

FORMULATION, DEVELOPMENT AND EVALUATION OF SUPPOSITORIES NOVEL DRUG DELIVERY SYSTEMS FOR AZITHROMYCIN AND PARACETAMOL A COMBINATION THERAPY

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ABSTRACT

Background: The oral administration of medication to pediatric patients, particularly during acute illness, is frequently complicated by challenges such as vomiting, poor palatability, and dysphagia. These issues can compromise the efficacy of essential treatments, including antibiotics and antipyretics, leading to uncertain dosing and potential therapeutic failure. Rectal administration offers a practical alternative, bypassing the gastrointestinal tract and providing a reliable route for drug delivery in uncooperative or ill children. **Objective:** This study aimed to develop and evaluate fixed-dose combination rectal suppository containing Azithromycin and Paracetamol. The primary goal was to create a physically and chemically stable formulation with appropriate quality attributes suitable for pediatric use. **Methods:** Eleven Suppository formulations were developed using the fusion (melt molding) method. Initial with hydrophilic polyethylene glycol (PEG) bases were conducted,

followed by with lipophilic Witepsol® bases. An optimized formulation (F11), composed of a Witepsol® H35/W76 blend, sodium citrate, sodium lauryl sulfate, and sodium starch glycolate, was selected for comprehensive evaluation. The final suppositories were assessed for physical properties (appearance, weight variation, disintegration time, softening time) and

chemical properties (pH and drug content) using a validated High-Performance Liquid Chromatography (HPLC) method for simultaneous quantification of both APIs. **Results:** Formulations using PEG bases failed to meet disintegration requirements (>30 minutes). In contrast, the optimized lipophilic Witepsol®-based formulation (F11) demonstrated excellent physical characteristics. The suppositories were homogenous, torpedo-shaped, and showed acceptable weight variation. They exhibited a rapid mean disintegration time of 4 minutes and 5 seconds at 37°C and a physiologically compatible pH of 7.5. The HPLC assay was specific and linear, confirming the drug content for Azithromycin and Paracetamol was 104.87% and 108.76% of the label claim, respectively, which is within standard pharmacopeial limits. **Conclusion:** It was concluded that the best Formulation F11 was found to be among the all formulations of Azithromycin and Paracetamol Suppositories NDDS. This novel dosage form offers a promising solution to improve treatment adherence and clinical outcomes in pediatric infectious diseases. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the NDDS (Novel Advanced Drug Delivery Systems) product development process.

KEYWORDS: Azithromycin Dihydrate, Paracetamol, Suppositories, Formulation, Evaluation, Antibiotics, Analgesic and Antipyretic, NDDS.

INTRODUCTION

Background^[1-24]

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and a high degree of tissue penetration. It was initially approved by the FDA in 1991. It is primarily used for the treatment of respiratory, enteric and genitourinary infections and may be used instead of other macrolides for some sexually transmitted and enteric infections. It is structurally related to erythromycin. Azithromycin is a second-generation, semi-synthetic macrolide antibiotic belonging to the azalide subclass. It acts by binding to the 50S subunit of bacterial ribosomes, inhibiting protein synthesis by blocking peptide translocation during the elongation phase. This mechanism confers bacteriostatic activity against susceptible organisms, although bactericidal effects can occur at higher concentrations or against certain pathogens. The spectrum of activity of azithromycin encompasses many clinically relevant pediatric pathogens, including respiratory tract pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*), certain enteric pathogens, and atypical organisms. This broad spectrum makes azithromycin

particularly valuable for empiric therapy in community-acquired infections. Pharmacokinetically, azithromycin demonstrates several advantageous properties for pediatric use. Following oral administration in children, it is rapidly absorbed, achieving peak plasma concentrations (C_{max}) of 224-383 $\mu\text{g/L}$ within approximately 2 hours, depending on age group and dosage regimen. However, its oral bioavailability is relatively low (approximately 38% in adults) due to first-pass metabolism.

A distinguishing pharmacokinetic feature of azithromycin is its extensive tissue distribution and intracellular accumulation. The drug achieves concentrations in infected tissues and cells that significantly exceed plasma levels, often by 10- to 100-fold. This distribution pattern, coupled with a long elimination half-life (32-64 hours in children), allows for once-daily dosing and short treatment courses, typically 3-5 days. In pediatric clinical practice, azithromycin is primarily used for respiratory tract infections (including community-acquired pneumonia, acute otitis media, and pharyngitis), skin and soft tissue infections, and certain sexually transmitted infections in adolescents. Standard pediatric dosing is 10 mg/kg on day one, followed by 5 mg/kg on days 2-5, or alternatively, a single 30 mg/kg dose in specific indications like acute otitis media.

Acetaminophen (paracetamol), also commonly known as *Tylenol*, is the most commonly taken analgesic worldwide and is recommended as first-line therapy in pain conditions by the World Health Organization (WHO). It is also used for its antipyretic effects, helping to reduce fever. This drug was initially approved by the U.S. FDA in 1951 and is available in a variety of forms including syrup form, regular tablets, effervescent tablets, injection, suppository, and other forms. Acetaminophen is often found combined with other drugs in more than 600 over the counter (OTC) allergy medications, cold medications, sleep medications, pain relievers, and other products. Confusion about dosing of this drug may be caused by the availability of different formulas, strengths, and dosage instructions for children of different ages. Due to the possibility of fatal overdose and liver failure associated with the incorrect use of acetaminophen, it is important to follow current and available national and manufacturer dosing guidelines while this drug is taken or prescribed. On September 22, 2025, the US FDA initiated a labeling change for acetaminophen products suggesting that the use of acetaminophen by pregnant women may be associated with an increased risk of neurological conditions such as autism and ADHD in children. While the FDA updated labeling to caution about potential risks, large studies, national and

international health authorities, and professional organizations - including the Society of Obstetricians and Gynecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) maintain that acetaminophen use in pregnancy remains a first-line therapeutic option when used at the lowest effective dose for the shortest required duration.

Paracetamol is a non-opioid analgesic and antipyretic with minimal anti-inflammatory properties. Its mechanism of action is not fully elucidated but is thought to involve inhibition of prostaglandin synthesis in the central nervous system and effects on descending serotonergic pathways. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol has minimal peripheral effects on cyclooxygenase enzymes, explaining its weak anti-inflammatory activity and favorable gastrointestinal safety profile.

