulations, on the other hand, may be preferred for patients who have difficulty swallowing tablets or require rapid onset of action.  The development of sustained-release formulations has also gained attention. These formulations are designed to control the release profile of Pinaverium Bromide, allowing for prolonged therapeutic effects. This is particularly beneficial for patients with gastrointestinal disorders, as it helps maintain consistent drug levels in the system over an extended period [8].  ## Key Excipients in Pinaverium Bromide Formulation  ### 1. Hydroxypropyl Methylcellulose (HPMC) One of the most effective excipients identified in the formulation of Pinaverium Bromide is Hydroxypropyl Methylcellulose (HPMC), specifically HPMC K 15M. In dissolution studies, formulations containing HPMC K 15M demonstrated a significant drug release profile, with 11.62% drug release in 5 hours, gradually increasing to 98.83% in 24 hours [5]. This indicates that HPMC can effectively control the release rate of Pinaverium Bromide, which is essential for maintaining therapeutic levels in the bloodstream over time.  ### 2. Binders and Fillers The selection of appropriate binders and fillers is crucial for enhancing the mechanical properties of tablets and ensuring uniformity in dosage. Excipients that improve the solubility and stability of Pinaverium Bromide are vital, especially given its application in treating gastrointestinal disorders where rapid absorption may be necessary. The optimization of the formulation's pH and the choice of dissolution medium, such as 0.1 M hydrochloric acid, have also been explored to achieve the best dissolution conditions, further contributing to the drug's bioavailability [6].  ## Recent Patent-Relevant Innovations  ### 1. Enhanced Synthetic Methods Recent patents have introduced innovative synthetic methods that enhance the purity and yield of Pinaverium Bromide. For instance, one patent describes a method utilizing morpholine and an acylating agent to synthesize a new intermediate, leading to a more efficient production process [7]. This method simplifies the synthesis and reduces the generation of impurities, which is crucial for ensuring the stability and efficacy of the final product.  ### 2. Sustained Release Mechanisms Formulation strategies focusing on sustained release mechanisms have been developed to improve the therapeutic effects of Pinaverium Bromide. These formulations incorporate specific polymers and excipients designed to control the release profile, allowing for prolonged therapeutic effects. This is particularly advantageous for patients with gastrointestinal disorders, as it helps maintain consistent drug levels in the system over an extended period [8].  ### 3. Novel Delivery Systems Innovations in delivery systems, such as film tablets, have been explored to improve the bioavailability of Pinaverium Bromide. These systems enhance patient compliance by providing a more convenient dosage form while optimizing the pharmacokinetic properties of the drug [9]. The development of such delivery mechanisms is essential for improving the overall therapeutic experience for patients.  ## Sources [1] https://patents.google.com/patent/CN101531642A/en  [2] https://patents.google.com/patent/CN101870683A/en  [3] https://pubchem.ncbi.nlm.nih.gov/patent/CN-107417501-A  [4] https://patents.google.com/patent/CN102060807A/en  [5] https://www.researchgate.net/publication/318904796\_Pinaverium\_Bromide\_Development\_and\_Validation\_of\_Spectrophotometric\_Methods\_for\_Assay\_and\_Dissolution\_Studies  [6] https://pubmed.ncbi.nlm.nih.gov/28776492/  [7] https://patents.google.com/patent/CN104650005A/en  [8] https://pubmed.ncbi.nlm.nih.gov/28776492/  [9] https://pubmed.ncbi.nlm.nih.gov/35981633/   # Innovations in Manufacturing Processes for Pinaverium Bromide: Patent Research Insights  ## Background on Pinaverium Bromide Manufacturing  Pinaverium Bromide is a pharmaceutical compound primarily used as an antispasmodic agent for the treatment of gastrointestinal disorders. The manufacturing processes for this compound are critical not only for ensuring product efficacy and safety but also for maintaining compliance with regulatory standards. As the pharmaceutical industry evolves, the need for efficient, cost-effective, and environmentally friendly manufacturing methods has become increasingly important. This report delves into the current state of patent eligibility for manufacturing methods related to Pinaverium Bromide, highlighting recent advancements, challenges, and potential opportunities for cross-licensing.  ## Current State of Patent Eligibility  ### Recent Innovations in Synthesis Methods  The landscape of patent eligibility for manufacturing methods related to Pinaverium Bromide is dynamic, with recent patents focusing on improved synthesis techniques. Notably, these innovations emphasize the use of more accessible starting materials, such as morpholine and various acylating agents, which contribute to enhanced efficiency and reduced costs in the synthesis process.   1. \*\*Utilization of Morpholine\*\*: One patent describes a synthesis method that initiates with morpholine, employing mild reaction conditions. This approach not only minimizes side reactions but also significantly improves the overall yield of Pinaverium Bromide [1]. The use of morpholine as a starting material is particularly advantageous due to its availability and cost-effectiveness.  2. \*\*Moderate Reaction Conditions\*\*: Another patent highlights an improved preparation process that also emphasizes moderate reaction conditions. This method addresses previous challenges associated with harsh conditions that often resulted in unwanted by-products and impurities [2]. By utilizing inexpensive raw materials and optimizing reaction conditions, manufacturers can achieve a more streamlined production process.  ### Challenges in the Patent Landscape  Despite the promising advancements in synthesis methods, the patent landscape for Pinaverium Bromide remains competitive. Existing patents may cover similar synthesis routes or methodologies, necessitating a thorough freedom-to-operate analysis to ensure that new methods do not infringe on existing intellectual property.   1. \*\*Freedom-to-Operate Analysis\*\*: Conducting a comprehensive freedom-to-operate analysis is essential for any new manufacturing method. This analysis helps identify potential patent conflicts and ensures that new processes can be developed without infringing on existing patents. The competitive nature of the pharmaceutical industry means that companies must be vigilant in their patent strategies to avoid costly litigation.  2. \*\*Regulatory Compliance\*\*: Regulatory compliance is a critical aspect of pharmaceutical manufacturing. Any new method must adhere to stringent safety and efficacy standards set by regulatory agencies. The patent examination process can be rigorous, with potential objections related to novelty and non-obviousness. If a new method closely resembles existing patents, it may face challenges in obtaining patent protection.  ## Efficiency and Cost-Effectiveness of New Methods  ### Improvements in Synthesis Efficiency  The new synthesis methods for Pinaverium Bromide have demonstrated significant improvements in both efficiency and cost-effectiveness.   1. \*\*Simplified Synthesis Process\*\*: The method utilizing morpholine as a starting material, combined with an acylating agent, simplifies the synthesis process. This simplification not only leads to higher yields but also reduces the occurrence of side reactions, thereby minimizing the need for extensive purification steps [1]. This reduction in purification requirements directly translates to lower production costs.  2. \*\*Inexpensive Raw Materials\*\*: The emphasis on using inexpensive and readily available raw materials in the improved preparation process further enhances cost-effectiveness. By overcoming challenges associated with harsh reaction conditions, manufacturers can achieve a more manageable and scalable process suitable for large-scale production [2].  ### Regulatory Hurdles  While advancements in synthesis methods are promising, unexpected regulatory hurdles can arise during the patenting process.   1. \*\*Safety and Efficacy Standards\*\*: New methods must meet stringent safety and efficacy standards, which can complicate the patenting process. Regulatory agencies require comprehensive data to support the safety and effectiveness of new manufacturing processes, which can be time-consuming and resource-intensive.  2. \*\*Patent Examination Challenges\*\*: The patent examination process can present challenges related to novelty and non-obviousness. If a new method closely resembles existing patents, it may face difficulties in obtaining patent protection. Therefore, conducting thorough prior art searches is essential to navigate these hurdles effectively.  ## Cross-Licensing Opportunities  ### Potential Collaborations  The competitive nature of the pharmaceutical industry presents opportunities for cross-licensing arrangements that could arise from the new synthesis methods for Pinaverium Bromide.   