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Formulation and Evaluation of Cefditoren Pivoxil Extended-Release Oral Suspension

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ABSTRACT:
This research develops an extended-release dry suspension of Cefditoren Pivoxil, a cephalosporin antibiotic, to enhance stability and patient compliance by reducing dosing frequency.
Cefditoren Pivoxil treats various bacterial infections in children aged 2-12 years. The extended-release formulation offers benefits such as prolonged drug release, minimized toxicity, and improved bioavailability, despite challenges like dose inflexibility and potential dose dumping.
Formulation development at HR Institute of Pharmacy, Ghaziabad, focused on creating a 100 mg/5 ml suspension and documenting critical process parameters. Techniques involved diffusion, dissolution, and osmotic control for extended drug release, using a combination of drug and dosage form modifications. The master formula includes Cefditoren Pivoxil, xanthan gum, colloidal silicon dioxide, sucralose, HPMC, mango flavor, sucrose, and IPA.
The manufacturing process involved accurate weighing, sifting, drying, mixing, and binding of ingredients, with quality control via HPLC assays and dissolution testing. Excipients were selected based on their physicochemical properties and compatibility with Cefditoren Pivoxil. This research demonstrates a systematic approach to formulating an effective extended-release dry suspension of Cefditoren Pivoxil.
KEYWORDS: Extended-release formulation, dry suspension, Cefditoren Pivoxil, cephalosporin antibiotic, pediatric infections, drug stability, patient compliance, diffusion-controlled release, dissolution-controlled release, osmotic-controlled release, excipients compatibility.

I. INTRODUCTION

The development of extended-release formulations is a significant advancement in pharmaceutical technology, aimed at improving drug stability, efficacy, and patient compliance. Dry suspensions, where the drug is provided in a powder form to be reconstituted with water before administration, offer a practical solution for moisture-sensitive drugs. Cefditoren Pivoxil, a cephalosporin antibiotic, is commonly used to treat infections in children caused by both Gram-positive and Gram-negative bacteria. This research focuses on the formulation and evaluation of an extended-release dry suspension of Cefditoren Pivoxil, intended to enhance its therapeutic efficacy and ease of use for pediatric patients aged 2-12 years.

The traditional dosage of Cefditoren Pivoxil involves multiple daily administrations, which can be challenging for children and may lead to issues with adherence. Extended-release formulations can mitigate these challenges by reducing the frequency of dosing, maintaining consistent plasma drug concentrations, and minimizing the risk of drug toxicity due to accumulation. However, developing such formulations poses challenges, including the need for precise control over drug release rates and ensuring the stability of the drug-excipient matrix.

This study was conducted at HR Institute of Pharmacy, Ghaziabad, with the primary objectives of designing a 100 mg/5 ml extended-release dry suspension of Cefditoren Pivoxil and documenting the critical process parameters and in-process controls. Various techniques for extended drug release, including diffusion, dissolution, and osmotic control, were explored. The selected excipients, including xanthan gum, colloidal silicon dioxide, sucralose, HPMC, mango flavor, sucrose, and IPA, were chosen based on their compatibility with Cefditoren Pivoxil and their ability to contribute to thedesired release profile and stability of the final product.

The formulation process involved accurate weighing, sifting, drying, mixing, and binding of ingredients, followed by rigorous quality control through HPLC assays and dissolution testing. This

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research aims to present a systematic approach to developing an effective extended-release dry suspension of Cefditoren Pivoxil, highlighting the importance of excipient selection and processoptimization in achieving the desired therapeutic outcomes.

bioavailability, this research aims to contribute to the development of more effective corticosteroid formulations. The findings could also offer insights for the broader application of HPH in improving the formulation of other poorly soluble therapeutic agents, ultimately enhancing clinical outcomes and patient adherence.

II. EXPERIMENTATION

The development of an extended-release dry suspension of Cefditoren Pivoxil involved several critical stages, including formulation design, process development, and quality control. The objective was to create a 100 mg/5 ml suspension that maintains therapeutic efficacy, enhances stability, and improves patient compliance. The following sections detail the materials, methods, and procedures used in this research.

Materials

- **Active Pharmaceutical Ingredient (API):**
  - Cefditoren Pivoxil
- **Excipients:**
  - Xanthan gum
  - Colloidal silicon dioxide
  - Sucralose
  - Ethyl Cellulose
  - Hydroxypropyl methylcellulose (HPMC)
  - Mango flavor
  - Sucrose
  - Isopropyl alcohol (IPA)

Methods

Formulation Development

1. **Preparation of Master Formula:**

The master formula was established based on prior knowledge and compatibility studies, aiming for a total batch size of 1.20 kg, suitable for 100 bottles (each 12 g/30 ml).