Pharmacokinetically, paracetamol demonstrates good oral bioavailability (approximately 60-89% in children), with peak plasma concentrations occurring within 30-60 minutes of oral administration. However, rectal absorption is generally slower and more variable, with bioavailability ranging from 24% to 98% depending on the formulation and individual factors. The elimination half-life of paracetamol in children ranges from 1-3 hours, necessitating multiple daily doses for sustained effect.

Paracetamol undergoes extensive hepatic metabolism, primarily via glucuronidation and sulfation, with a minor pathway involving cytochrome P450 enzymes (particularly CYP2E1) leading to the formation of a potentially toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). At therapeutic doses, this metabolite is efficiently detoxified by glutathione conjugation, but in overdose situations, glutathione stores may be depleted, leading to hepatotoxicity. In pediatric practice, paracetamol is widely used for fever management and pain control in various clinical scenarios, including infectious diseases. Standard pediatric dosing is 10-15 mg/kg every 4-6 hours, with a maximum of 4-5 doses per 24 hours. The drug's favorable safety profile at therapeutic doses makes it a first-line antipyretic in pediatric populations, though careful attention to proper dosing is essential to avoid toxicity.

Rationale for Combination

The combination of azithromycin and paracetamol addresses complementary aspects of bacterial infection management: pathogen eradication and symptom control. While there are no direct pharmacokinetic interactions reported between these agents that would preclude

their co-administration, their combined use in a single formulation represents a novel approach that could potentially enhance treatment acceptability, compliance, and outcomes in pediatric populations. Recent research has suggested potential synergistic effects between certain antibiotics, including azithromycin, and paracetamol, though this area requires further investigation. Even without direct antimicrobial synergy, the symptomatic relief provided by paracetamol may indirectly support antibiotic effectiveness by improving overall patient condition and potentially enhancing immune function through fever control.

Advanced Rectal Formulation Strategies

Recent advances in rectal drug delivery have focused on enhancing drug bioavailability, improving patient acceptability, and developing controlled-release systems. Several innovative approaches have emerged: Hollow-type suppositories: containing a central cavity filled with drug in solid, liquid, or semi-solid form. This design prevents direct contact between the drug and suppository base, potentially reducing incompatibilities and allowing for controlled release characteristics. Dimple-type suppositories: with one or more surface indentations where drugs are concentrated. This design aims to enhance drug release by creating a concentration gradient for passive diffusion across the rectal mucosa. Liquid suppositories: incorporating thermosensitive or mucoadhesive polymers (or both) that remain liquid at room temperature for easy administration but solidify or thicken at body temperature to enhance retention. These formulations offer the ease of administration associated with liquid forms while minimizing leakage issues. Self-emulsifying drug delivery systems (SEDDS): designed to form oil-in-water emulsions upon contact with rectal fluids, enhancing the solubility and absorption of poorly water-soluble drugs. This approach has shown promising results for improving the bioavailability of various drugs administered rectally. Ion composition-modified enemas: designed to optimize drug delivery either locally or systemically. Research has demonstrated that the osmolarity and electrolyte composition of the enema can significantly influence whether the drug acts locally in the colorectal tissue or is absorbed systemically.

Studies on Rectal Antibiotic Delivery in Pediatrics

Several studies have investigated the rectal administration of antibiotics in pediatric populations, though this approach remains less common than oral or parenteral routes. Early studies focused primarily on aminopenicillins, with variable results regarding bioavailability and clinical efficacy. For rectal azithromycin specifically, limited research is available. One

published study reported a measurable but low (3.2%) bioavailability for a basic azithromycin suppository formulation. However, more recent research has demonstrated that optimized formulations can significantly enhance rectal bioavailability.

A promising study by Kauss *et al.* (2013) developed and characterized a polyethylene glycol (PEG) solid solution suppository formulation of azithromycin for pediatric use. In animal models, this formulation achieved approximately 43% bioavailability relative to intravenous administration, which compared favorably to the target of 38% (oral product bioavailability in humans). This suggests that with appropriate formulation strategies, the rectal bioavailability of azithromycin can approach that of oral administration.

Another study by Kauss *et al.* (2012) screened various azithromycin rectal formulations, including hydrogels, hard gelatin capsules, and PEG suppositories, comparing their *in vivo* bioavailability in rabbits. The PEG suppository demonstrated the highest bioavailability (approximately 28% relative to IV) and produced plasma concentrations potentially sufficient for therapeutic effect. However, the onset of action was somewhat delayed compared to other formulations, with peak plasma concentrations occurring approximately 1.67 hours after administration.

These findings suggest that with optimal formulation design, rectal administration of azithromycin can achieve clinically relevant bioavailability, potentially providing a viable alternative to oral administration in specific pediatric scenarios. However, the literature on rectal co-administration of azithromycin with other drugs, including paracetamol, remains sparse, highlighting a knowledge gap that the current research aims to address.

Studies on Combined Antibiotic-Antipyretic Formulations

The concept of combining antibiotics with antipyretics in a single dosage form represents a relatively novel approach in pharmaceutical development, with limited published studies specifically addressing this combination. Most clinical practice involves the separate administration of these drug classes, with antibiotics targeting the infectious pathogen and antipyretics/analgesics managing associated symptoms.

Rationale for Combined Formulations

Several theoretical advantages support the development of combined antibiotic-antipyretic formulations: Simplified administration: Combination products reduce the number of medications to be administered, potentially improving adherence, especially in pediatric populations where medication administration can be challenging. Coordinated symptom management and antimicrobial therapy: Simultaneous delivery ensures that fever and pain are addressed concurrently with the initiation of antimicrobial activity. Potential pharmacological interactions: Some studies suggest that certain antipyretics may influence immune function or antibiotic efficacy, though the clinical significance of these effects requires further investigation. Practical considerations in resource-limited settings: In areas with limited healthcare access, simplified regimens that address both infection and symptoms could be particularly valuable.

Pharmaceutical Research Paths^[25-82]

Pharmaceutical research is characterized by having both a natural source and synthetic source for primary active raw materials and excipients, each source is mainly prepared to the effectiveness and safety of the drug.

The development of pharmaceutical dosage forms is the basis for delivering the drug to the body. The development of drug delivery systems makes the drug the fastest to arrive, most effective, accurate. and in fast time. Some systems were need to prolong the effect, so they operate with controlled delay system.

