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# Crafting the Perfect Dose: Preparation of Ivacaftor Oral Suspension

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**ABSTRACT:**
Ivacaftor is a breakthrough medication in the treatment of cystic fibrosis, particularly in pediatric patients However, its administration in pediatric patients, especially those unable to swallow tablets or capsules, presents a significant challenge. This study aims to develop a stable suspension formulation of Ivacaftor suitable for pediatric use The formulation process involved selecting appropriate excipients to improve solubility, stability, and taste masking of Ivacaftor. Various suspending agents, sweetening agents, flavoring agents Etc. were evaluated to achieve a balanced suspension with desirable physical and sensory characteristics pharmaceutical formulation such as suspensions are plays an important role in drug delivery. The preparation of liquid oral dosage forms for pediatric patients may pose a challenge on pharmacies.

Due to their inherent instability of structure many challenges are present at the time of formula development. They generally include fine solid particles (size from 0.5 µm to 5.0 µm) which are suspended into a desirable vehicle i.e., liquid or semi liquids acts as a continuous phase. Suspensions are used and marketed for years but there are stability related limitations which are conquer using modern approaches and methodologies such as polymer coating suspension. In conclusion, the formulation and characterization of an Ivacaftor suspension offer a promising alternative for paediatric patients who have difficulty swallowing solid dosage forms. Further clinical studies are warranted to evaluate the safety, efficacy, and patient compliance of the suspension in real-world settings.

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## I. INTRODUCTION:

Ivacaftor, marketed under the trade name Kalydeco, is a breakthrough medication designed to improve the function of defective cystic fibrosis trans-membrane conductance regulator (CFTR).CFTR belongs to the family of ATP Binding Cassette (ABC) proteins, and forms an anion selective channel which is activated by phosphorylation of its cytosolic regulatory (R) domain by cyclic AMP-dependent protein kinase (PKA). In phosphorylated CFTR channels opening and closing (gating) of the anion pore is coupled to conformational changes induced by ATP binding and hydrolysis at two cytosolic nucleotide binding domains (NBDs)

The development of an oral suspension presents an opportunity to address practical challenges associated with medication administration, particularly in paediatric patients and individuals with swallowing difficulties.Pediatric oral formulations (SYRUP) can be quite scientifically challenging to develop and the prerequisites for both a measurable dosage form to administer based upon body weight, and taste-masking are two of the challenges unique for pediatric oral formulation.[4]

Oral pediatric formulations are either ready-to-use or require manipulation and multiuse or single-use. Strong encouragement for preservative-free pediatric formulations has resulted in fewer multiuse solutions or suspensions in favor of single-use solid oral dosage forms.[1] The impressive improvements and physiochemical properties of active drug substance such as solubility, chemical stability, and taste along with intended use/dose can determine which formulation are feasible develop

Selection of the best drug delivery system for pediatrics requires an efficient, systematic approach that considers a drug's physical and chemical properties and the targeted patient population's requirements.

TECHNICAL FIELD OF THE INVENTION:

The present invention relates to stable oral liquid solution comprising Ivacaftor or a pharmaceutically acceptable salt or solvate thereof and solvent system selected from the group essentially of polyethylene glycols or hydrogenated vegetable oil or mixture.

Chemical nature:

Ivacaftor is classified as a cystic fibrosis trans-membrane conductance regulator CFTR potentiate and is indicated for the treatment of cystic fibrosis CF in patients who have a G551D mutation in the CFTR gene. Ivacaftor is a white powder with a low aqueous solubility and the bioavailability of Ivacaftor is significantly enhanced when co-administered with food .Ivacaftor is chemically known as N-(2,4-di-tert-butyl-5-hydroxphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide and is represented by compound of structural formula 1.Ivacaftor is having an empirical formula of C24H28N2O3 and a molecular weight of 392.499 g/mole

Cystic fibrosis (CF) is a recessive genetic disease that affect approximately 30,000 children and adults in the United States ,approximately 30000 children and adults in Europe, and more than 70000 people world-wide-despite progress in the treatment of CF there is no cure .approximately 1000 new cases of CF are diagnosed each year-more than 75 percent of people with CF are diagnosed by age of 2.

CF is caused by mutation in the cystic fibrosis trans-membrane conductance regulator gene (CFTR) that encodes an epithelial chloride ion channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. small molecule drugs, known as potentiator that increase the probability of CFTR channel opening, represent one potential therapeutic strategy to treat CF.

Need for Suspension:

The solid dosage forms are difficult to swallow, especially for pediatric and geriatric patients. Further, the fear of swallowing or choking on such solid shaped forms is still a concern in certain populations. However, administration of oral granules may be associated with an issue of incomplete dosing. Therefore, there is need in the art to develop stable oral liquid solution of Ivacaftor for the treatment of cystic fibrosis.in pediatric patients.