1. \*\*Leveraging Complementary Patents\*\*: Companies that develop innovative manufacturing processes may find value in collaborating with others who hold complementary patents. For instance, if one company has developed a novel synthesis route that significantly improves yield and reduces costs, while another company has expertise in scaling up production or has access to unique raw materials, a cross-licensing agreement could be mutually beneficial.  2. \*\*Accelerating Time-to-Market\*\*: Cross-licensing agreements can allow both parties to leverage each other's strengths, enhance their product offerings, and potentially accelerate time-to-market for new formulations of Pinaverium Bromide or related compounds. This collaborative approach can lead to more efficient development cycles and improved market competitiveness.  ## Future Trends in Pharmaceutical Manufacturing  ### Sustainability and Green Chemistry  The future of manufacturing processes for pharmaceutical products like Pinaverium Bromide is likely to be shaped by several key trends.  1. \*\*Emphasis on Sustainability\*\*: There is a growing emphasis on sustainability and green chemistry within the pharmaceutical industry. Manufacturers are increasingly seeking ways to reduce waste and minimize environmental impact, which may lead to the adoption of more eco-friendly reagents and processes. This shift towards sustainability aligns with global efforts to promote environmentally responsible manufacturing practices.  2. \*\*Adoption of Advanced Technologies\*\*: Advancements in technology, such as automation and process analytical technology (PAT), will play a significant role in optimizing manufacturing processes. These technologies can enhance real-time monitoring and control of production, leading to improved consistency and quality of the final product.  ### Continuous Manufacturing Processes  1. \*\*Efficiency in Production\*\*: As regulatory agencies continue to evolve their guidelines, there may be a greater focus on continuous manufacturing processes. This approach allows for more efficient production and can reduce the time and costs associated with batch manufacturing. Continuous manufacturing can also enhance product quality by minimizing variability in production.  2. \*\*Responsiveness to Market Demands\*\*: The pharmaceutical manufacturing landscape is likely to become more innovative, efficient, and responsive to market demands in the coming years. Companies that embrace these trends will be better positioned to meet the evolving needs of patients and healthcare providers.  ## Sources  [1] CN104650005A - Pinaverium bromide synthesis method - Google Patents  [2] CN102060807B - Improved preparation process of pinaverium bromide - Google Patents  # Investigating Impurities and Stability Solutions for Pinaverium Bromide: A Patent Research Perspective  ## Background on Pinaverium Bromide  Pinaverium Bromide is a pharmaceutical compound primarily used as an antispasmodic agent for the treatment of gastrointestinal disorders. Its efficacy is closely tied to its stability and purity, which can be significantly affected by the synthesis methods and formulation strategies employed during its production. Understanding the impurity profiles and degradation pathways of Pinaverium Bromide is essential for ensuring its safety and effectiveness, as well as for developing patentable innovations that can enhance its stability and shelf life.  ## Impurity Profiles in Pinaverium Bromide  ### Sources of Impurities  The synthesis methods for Pinaverium Bromide can introduce various impurities and degradation products. One notable source of impurities arises from the choice of starting materials. Patents indicate that utilizing cheaper and more readily available starting materials can lead to a reduction in side reactions, thereby minimizing the formation of impurities [3]. However, this approach must be balanced with the potential for introducing impurities from these less refined materials.  Additionally, the formulation of the drug plays a critical role in its stability. For instance, sustained-release tablet formulations have been shown to maintain stable blood concentrations, suggesting that the selection and ratio of excipients can significantly influence the impurity profile of the final product [2]. This highlights the importance of careful formulation design in mitigating impurity formation.  ### Degradation Products  Degradation products can emerge during storage, particularly under conditions of heat and humidity. These degradation products not only affect the efficacy of Pinaverium Bromide but can also pose safety risks. Identifying these degradation pathways is crucial for developing effective mitigation strategies. Forced degradation studies are instrumental in this regard, as they help elucidate the conditions under which these impurities form and the specific degradation pathways involved [1].  ## Strategies for Mitigating Impurities  ### Forced Degradation Studies  Conducting forced degradation studies is a vital strategy for identifying potential degradation pathways and the conditions that lead to impurity formation. By understanding these pathways, researchers can select appropriate stabilizers or modify the formulation to enhance stability. For example, the use of specific excipients with stabilizing properties can significantly reduce the formation of degradation products during storage [1].  ### Optimizing Synthesis Conditions  Optimizing the synthesis conditions is another critical approach to minimizing impurities. The patent literature suggests that employing milder reaction conditions and carefully selecting starting materials can significantly reduce unwanted side reactions, thereby lowering impurity levels in the final product [2]. This optimization not only enhances the purity of Pinaverium Bromide but also has implications for patenting novel synthesis methods that demonstrate improved outcomes.  ## Novel Stabilizers and Formulation Techniques  ### Promising Stabilizers  Several stabilizers have shown promise in enhancing the shelf life of Pinaverium Bromide. For instance, the use of cyclodextrins can form inclusion complexes with the active pharmaceutical ingredient (API), effectively reducing its exposure to moisture and light—two common factors contributing to degradation [1]. This approach not only improves stability but also opens avenues for patentable innovations.  Additionally, incorporating antioxidants can help mitigate oxidative degradation, which is particularly relevant for compounds sensitive to oxidation. These stabilizers can be considered for patentable innovations if they demonstrate significant improvements in stability or efficacy compared to existing formulations [2].  ### Innovative Formulation Techniques  Exploring novel formulation techniques, such as microencapsulation or lipid-based delivery systems, presents further opportunities for enhancing the stability of Pinaverium Bromide. These methods can protect the API from environmental factors and control its release profile, thereby improving both stability and therapeutic effectiveness [3]. The development of such innovative formulations could lead to patentable solutions that significantly enhance the product's marketability and therapeutic potential.  ## Conclusion  The investigation into the impurities, degradation products, and stability issues associated with Pinaverium Bromide reveals a complex interplay between synthesis methods and formulation strategies. By identifying impurity sources and degradation pathways, researchers can develop effective mitigation strategies that not only enhance the stability and shelf life of the drug but also pave the way for patentable innovations in stabilizers and formulation techniques.  ## Sources [1] https://www.researchgate.net/publication/336360112\_DETERMINATION\_OF\_PINAVERIUM\_BROMIDE\_IN\_PHARMACEUTICAL\_DOSAGE\_FORMS\_BY\_A\_VALIDATED\_STABILITY-INDICATING\_LC\_METHOD  [2] https://patents.google.com/patent/CN101467975A/en  [3] https://patents.google.com/patent/CN104650005A/en   ---  - Conclusions.  The comprehensive analysis of Pinaverium Bromide highlights its significance as an antispasmodic agent for gastrointestinal disorders, emphasizing the critical role of synthesis pathways, polymorphic variations, formulation strategies, and manufacturing processes in optimizing its efficacy and stability. Recent advancements in synthesis methodologies have improved efficiency and cost-effectiveness, while innovative formulation techniques have enhanced bioavailability and patient compliance. Additionally, understanding impurity profiles and degradation pathways is essential for developing effective stability solutions. Collectively, these insights not only inform current practices but also present valuable opportunities for patentable innovations, ensuring the continued advancement of Pinaverium Bromide in the pharmaceutical landscape. |

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| 1. **REFERENCES** (Specify the references throughout the document with numbers between brackets i.e. [1]) |
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| 1. **AUTHORIZATIONS** |

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| **PERFORMED BY:** | | | **REVIEWED BY:** | | | **APPROVED BY:** | |
| Name: |  |  | Name: |  |  | Name: |  |
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| Area: |  |  | Area: |  |  | Area: |  |
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