All of this development through the various methods of administrating medicine to the body requires developing the medicine, starting from natural and synthetic sources of raw materials for the active ingredients and excipients that are used in formulating medicines in their various dosage forms. The research related to this path is research in drug design or drug extraction, preformulation studies, formulations, evaluation research and stability studies. Clinical studies are important in the development of pharmaceutical dosage forms, and pharmacovigilance follow-up services the safety of medicines. Studying Pharmacoeconomics saves the cost of drug manufacturing, industrial pharmaceutical research and development of production lines, which makes pharmaceutical dosage forms in continues development.

Pharmaceutical care and treatments depend mainly on prescribing medications, taking into account the most important factor, which is drug delivery systems. Research and studies on the effectiveness and use of medicines, their mechanism of action, and safety are all relevant

to the manufacture of pharmaceutical dosage forms. Pharmacokinetics and pharmacodynamics research is considered the most important factor in developing novel drug delivery systems NDDS. The continuous development in the pharmaceutical industry is accelerating in the development of drug delivery systems that serve to improve human healthcare.

Dosage Forms and Novel Drug Delivery Systems^[83-150]

The drug is defined as a substance recognized by official pharmacopoeia / In house (IH) which, is intended for its use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Rarely drug is given in its pure chemical form. To ease the drug administration by a human being, it is essential to convert it into physical form in which drug is dispensed known as dosage form. The dosage form is a package of Active Pharmaceutical Ingredient (API) along with selective non medicinal compounds known as excipients.

Dosage forms are the means by which drug molecules are delivered to sites of action within the body. The need for dosage forms: Accurate dose, protection e.g. coated tablets, sealed ampules, protection from gastric juice, masking taste and odor, placement of drugs within body tissues, sustained release medication, controlled release medication, optimal drug action, insertion of drugs into body cavities and use of desired vehicle for insoluble drugs.

A dosage form refers to the specific physical formulation through which a medicinal substance is administered to achieve therapeutic effects. Dosage forms act as delivery systems that transport active pharmaceutical ingredients (APIs) to their intended sites of action within the body, enhancing therapeutic outcomes while reducing potential adverse effects. The selection of an appropriate dosage form depends on factors such as the drug's physicochemical characteristics, the desired route of administration, the patient's clinical condition, and considerations related to age and ease of use. Pharmaceutical dosage forms are composed of two essential components.

Active Pharmaceutical Ingredient (API)

The pharmacologically active compound responsible for producing the desired therapeutic effect.

Pharmaceutical Excipients

Inactive substances incorporated into the formulation to ensure stability, enhance bioavailability, improve patient acceptability, or facilitate the manufacturing process. Common excipients include colorants, sweeteners, flavoring agents, surfactants, solubilizers, antioxidants, preservatives, thickening agents, suspending agents, binders, solvents, lubricants, and lipid-based materials.

The major biopharmaceutical considerations include: Pharmacodynamic Considerations, therapeutic objective, toxic effect, adverse reactions of candidate drug molecule. Drug Consideration: Physicochemical characterization of the candidate drug molecules. Drug Product Consideration: Bioavailability of candidate drug molecule, pharmacokinetics of candidate drug molecule, desired drug dosage form, route of administration for the candidate drug molecule, and desired dose of the candidate drug molecule. Patient Consideration: Compliance and acceptability of the final drug product. Manufacturing Considerations: Cost, availability of pharmaceutical raw materials, stability and quality.

Formulation and Development

This stage involves the actual combination of candidate drug molecule with various excipients and also optimizing the concentration at which each excipient is used. The choice of excipients depends on the properties of the drug molecule and the nature of the intended drug product.

Classification of Dosage Forms

Pharmaceutical dosage forms can be classified in multiple ways, depending on their physical nature, route of administration, site of application, or intended therapeutic use and related data as shown in Tables (1 to 5).

No.	Table 1: Dosage Form Classifications Based on Physical Form State.	
1	Solid Dosage Forms	Powders, Tablets, Effervescent tablets, Capsules, Soft Gelatin Capsule (SGC), Hard Gelatin Capsule (HGC) Lozenges/Troches, Granules, Effervescent Granules, Chewable, Pills, Insufflation, Cachets, snuffs, Spansules, Hypodermic Tablets, Tablet Triturates, Dental Cones, Pastilles, Pessaries, Vaginal Rings, Transdermal Patches, Suppositories, Implants, Ocular Inserts, Film coated tablet, Orodispersible Tablets, Enteric-Coated Tablets, Dispensing Tablets, Tablet Triturates, Lollipops, Chewing Gum.
2	Semi Solid Dosage Forms	Creams, Ointments, Pastes, Gels, Poultices, Suppositories, Hair colors, Shampoos, Lipsticks, Avaleha.

3	Liquid Dosage Forms	Syrups, Mixtures, Linctuses, Elixirs, Gargles, Mouthwashes, Lotions, Oral Drops, Nasal Drops, Ear Drops, Suspensions, Emulsions, Eye Washes, Liniments, Enemas, Irrigations, Draughts, Eye Drops, Douches, Drops, Tinctures, Spirits, Injections, Collodion, Paints, Throat Paints, Oxymels, Aromatic Waters. Extracts, Inhalants.
4	Gaseous Dosage Forms	Pressurized dispensers, Inhalers, Aerosols, Nebulizers, Sprays, Metered Dose Inhalers (MDIs), Dry Powder Inhalers (DPIs).
5	Special Drug Delivery System	Ocular Inserts, Progestaserts, Intra –Uterine, Liposomes, Prodrugs, Transdermal Patches.

No.	Table 2: Dosage Form Classifications Based on Route of Administration.	
1	Oral Dosage Forms	Powders, Granules, Tablets, Capsules, Suspension, Gels, Pills, Elixirs, Syrups, Emulsion.
2	Parenteral Dosage Forms	Solutions, Suspensions, Emulsions.
3	Trans dermal Dosage Forms	Ointments, Powders, Creams, Lotions, Pastes.
4	Intra ocular Dosage Forms	Solutions, Suspension, Ointments, Gels.
5	Conjunctival Dosage Forms	Ointments
6	Vaginal Dosage Forms	Solutions, Tablets, Ointments, Creams, Suppositories, Douches.
7	Sublingual Dosage Forms	Tablets, Lozenges.
8	Intra-Nasal Dosage Forms	Solutions, Sprays, Inhalations, Gels.
9	Rectal Dosage Forms	Ointments, Suppositories, Enemas.
10	Pulmonary Dosage Forms	Aerosols
11	Urethral Dosage Forms	Suppositories.
12	Intra-Otic Dosage Forms	Solutions, Suspension, Douches, Ear Powders.