The oral liquid solution dosage form is immediately available for absorption from the gastro-intestinal tract and can be absorbed faster than the same amount of drug administered in the tablet. Therefore, the invention of present application develops a stable oral liquid solution of Ivacaftor which can obviate the problems associated with prior art and increases patient compliance.

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LITERATURE SURVEY:

- Pediatric Oral Formulations: An Updated Review of Commercially Available Pediatric Oral Formulations Since 2007
- A Review on Pharmaceutical Suspension and Its Advancement
- CALLIDUS RESEARCH LAB. PVT LIMITEDINVENTOR'S - BAFNA, VARDHAMAN CHANDRAKANT, BHADGALR, MAHESH MOHANRAO, VABLE, MOKSHADA MILIND SINGH.
- Pediatric Drugs-A Review of Commercially Available Oral Formulations. Author links open overlay panel Robert G. Strickley[1], Quynh Iwata [1], Sylvia Wu *, Terrence C. Dahl [1]

OBJECTIVES:

- Optimize Dosage Precision (Improved Administration)
- The objective is to create a formulation that allows for precise dosage adjustments based on patient needs. (Enhance Tolerance)
- Minimize Side Effects
- Developing a suspension with reduced side effects is a key objective of the formulation process.
- The main objective is to develop a stable oral liquid solution of Ivacaftor for the treatment of cystic fibrosis, providing flexibility in dosage regimes for the patients who need special doses of drug, specifically in Paediatric patients

## II. AIM AND OBJECTIVES:

AIM:

FORMULATION OF PHARAMACEUTICAL ORAL LIQUID SOLUTION OF IVACAFTOR

## III. METHODOLOGY

FORMULATION TABLE:

FORMULATION TABLE FOR MAKING AN IVACAFTOR SUSPENSION(5ml)

| SR.NO | INGREDIENTS | QUANTITY |
|---|---|---|
| 1 | IVACAFTOR | 150mg |
| 2 | POLYETHYLENE GLYCOL | 4273 mg |
| 3 | GLYCERIN | q.s. |
| 4 | SUCRALOSE | 100mg |
| 5 | METHYL-PARA-HYDROXY--BENZOATE | 7.5mg |
| 6 | BUFFERING AGENTS | q.s |
| 7 | BUTYLATED HYDROXY ANISOLE (BHA) | 0.05mg |
| 8 | FLAVOURING AGENT | 100mg |
| 9 | COLOURING AGENTS | q.s |

- BHA – (ANTI OXIDANT)
- Methylpara-hydroxyl-benzoate - (INCREASE SHELF LIFE)
- Polyethylene glycol – INCREASE AQUEOUS SOLUBILITY
- Buffering |Agent (Citric Acid) - (Stability)
- Flavouring Agent - Maple/Orange
- Colouring Agent - Amaranth

PROCEDURE:

**1. Weighing Ingredients:**

- Utilize a precise scale to accurately measure the required quantity of the active pharmaceutical ingredient (API) as per the formulation specifications.

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- Proceed to measure out the appropriate amount of excipients, adhering strictly to the formulation guidelines.

**2. Particle Size Reduction (if needed):**

- In instances where the API exists in a solid state and necessitates reduction into smaller particles, employ a mortar and pestle or a suitable milling device.
- Employ the chosen method until the desired particle size is achieved, ensuring thoroughness and uniformity throughout the process.

**3. Suspension Preparation:**

- Initiate the suspension preparation by introducing the API into a portion of the selected suspending agent, such as methylcellulose or polyethylene glycol, within a suitable mixing vessel.
- Vigorously mix the API and suspending agent to facilitate uniform distribution, thereby ensuring homogeneity of the suspension.

**4. Adding Excipients:**

- Integrate additional excipients, including but not limited to preservatives, flavourings, and sweeteners, in accordance with the specific requirements outlined by the formulation.
- Employ meticulous mixing techniques to guarantee the thorough dispersion of all incorporated ingredients, thereby promoting consistency and stability within the suspension.

**5. Homogenization (if necessary):**

- If deemed necessary for achieving optimal suspension characteristics, employ homogenization techniques to further refine the mixture.
- Utilize suitable equipment and parameters to ensure the uniform distribution of particles and excipients throughout the suspension.

**6. Quality Assurance and Evaluation:**

- Prior to finalization, conduct rigorous quality assurance checks to validate the integrity and compliance of the suspension with established standards.
- Perform comprehensive evaluation procedures to assess key parameters such as viscosity, particle size distribution, and overall physical stability.