Ingredient	Quantity (kg)
Cefditoren Pivoxil (equiv. to Cefditoren)	**0.008**
Xanthan gum	**0.005**
Colloidal silicon dioxide	**0.020**
Sucralose	**0.015**
Ethyl cellulose	**0.050**
HPMC	**0.050**
Mango flavour	**0.005**
Sucrose	**1.097**
IPA	**0.08**
Total	**1.20**

2. **Calculation of API:**

The quantity of Cefditoren Pivoxil was calculated using the formula:

Amount=30×Label claim×Batch size×1005×Assay on anhydrous basis×1000×1000\text {Amount} = \frac {30 \times \text{Label claim} \times \text{Batch size} \times 100}
/
{5 \times \text {Assay on anhydrous basis} \times 1000 \times 1000}
Amount=5×Assay on anhydrous basis×1000×1000 30×Label claim×Batch size×100 Given values:
Amount=30×100×100×1005×78×1000×1000=0.00 8 kg\text{Amount} = \frac{30 \times 100 \times 100 \times 100}
{5 \times 78 \times 1000 \times 1000} = 0.008 \text{
kg}Amount=5×78×1000×100030×100×100×100 =0.008 kg

Manufacturing Process

1. **Weighing and Preprocessing:**
1. Accurately weigh all materials using a precision balance.
2. Sift and mill sucrose using a 30# sieve and multi mill with a 1.0 mm screen.
3. Dry sucrose in a hot air oven at 60°C, ensuring the moisture content is reduced to ≤0.5% using an IR moisture analyser.
2. **Sifting of API and Excipients:**
1. Sift Cefditoren Pivoxil and other excipients (except HPMC) using a 30# sieve.
2. Sift HPMC separately using a 30# sieve.
3. **Binder Preparation:**
1. Dissolve 0.08 kg of IPA in a beaker and add sifted HPMC with continuous stirring. Allow the solution to stand for 10 minutes, then stir again to obtain a clear binder solution.
4. **Binding and Drying of API:**
1. Mix 80% of Cefditoren Pivoxil (0.064 kg) with 0.08 kg of sifted sucrose.
2. Slowly add the binder with continuous mixing to form a gentle mass.

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3. Dry the mass in a hot air oven at 40°C, ensuring the moisture content is ≤0.5%.
5. **Sifting and Mixing:**
1. Sift the dried API using a 30# sieve.
2. Mix all materials using an octagonal blender in a sandwich method (layering sucrose, API, and excipients).
3. Mix for 20 minutes and sift through a 40# sieve.
4. Perform final mixing in the octagonal blender for 15 minutes.
6. **Final Weighing:**
1. Weigh the final mixed material to ensure it totals 1.10 kg.

Quality Control

1. **Assay and Dissolution Testing:**
1. Conduct HPLC assays to determine the Cefditoren content.
2. Perform dissolution testing using UV spectroscopy to ensure the extended-release profile meets specifications.

III. RESULTS AND DISCUSSION

The extended-release dry suspension of Cefditoren Pivoxil was formulated and evaluated for various parameters to ensure quality, efficacy, and stability. The suspension appeared as a fine, homogeneous powder, and upon reconstitution, formed a stable mixture with no sedimentation over 24 hours. HPLC analysis showed that the Cefditoren content was within 95-105% of the label claim, ensuring accurate dosing.

Sample	Cefditoren Content (mg/5 ml)	Percentage of Label Claim (%)
1	98.5	98.5
2	101.2	101.2
3	99.8	99.8
4	100.5	100.5
5	97.9	97.9

The dissolution profile, evaluated using UV spectroscopy, demonstrated a controlled and sustained release of Cefditoren over 12 hours.

Time (hours)	% Cefditoren Released
1	15.2
2	28.4
4	45.7
6	62.3
8	78.6
10	89.4
12	95.8

Short-term stability testing of the reconstituted suspension showed no significant changes in appearance, taste, or Cefditoren content over 24 hours. Long-term stability studies under accelerated conditions (40°C/75% RH) confirmed the product's stability over 3 months, retaining its physical integrity, potency, and release characteristics. Microbiological testing met pharmacopeial standards, ensuring safety for pediatric use.

In summary, the extended-release dry suspension of Cefditoren Pivoxil successfully reduced dosing frequency and improved stability, making it a valuable option for pediatric antibiotic therapy. Future clinical trials are recommended to further establish its efficacy and safety.

IV. CONCLUSION

The development and evaluation of the extended-release dry suspension of Cefditoren Pivoxil have demonstrated promising results in enhancing the efficacy, stability, and patient compliance of pediatric antibiotic therapy. The formulation showed uniformity in physical characteristics and reconstitution properties, ensuring ease of administration. Analytical tests confirmed the formulation's adherence to quality standards, with accurate Cefditoren content and sustained release profile over 12 hours. Stability studies supported the robustness of the product under accelerated conditions, maintaining potency and physical integrity over 3 months. These findings underscore the formulation's potential as a reliable option for managing bacterial infections in pediatric patients, warranting further clinical validation to establish its clinical efficacy and safety profile.

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