No.	Table 3: Dosage Form Classifications Based on Site of Application.	
1	Skin	Powders, Emulsion, Gels, Ointments, Creams, Pastes, Lotion, Suspension, Solutions, Shampoos, Lipsticks, Liniments, Douches.
2	Eye	Ointments, Gels, Eye Drops, Eye Wash, Eye Lotion, Eye Packs, Contact Lenses.
3	Tooth	Powders, Pastes, Spray, Dental cone, Dentrifices.
4	Hand	Powder, Emulsion, Gels, Suspension, Ointments, Creams, Paste, Lotions.
5	Foot	Powder, Emulsions, Gels, Ointments, Creams, Lotions.
6	Hair	Gels, Creams, Hair serums, Hair oils, Hair Sprays, Hair colours.
7	Nose	Aerosols, Insufflations, Snuffs, Gels.
8	Ear	Ear Drops, Douches, Ear Powders.

9	Vaginal	Solutions, Tablets, Ointments, Creams, Suppositories, Douches.
10	Rectal	Ointments, Suppositories, Enemas.

Table 4: Dosage Form Classifications Based on Use.

Internal	Powders, Tablets, Capsules, Emulsion, Syrups, Elixirs, Gels, Pills, Suspension, Avaleha, Pessaries, Suppositories.
External	Aerosols, Ointments, Creams, Powders, Pastes, Lotions, Sprays, Inhalations, Liniments, Throat Paints, Plasters, Jellies, Aerosols, Pellets, Trans dermal Patches.

Table 5: Routes, Dosage Forms, and Uses.

Dosage Form	Route of Administration	Purpose/Use
Tablets/Capsules	Oral	Purpose/Use Convenient systemic delivery
Solutions/Suspensions	Oral/Topical	Rapid action, suitable for children
Injections/Infusions	Parenteral	Fast action, emergency use
Inhalers/Nebulizers	Inhalation	Respiratory therapy
Ointments/Creams/Gels	Topical	Local skin or mucosal treatment
Suppositories/Enemas	Rectal/Vaginal	Local/systemic when oral not possible
Transdermal Patches	Skin	Long-term controlled systemic effect
Modified/Controlled Forms	Varies	Targeted or sustained drug delivery

Suppositories

A suppository is a dosage form used to deliver medications by insertion into a body orifice where it dissolves or melts to exert local or systemic effects. There are three types of suppositories, each to insert into a different section: rectal suppositories into the rectum, vaginal suppositories into the vagina, and urethral suppositories into the urethra of a male. The name "suppositorium" derives from the Latin word *supponere*, which means "substitute". Suppositories can also be administered vaginally. It is commonly referred to as pessaries. The word Pessaries was derived from Greek word "pessarium", which means pesos, meaning "oval stone". Rectal Suppositories: Rectal suppositories come in different shapes and sizes but are usually narrowed at one end. Rectal suppositories can deliver many types of medication. For instance, they may contain glycerin to treat constipation or acetaminophen to treat a fever. Medication from a rectal suppository tends to work quickly. This is because the suppository melts inside the body and is absorbed directly into the bloodstream.

Vaginal Suppositories: Vaginal suppositories are solid medications that are inserted into the vagina with a special applicator. The body absorbs drugs from vaginal suppositories quickly. They work faster than medications you take by mouth. This is because suppositories melt

inside the body and absorb directly into the bloodstream. Urethral Suppositories: Urethral suppositories called bougies are pencil shape. Those intended for males weigh 4gm each and are 100-150 mm long. Those for females are 2gm each and 60-75 mm in length. Nasal Suppositories: Nasal suppositories called nasal bougies or buginaria meant for introduction into nasal cavity. They are prepared with glycerogelatin base. They weigh about 1gm and length 9-10cm. Ear Cones: Aurinaria and meant for introduction into ear. Rarely used Theobroma oil used as base. Prepared in urethral bougies mold and cut according to size.

Ideal Properties of Suppository Bases

It should be non-irritant and non-reactive. It should melt at body temperature. It must maintain the proper shape and size. It should be stable in storage conditions. It should shrink sufficiently to remove mold. It should not interfere in the release or absorption of the drug.

Advantages of Suppository

It's easy to use for those patients, who are unable to take oral medication. Increase the bioavailability of drugs. Very useful to get local effects. It avoids the first-pass metabolism. It provides rapid action. Best for vaginal and rectum fungal infection.

Disadvantages of Suppository

It can cause irritation in some patients. Some patients feel embarrassed. Preparation is complicated compared to liquid and tablets. Need low temperature to store. Very few drugs can be delivered by this type of dosage form. Pharmaceutical suppositories dosage forms can be classified in multiple ways, depending on their physical nature, route of administration, site of application, or intended therapeutic use and related data as shown in Tables (6 to 8).

Table 6: Classification of Suppositories.

No.	Traditional Suppositories	Based on the Application Area	Newer Suppositories
1	Rectal Suppositories	2 g for Adults 1 g for Children	Tablet Suppositories
2	Vaginal Suppositories	"pessaries" Drop or Oval shaped 3-5 g	Layered Suppositories
3	Urethral Suppositories	"bougie" 125 mm length, 4 g for men, 50 mm length, 2 g for women	Coated Suppositories
4	Nasal Suppositories		Capsule Suppositories
5	Ear Cones		

Table 7: Some Suppositories for Various Pathologies.

No.	Pathology	Ingredients in Suppositories
1	Bleeding Hemorrhoids	Local anesthetics, vasoconstrictors, and Calcium dobiselate
2	Hemorrhoidal Thrombosis	Local anesthetics, vasoconstrictors, and calcium dobiselate
3	Anal Fissure	Local anesthetics, steroids, protectants, antiseptics, keratolytic and Policresulen
4	Pruritus Ani	Steroids, astringents, and protectants
5	Anal Cryptitis and Proctitis	Local anesthetics, astringents and antiseptics
6	Anal Rhagades	Keratolytic, antiseptics, and policresulen
7	Post Anal Surgery	Local anesthetics, vasoconstrictors, antiseptics, and calcium dobiselate

Table 8: Relationship Between Drug Release and Drug-Suppository Base.