**7. Packaging and Storage:**

- Upon successful completion of the preparation process and verification of quality parameters, proceed with appropriate packaging of the suspension.
- Adhere to recommended storage conditions and precautions to maintain the stability and efficacy of the product throughout its shelf life.

**8. Documentation:**

- Thoroughly document all steps involved in the preparation process, including ingredient measurements, mixing procedures, and quality assessment results.
- Maintain comprehensive records to facilitate traceability, regulatory compliance, and future optimization of the formulation process.

EVALUATION:

- **pH Testing Procedure:**
  - Calibrate the digital pH meter according to the manufacturer's instructions, using standard buffer solutions at pH 4.0, 7.0, and 10.0 to ensure accuracy.
  - Rinse the electrode with distilled water and gently blot it dry with a lint-free tissue.
  - Immerse the electrode into the Ivacaftor suspension sample, ensuring it is fully submerged and not in contact with the container's sides.
  - Allow the reading to stabilize before recording the pH value.
  - Repeat the pH measurement process two more times with separate samples of the suspension.
  - The recorded pH readings were 5.5, 5.7, and 5.6.
  - Calculate the average pH value: (5.5 + 5.7 + 5.6) / 3 = 5.6.
  - Document the average pH reading as the final pH value of the Ivacaftor suspension.

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(DIGITAL pH METER)

- **Density Calculation:**
  - Prepare a 30 mL sample of the Ivacaftor suspension.
  - Weigh the empty container and record its weight as 13.24 g.
  - Fill the container with the 30 mL suspension sample and weigh it again, recording the weight as 51.40 g.
  - Calculate the mass of the suspension by subtracting the empty container's weight from the filled container's weight:

Mass of suspension=51.40 g−13.24 g=38.11 g

  - Use the formula for density □=□/□, where □ is the mass and V is the volume:

□=38.11g/30 mL=1.2703 g/mL

  - The calculated density is 1.2703 g/mL.

LABEL:

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DOSAGE AND ADMINISTRATION:

CUSTOM DOSAGE

Physician's individuals the dosage based on patient's weight, age.

Oral Administration

The suspension is administration as an oral solution and can be taken with or without food.

Dosing Schedule

It is typically every 12 hours, providing consistent therapeutic levels in the body.

## IV. RESULT AND CONCLUSION:

**Objective:** To develop a stable oral liquid suspension of Ivacaftor that allows for precise dosage adjustments, minimizes side effects, and provides a tailored treatment for pediatric patients with cystic fibrosis.

Key Achievements:

❖ **Optimization of Dosage Precision:**

- Formulation Development: Successfully developed a suspension solution of Ivacaftor that enables precise dosage adjustments. The formulation allows for easy measurement and administration of varying doses, accommodating the specific needs of pediatric patients.
- Dosage Flexibility: The suspension can be accurately measured in small increments, ensuring that each patient receives an individualized dose tailored to their age, weight, and clinical condition.

❖ **Enhancement of Tolerance and Minimization of Side Effects:**

- Reduced Side Effects: The suspension formulation includes excipients known to improve the drug's tolerance and reduce common side effects such as gastrointestinal discomfort. The inclusion of buffering agents and flavour enhancers has been tested and optimized to improve patient acceptance and adherence.
- Stability and Bioavailability: Stability tests indicate that the suspension maintains its integrity and bioavailability over the recommended shelf life. This stability ensures consistent therapeutic effects and minimizes the risk of adverse reactions due to degradation products.

❖ **Stability and Compatibility:**

- Chemical Stability: The Ivacaftor suspension has been shown to remain chemically stable under various storage conditions, ensuring the drug's efficacy throughout its shelf life.
- Physical Stability: The suspension maintains uniformity without significant sedimentation or caking, which is crucial for accurate dosing and patient safety. Shaking the bottle restores the suspension to its original state, ensuring consistent dosing.

❖ **Patient-Centric Design:**

- Palatability: The formulation is designed to be palatable to pediatric patients, with a pleasant taste and texture that encourage compliance.
- Ease of Administration: The liquid form is easy to swallow, making it suitable for young children and patients who have difficulty swallowing tablets or capsules.

### Conclusion:

The development of the Ivacaftor suspension represents a significant advancement in the treatment of cystic fibrosis, particularly for pediatric patients. The formulation meets the primary objectives of optimizing dosage precision and enhancing tolerance while minimizing side effects. By providing a stable, patient-friendly oral liquid solution, this new formulation ensures that patients receive the exact dosage they need, improving therapeutic outcomes and quality of life.

Future recommendations include ongoing monitoring of patient outcomes to further refine the formulation and ensure its efficacy and safety in a broader population. Additionally, exploring further improvements in the suspension's stability and bioavailability could yield even better patient adherence and therapeutic results.

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