No.	Active Ingredient (Drug)	Base Release Rate
1	Oil Soluble Active Ingredient-Oily Vehicle	Retarded rate of release and minimum escaping efficiency
2	Hydrophilic Active Ingredient - Oily Base	Faster dissolution rate
3	Oil Soluble Active Ingredient – Hydrophilic Base	Optimal dissolution rate
4	Hydrophilic Active Ingredient - Hydrophilic Base	Slow dissolution rate

In the present study, it was proposed to formulation and evaluation of Azithromycin Dihydrate and Paracetamol (Acetaminophen) Suppositories Novel Drug Delivery Systems. This novel dosage form offers a promising solution to improve treatment adherence and clinical outcomes in pediatric infectious diseases.

MATERIALS AND METHODS

MATERIALS

Azithromycin Dihydrate: Active Pharmaceutical Ingredient (API), Zhejiang Guobang Pharmaceutical Co. Ltd., China. Paracetamol (Acetaminophen): Active Pharmaceutical Ingredient (API), Anhui Pharmaceutical Co. Ltd., China. Witepsol H35 and Witepsol W76: Lipophilic suppository bases, IOI Oleochemical, Germany. Sodium Citrate: Buffer agent/Stabilizer, Magnesia GMBH, Germany. Sodium Lauryl Sulfate (SLS): Anionic surfactant/Solubilizing agent, Vinamax Organics PVT. Ltd., India. Sodium Starch Glycolate: Super-disintegrant, DFE Pharma Excipient GMPH, Germany. Polyethylene Glycol (PEG) 400: Hydrophilic base component/Solvent, Magnesia GMBH, Germany. Polyethylene Glycol (PEG) 6000: Hydrophilic base component, Magnesia GMBH, Germany. Tween 80

(Polysorbate 80): Non-ionic surfactant, Magnesia GMBH, Germany. 0.1N Hydrochloric Acid (HCl). Potassium Bromide (KBr). Distilled Water (DW). Phosphate Buffer.

Equipment's

UV-Visible Spectrophotometer: Model N630, Jasco, Japan. Infrared (IR) Spectrometer: Model Nicolet IS10, Thermo Scientific, USA. Melting Point Tester: Model SMP30, Stuart (Bibby Scientific), UK. High-Performance Liquid Chromatography (HPLC) System: Model LC-2050C 3D, Shimadzu, Japan. pH Meter: Model 3520, Jenway, Hong Kong. Analytical Balance: Model Sartorius, Mettler, USA. Hot Plate/Heater: Model GMR 160, Geremi, UK. Oven: Model GPS.100 CLAD250 DIG, Widnes Cheshire, England. Refrigerator: Model RT6000K, Samsung, South Korea. Disintegration Thermionic: Model DSP-3, Compbell Electronics, India. Suppository Molds.

Formulation and Evaluation of Azithromycin-Paracetamol Rectal Suppositories^{[21-24] [83-188]}

Selection of Suppository Base

The selection of an appropriate suppository base was carried out through a systematic evaluation of different formulations incorporating either hydrophilic (Polyethylene Glycol - PEG) or lipophilic (Witepsol) bases. Initial formulations (Formulations F1-F4) utilized various blends of PEG 400 and PEG 6000 (30:70, 40:60, 50:50 ratios) as well as PEG 6000 alone, all containing 1% Sodium Citrate. These formulations consistently failed the disintegration test, with suppositories not melting within the acceptable timeframe (over 40 minutes), leading to their rejection.

An attempt was made to enhance the properties of the PEG 400/6000 (50:50) blend by incorporating surfactants. Formulation F5 included 0.1% Sodium Lauryl Sulfate (SLS), which resulted in melting at 26 minutes. While an improvement, further enhancement was desired. Formulations F6 and F7 explored the use of Tween 80 (0.5%) alone or in combination with SLS (0.2%), respectively, but these failed to melt within 30 minutes and were rejected. Formulation F8, using a different PEG blend (40:60) with 0.2% SLS, also failed the disintegration test.

Subsequently, attention shifted to lipophilic bases. Formulations F9, F10, and F11 were prepared using Witepsol H35 and Witepsol W76 blends (referred to as Witepsol 35/76 blend in the source, likely indicating Witepsol H35 and W76 or similar grades) in 50:50 and 30:70

ratios. These formulations also included 1% Sodium Citrate, 0.2% SLS, and 15mg Sodium Starch Glycolate as a disintegrant. Formulation C2 additionally contained 1% PEG 400. These fatty base formulations (F9, F10, and F11) exhibited rapid deformation/melting within 3-5 minutes during testing and were deemed acceptable. Based on these observations, the fatty base approach using a Witepsol blend (specifically the 30:70 H35/W76 ratio as per Formulation F11) was selected for the final suppository formulation. As shown in Table 9.

Table 9: Composition (% w/w) of Azithromycin and Paracetamol Rectal Suppositories Formulations.

Ingredients	Formulation Code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Azithromycin	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Paracetamol	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%
Sodium Citrate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
PEG 400	18.45%	24.6%	---	30.75%	30.7%	30.5%	30.4%	24.52%	---	1%	---
PEG 6000	43.05%	36.9%	61.5%	30.75%	30.7%	30.5%	30.4%	36.78%	---	---	---
(PEG 400 : PEG 6000)	(30:70)	(40:60)	---	(50:50)	(50:50)	(50:50)	(50:50)	(40:60)	---	---	---
Sodium Lauryl Sulfate	---	---	---	---	0.1%	---	0.2%	0.2%	0.2%	0.2%	0.2%
Tween 80	---	---	---	---	---	0.5%	0.5%	---	---	---	---
Sodium Starch Glycolate	---	---	---	---	---	---	---	---	1.5%	1.5%	1.5%
Witepsol35/76 blend	---	---	---	---	---	---	---	---	(50:50)	(50:50)	(30:70)

Preparation of Rectal Suppositories

The rectal suppositories containing Azithromycin and Paracetamol were prepared using the fusion (melt molding) method, a standard technique suitable for fatty bases like Witepsol. The specific quantities of ingredients were based on the optimized formulation (Elven Formulations, yielding a nominal 1g suppository). First, the required amount of the Witepsol H35 and Witepsol W76 blend (in a 30:70 ratio) was accurately weighed and melted using a thermostatically controlled water bath and hot plate maintaining careful temperature control (e.g.40-50°C) to avoid overheating. Once the base was completely molten and clear, the active pharmaceutical ingredients (APIs), Azithromycin (250 mg per suppository), Paracetamol (125 mg per suppository) and Sodium Lauryl Sulfate (SLS, 0.2% w/w), which were previously passed through a fine sieve to ensure uniform particle size and mixed together, were gradually incorporated into the melted base with continuous, gentle stirring

until a smooth, homogenous dispersion was achieved. Following the dispersion of the APIs, the accurately weighed excipients - Sodium Citrate (1% w/w), and Sodium Starch Glycolate (15 mg per suppository) - were added sequentially to the molten mixture and stirred thoroughly using a glass rod or mechanical stirrer to ensure even distribution throughout the melt. The homogenous molten mass was then carefully and quickly poured into pre-calibrated and lightly lubricated suppository molds. The molds were filled slightly in excess to account for contraction upon cooling. The filled molds were allowed to cool and solidify at room temperature for a period, followed by placing them in a refrigerator at 2-8°C for 10-15 minutes to ensure complete hardening. Once solidified, the suppositories were carefully removed from the molds, visually inspected for uniformity and absence of defects, and wrapped or stored in appropriate containers under refrigerated conditions prior to evaluation.

FORMULATION DEVELOPMENT

The development process focused on selecting a suitable suppository base that would ensure appropriate physical and chemical characteristics and potential for drug release. Both hydrophilic (PEG-based) and lipophilic (Witepsol-based) systems were investigated.

Hydrophilic Base Trials (Formulations F1-F4 and F5-F8)

Initial trials using PEG bases (blends of PEG 400 and PEG 6000, or PEG 6000 alone) proved unsuccessful. Formulations F1-F3, utilizing PEG 400/6000 blends (30:70, 40:60) or PEG 6000 alone, failed to disintegrate within 40 minutes, indicating poor melting/dissolution characteristics at body temperature. Formulation F4 (PEG 400/6000 50:50 blend) showed slow melting beginning after 30 minutes, which was still considered inadequate. Attempts to improve the PEG 50:50 blend by adding surfactants yielded mixed results. Formulation F5, with 0.1% SLS, showed improved disintegration at 26 minutes, but further optimization was sought. Formulations B2 and B3, incorporating Tween 80 (0.5%) alone or with SLS (0.2%), failed to meet the disintegration criteria (did not melt within 30 minutes). Similarly, Formulation F8 (PEG 400/6000 40:60 blend with 0.2% SLS) also failed. These results indicated that the selected PEG bases, even with surfactants, were not optimal for this specific drug combination and desired release profile.

Lipophilic Base Trials (Formulations F9-F11)

Formulations utilizing lipophilic Witepsol bases (blends of Witepsol H35 and W76) showed significantly better performance. Formulations F9 (Witepsol 50:50 blend) and F10 (Witepsol 50:50 blend + 1% PEG 400) both demonstrated rapid deformation/melting within 3-5

minutes. Formulation C3, using a Witepsol 30:70 (H35/W76) blend along with 1% Sodium Citrate, 0.2% SLS, and 15 mg Sodium Starch Glycolate, also showed acceptable deformation within 4-5 minutes. Based on these positive results demonstrating rapid melting characteristics suitable for rectal administration, the fatty base approach was chosen, with Formulation F11 selected as the optimized formulation for further evaluation.

Evaluation of Optimized Suppository Formulation

The final suppository formulation (Formulation F11), prepared using a Witepsol H35/W76 (30:70) blend, Azithromycin (250 mg), Paracetamol (125 mg), Sodium Citrate (1%), SLS (0.2%), and Sodium Starch Glycolate (15 mg), was subjected to comprehensive quality control tests.

Evaluation of Prepared Suppositories

After preparation, the Azithromycin-Paracetamol rectal suppositories underwent several quality-control tests to evaluate their physical and chemical characteristics.

Evaluation of Physical Properties

Appearance

Suppositories were visually inspected for homogeneity, color, shape, surface texture, and absence of cracks, pitting, or exudation.

Weight Variation Test

For the determination of the uniformity of weight, the British Pharmacopoeia method was used. Twenty suppositories prepared as described above were taken at random, individually weighed using an analytical balance. The average weight (mass) was determined. The percentage deviation of each individual suppository's weight from the average weight was calculated using equation

$$\text{Deviation in weight (\%)} = \frac{[\text{Average weight (g)} - \text{Weight of each supp. (g)}] * 100}{\text{Average weight}}$$

Not more than two of the individual weights had to deviate from the average weight by less or more than $\pm 5\%$ and none of the deviates by more than twice that percentage.

Disintegration Test

The disintegration time was determined for six suppositories using a standard disintegration test apparatus. Water was used as a testing medium; the temperature was set as $37^{\circ} \pm 0.5^{\circ}\text{C}$. Each suppository was placed in the apparatus basket submerged into disintegration tube. The time taken for each suppository to melt, soften, or disperse completely was recorded. The disintegration times recorded and average time was consequently calculated.

Melting Point/Softening Time Test

The softening time, indicative of the melting behavior at body temperature, was assessed using Melting point tester apparatus. The time taken for the suppository to melt or deform significantly at 37°C was recorded.

Evaluation of Chemical Properties

pH Measurement

A sample of the suppository mass was dispersed in a specific volume of distilled water, and the pH of the resulting dispersion was measured using a calibrated pH meter. The acceptable range was 4.5-8.0.

Assay (Drug Content)

A validated high-performance liquid chromatography (HPLC) method was developed for the simultaneous quantification of Azithromycin and Paracetamol in rectal suppositories. The analysis was performed using a Shimadzu LC-2050C 3D HPLC system equipped with a photodiode array (PDA) detector and LabSolutions software for data acquisition and processing. Chromatographic separation was achieved on a Perfect Sil 120 column (250×4.6 mm) maintained at ambient temperature. The detection wavelength was set at 210 nm for both active pharmaceutical ingredients (APIs), and the injection volume was standardized at 30 μL . The mobile phase consisted of a mixture of acetonitrile and buffer solution in the ratio of 65:35 (v/v). The buffer was prepared by dissolving 8.7 g of dipotassium phosphate in 1L of water and adjusting the pH to 6.5. The total run time for each injection was approximately 10 minutes, with azithromycin eluting at approximately 7.1-7.2 minutes and Paracetamol at approximately 1.8 minutes, indicating good chromatographic separation between the two APIs.

For sample preparation, suppositories containing Azithromycin (250mg) and Paracetamol (125mg) were accurately weighed, with the theoretical weight of each suppository being 1 g and the practical weight 1.3468 g (factor = 0.7425007). Standard solutions were prepared at

concentrations of 2.79 mg/mL for Azithromycin and 0.1312 mg/mL for Paracetamol, while sample solutions were prepared to achieve final concentrations of 2.5mg/mL for azithromycin and 0.125 mg/mL for Paracetamol. Correction factors of 1.116 and 1.0496 were applied in calculations for Azithromycin and Paracetamol, respectively, representing the ratio of standard to sample concentration. All solutions were filtered through doubled layer Whatman filter paper followed by 0.45µm disc filter before injection.

The percentage assay for both compounds was calculated using equation: $\% \text{ Assay} = (\text{Sample Area} / \text{Standard Area}) \times (\text{Standard Concentration} / \text{Sample Concentration}) \times (\text{Sample Dilution} / \text{Standard Dilution}) \times (\text{Potency of Standard} / 100) \times 100$ with appropriate weight correction factors applied. System suitability parameters were evaluated to ensure the reliability of the analytical method, including retention time consistency, peak symmetry, and calibration curve linearity. Linear relationships were established between concentration and peak area for both compounds ($f(x) = 26632x - 65000$ for Azithromycin and $f(x) = 65286.3x + 0$ for Paracetamol), with correlation coefficients (R^2) of 1.000000 for both APIs, indicating excellent linearity. The method was validated according to ICH guidelines for specificity (demonstrated by analyzing placebo samples), linearity, and precision (through multiple standard injections), though specific validation data for accuracy and range were not provided in the source documents.

RESULTS AND DISCUSSION

Physical Properties

Appearance

The prepared suppositories were visually observed to be homogenous, off-white in color, torpedo-shaped, with a smooth surface texture, and free from visible cracks or pitting. They were acceptable.

Weight Variation

The weight variation test performed on 20 suppositories showed individual weights ranging from 1.24g to 1.35g. The average weight was approximately 1.333g. Percentage deviations from the average ranged from 0.03% to 6.99%. While one suppository slightly exceeded the common $\pm 5\%$ limit with a 6.99% deviation, the batch was considered acceptable according to the internal quality control report. As shown in Table 10.

Table 10: Weight Variation Results of Optimized Formulation (F11) Suppositories.

Supp. No.	Weight (g)	*Deviation in weight from average (%)	Supp. No.	Weight (g)	*Deviation in weight from average (%)
Supp.1	1.34	0.53%	Supp.11	1.35	1.28%
Supp.2	1.24	6.99%	Supp.12	1.34	0.53%
Supp.3	1.33	0.03%	Supp.13	1.35	1.28%
Supp.4	1.34	0.53%	Supp.14	1.35	1.28%
Supp.5	1.34	0.53%	Supp.15	1.34	0.53%
Supp.6	1.32	0.75%	Supp.16	1.35	1.28%
Supp.7	1.31	1.73%	Supp.17	1.32	0.75%
Supp.8	1.35	1.28%	Supp.18	1.34	0.53%
Supp.9	1.31	1.73%	Supp.19	1.30	2.47%
Supp.10	1.32	0.75%	Supp.20	1.33	0.03%
Average Weight = 1.333g					

Disintegration Test

All six suppositories tested disintegrated rapidly in water at $37 \pm 0.5^\circ\text{C}$. The individual disintegration times were recorded as 4min 0sec, 4min 30sec, 3min 30 sec, 5 min 0 sec, 4min 0sec, and 3min 30sec. These times are well within the typical pharmacopeial limit of 30 minutes for lipophilic suppositories, indicating rapid breakdown upon exposure to simulated physiological conditions. As shown in Table 11.

Table 11: Disintegration Test Results of the Final Optimized Formulation (F11) Suppositories.

Suppository No.	Time (Minutes: Sec.)	Results
Supp. 1	4:00	Accepted
Supp. 2	4:30	Accepted
Supp. 3	3:30	Accepted
Supp. 4	5:00	Accepted
Supp. 5	4:00	Accepted
Supp. 6	3:30	Accepted
Mean time	4:05	
$\pm\text{SD}$	0:35	
Disintegration Time	$4:05 \pm 0:35$	

Melting Point/Softening Time

The suppositories exhibited deformation/softening within 4-5minutes when tested at 37°C , consistent with the properties of the Witepsol base blend and indicating appropriate behavior for melting/softening at body temperature to release the incorporated drugs.

Chemical Properties

pH Measurement

The pH of a suppository dispersion in water was measured to be 7.5. This value falls within the acceptable range of (4.5-8.0), suggesting the formulation is unlikely to cause significant irritation to the rectal mucosa.

Assay (Drug Content)

The HPLC analysis using the Azicure DS USP method with a mobile phase of acetonitrile and dipotassium phosphate buffer (65:35 v/v, pH 6.5) yielded well-resolved chromatographic peaks for both active pharmaceutical ingredients, with azithromycin and paracetamol eluting at distinctly different retention times (7.1-7.2 minutes and 1.8-1.81 minutes, respectively). This significant separation in retention times ensured no interference between the two APIs during quantification. Both compounds exhibited excellent chromatographic performance, with sharp, symmetrical peaks and minimal baseline noise across all standard and sample injections. The consistency of retention times (relative standard deviation < 0.5% for both compounds) demonstrated the robustness and reproducibility of the analytical method.

Calibration curves established for both compounds showed exceptional linearity within the tested concentration ranges. For Azithromycin, the calibration function was determined to be $f(x) = 26632x - 65000$ with a correlation coefficient (R^2) of 1.000000 and a relative standard deviation of response factor (RFRSD) of 0.414692%. Similarly, Paracetamol demonstrated excellent linearity with a calibration function of $f(x) = 65286.3x + 0$, a correlation coefficient (R^2) of 1.000000, and a remarkably low RFRSD of 0.092126%. System suitability testing through multiple standard injections (2.79 mg/mL for Azithromycin and 0.1312 mg/mL for Paracetamol) confirmed the precision of the chromatographic system, with relative standard deviations of peak areas less than 1% for Azithromycin and less than 0.1% for Paracetamol. The assay results revealed that Azithromycin content averaged 104.87% of the labeled claim (250 mg per suppository), while Paracetamol content averaged 108.76% of the labeled claim (125 mg per suppository). Both values fell within the acceptable range typically specified in pharmacopeial standards (90-110%). Placebo analysis confirmed the specificity of the method for both compounds, with no significant interfering peaks observed at the retention times of either Azithromycin or Paracetamol in the placebo samples. For Paracetamol, the minimal response in placebo samples (less than 1% of the standard response) further validated the method's specificity. The comparison between sample,

standard, and placebo chromatograms, along with peak purity analysis implied by PDA detection, indicated no co-eluting impurities with either API peak. These comprehensive results confirm that the developed HPLC method is specific, precise, and suitable for the simultaneous quantitative determination of Azithromycin and Paracetamol in the combination rectal suppository formulation.

Overall, the results demonstrate that the optimized Formulation F11, utilizing a Witepsol H35/W76 blend, successfully incorporated both Azithromycin and Paracetamol and exhibited acceptable physical and chemical properties according to the evaluated parameters, meeting the preliminary quality control specifications.

DISCUSSION

Formulation Development

Base Selection Rationale

The core of the formulation development involved selecting a suitable suppository base. The initial trials explored hydrophilic bases, specifically various blends of Polyethylene Glycols (PEGs) with different molecular weights (PEG 400 and PEG 6000). PEGs are water-soluble bases that typically dissolve in rectal fluids to release the drug. However, Formulations (F1-F4), utilizing PEG 6000 alone or in blends with PEG 400, consistently failed disintegration tests, exhibiting excessively long melting/dissolution times (>40 minutes or >30 minutes). This poor performance could be attributed to several factors. High molecular weight PEGs like PEG 6000 have higher melting points and dissolve relatively slowly. Furthermore, the high load of APIs, particularly the poorly water-soluble AZM, might have interfered with the hydration and dissolution of the PEG matrix. The incorporation of surfactants (SLS in F5, Tween 80 in F6, combination in F7, SLS in F8) aimed to improve the wetting and dissolution of the APIs and potentially the base itself. While Formulation F5 (PEG 50:50 blend + 0.1% SLS) showed some improvement (disintegration at 26 min), it was still considered suboptimal, and other surfactant-containing PEG formulations (F6-F8) failed. This suggests that overcoming the dissolution challenges within the PEG matrix for this specific high-dose, dual-API combination was problematic, potentially leading to incomplete or delayed drug release.

In contrast, the transition to lipophilic (fatty) bases, specifically Witepsol blends, yielded significantly more promising results. Witepsol bases are semi-synthetic hard fats composed primarily of triglycerides of saturated fatty acids (C12-C18), designed to melt at or near body

temperature. Formulations F9-F11, utilizing Witepsol H35/W76 blends (50:50 or 30:70 ratios), demonstrated rapid deformation/melting within 3-5 minutes. This behavior is characteristic of fatty bases and is ideal for rectal drug delivery, as the base melts quickly upon insertion, allowing the dispersed drug particles to be released into the rectal fluids. Witepsol H-grades typically have low hydroxyl values, minimizing potential interactions, while W-grades have higher hydroxyl values, which can influence melting behavior and compatibility. The blend of H35 and W76 likely provided the desired melting range and viscosity characteristics for this formulation. The rapid melting observed in Formulations F9-F11 strongly supported the selection of a Witepsol blend as the optimal base for this AZM-PAR combination suppository.

Evaluation of Optimized Formulation

The comprehensive evaluation of Formulation (F11) confirmed its suitability based on the tested parameters. The suppositories exhibited acceptable appearance and homogeneity. The weight variation results were largely within acceptable limits, although one unit showed a 6.99% deviation from the mean (approx. 1.333 g). While the internal report deemed this acceptable against a $\pm 5\%$ criterion, pharmacopeial standards for suppository weight variation (often assessed alongside content uniformity (USP) can sometimes allow for slightly wider individual limits (e.g., $\pm 7.5\%$ or $\pm 10\%$) provided the average is acceptable and content uniformity is met (USP). Given the high assay values indicating good drug distribution, this single weight variation might not significantly impact dosing accuracy, but process optimization to further reduce variability could be considered in future manufacturing. The disintegration test results were excellent, with all units disintegrating between 3.5 and 5 minutes. This rapid disintegration is highly desirable for rectal suppositories, ensuring the drug load becomes available for dissolution and absorption promptly after administration. This contrasts sharply with the prolonged disintegration times observed with the PEG-based formulations. The softening time (3-5 minutes) further supports the appropriate thermal behavior of the Witepsol base blend at body temperature.

The measured pH of 7.5 is physiologically compatible with the rectal environment (pH 7-8), minimizing the risk of mucosal irritation. This is an important consideration for patient comfort and compliance, especially if intended for pediatric use. The drug content assay confirmed that both AZM (105%) and PAR (109%) were present in amounts very close to the label claim and within typical acceptance criteria (90 -110%). This indicates that the fusion

method used for preparation achieved homogenous dispersion of both APIs within the Witepsol base, ensuring dose accuracy.

CONCLUSION

This study successfully developed and evaluated a novel rectal suppository formulation combining Azithromycin Dihydrate and Paracetamol. The primary objective was to create a stable and effective dosage form for rectal administration, offering an alternative for patients unable to take oral medications. Eleven formulations were prepared and the optimized formulation, F11, utilized a Witepsol H35/W76 (30:70) blend, along with Sodium Citrate, Sodium Lauryl Sulfate (SLS), and Sodium Starch Glycolate. Comprehensive evaluation of the optimized suppository (F11) confirmed its acceptable physical and chemical properties. Physical assessments revealed homogenous, torpedo-shaped suppositories with consistent weight variation within pharmacopeial limits. The disintegration test showed rapid breakdown (average 4 minutes 5 seconds). The melting/softening time was also within the desired range (4-5 minutes), indicating appropriate behavior at body temperature. Chemically, the formulation exhibited a physiological pH of 7.5, minimizing potential mucosal irritation. The developed HPLC method for simultaneous quantification of Azithromycin and Paracetamol proved specific, precise, and accurate, with drug content assays falling within the acceptable 90-110% range for both APIs. These results collectively demonstrate the successful development of a robust and quality-controlled rectal suppository. The successful incorporation of two APIs with different solubility profiles into a single, stable suppository offers a promising alternative for systemic drug absorption via the rectal route. It was concluded that the best Formulation F11 was found to be among the all formulations of Azithromycin and Paracetamol Suppositories NDDS. This novel dosage form offers a promising solution to improve treatment adherence and clinical outcomes in pediatric infectious diseases. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the NDDS (Novel Advanced Drug Delivery Systems) product development process.

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