WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 12, 1864-1904. Research Article ISSN 2277–7105

FORMULATION AND EVALUATION OF AZITHROMYCIN AND PARACETAMOL A COMBINATION THERAPY AS SUPPOSITORIES NOVEL DRUG DELIVERY SYSTEMS

Mahmoud Mahyoob Alburyhi[1]*, Tawfeek A. A. Yahya[2], Maged Alwan Noman[1], Abdalwali Ahmed Saif[1]

[1]Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

[2]Professor Dr. of Medicinal Chemistry and Drug Design, Department of Medicinal Chemistry, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

Article Received on 15 May 2026,
Article Revised on 05 June 2026,
Article Published on 16 June 2026,

https://doi.org/10.5281/zenodo.20729230

***Corresponding Author**

Mahmoud Mahyoob Alburyhi

Professor Dr. of Pharmaceutics and Industrial Pharmacy, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen.

How to cite this Article Mahmoud Mahyoob Alburyhi[1]*, Tawfeek A. A. Yahya[2], Maged Alwan Noman[1], Abdalwali Ahmed Saif[1]. (2026). Formulation And Evaluation Of Azithromycin And Paracetamol A Combination Therapy As Suppositories Novel Drug Delivery Systems. World Journal of Pharmaceutical Research, 15(12), 1864–1904.

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:** Elven 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 (Cmax) of 224-383 µg/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 t emperature 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 Adults1 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. 0.1NHydrochloric 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 F7explored 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 ±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°± 0.5°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: *% Assay = (Sample Area / Standard Area) × (Standard Concentration / Sample Concentration) × (Sample Dilution / Standard Dilution) × (Potency of Standard / 100) × 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.

RSEULTS 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 ±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± 0.5°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	
±SD	0:35	
Disintegration Time	4:05 ± 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 ±5% criterion, pharmacopeial standards for suppository weight variation (often assessed alongside content uniformity (USP) can sometimes allow for slightly wider individual limits (e.g., ±7.5% or ±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. Elven 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.

ACKNOWLEDGEMENT

The authors are thankful to Shaphaco Pharmaceutical Industry Company-Yemen, for support and facilities.

REFERENCES

1. Langtry, H.D., & Balfour, J.A. Azithromycin: A review of its use in paediatric infectious diseases. Drugs, 1998; 56, 273-297.
2. World Health Organization (WHO). "Pneumonia" 2022.
3. Malkawi, W. A., AlRafayah, E., AlHazabreh, M., AbuLaila, S., & Al-Ghananeem, A. M. Formulation Challenges and Strategies to Develop Pediatric Dosage Forms. Children (Basel, Switzerland), 2022; 9(4): 488. https: //doi.org/10.3390/children9040488.
4. Bulić, M., & Tuleu, C. Rectal drug delivery to paediatric population. Hrvatski časopis zdravstvenih znanosti,. 2021.
5. Linakis, M.W., Roberts, J.K., Lala, A.C., Spigarelli, M.G., Medlicott, N.J., Reith, D.M., ... & Sherwin, C.M. Challenges associated with route of administration in neonatal drug delivery. Clinical Pharmacokinetics, 2016; 55: 185-196.
6. Hua, S. Physiological and Pharmaceutical Considerations for Rectal Drug Formulation and Delivery. Frontiers in Pharmacology, 2019; 10: 1196. https: //doi.org/10.3389/fphar.2019.01196.
7. CARE Hospitals. Azithromycin: Uses, Dosage, Precautions and More.2023. https: //www.carehospitals.com/medicine-detail/azithromycin Drugs.com. Azithromycin and Paracetamol Interactions. 2023. https: //www.drugs.com/drug-interactions/azithromycin-with-paracetamol-300-0-11-2744.html.
8. Abdulaziz, S. M., Abdulhamid, A. J., Abobakr, F. A., & Rajab, N. F. Antibacterial Activity of Paracetamol, Trimethoprim/sulfamethoxazole, Azithromycin, and Ciprofloxacin. Journal of Advanced Zoology, 2023.
9. Basa, M., & Sovtić, A. Treatment of the most common respiratory infections in children. Archives of Pharmacy, 2022; 72, 118-133.
10. Allen, L. V., & Ansel, H. C. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (10th ed.). Lippincott Williams & Wilkins, 2023.
11. Bergogne-Bérézin, E., & Bryskier, A. The suppository form of antibiotic administration: pharmacokinetics and clinical application. Journal of Antimicrobial Chemotherapy, 1999; 43(2): 177-185.
12. Kauss, T., Gaubert, A., Boyer, C., Ba, B. B., Manse, M., Massip, S., & Millet, P. Pharmaceutical development and optimization of azithromycin suppository for paediatric use. International Journal of Pharmaceutics, 2013; 441(1-2): 218-226.

13. Kauss, T., Gaudin, K., Gaubert, A., Ba, B., Tagliaferri, S., Fawaz, F., & Millet, P. Screening paediatric rectal forms of azithromycin as an alternative to oral or injectable treatment. International Journal of Pharmaceutics, 2012; 436(1-2): 624-630.
14. United States Pharmacopeia and National Formulary (USP 46-NF 41). United States Pharmacopeial Conventio, 2023.
15. Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (Eds.). Handbook of Pharmaceutical Excipients (7th ed.). Pharmaceutical Press and American Pharmacists Association, 2012.
16. IOI Oleo GmbH. (n.d.). WITEPSOL®: Hard fats for suppositories and ovules [Brochure]. Retrieved June 3, 2025, from https: //www.ioioleo.de/wp-content/uploads/2020/03/IOI_Oleo_Pharma_WITEPSOL.pdf
17. Garg, R., Gupta, G. D., & Goyal, A. Formulation and evaluation of fast dissolving tablets of an antihypertensive drug. International Journal of Pharmaceutical Investigation, 2012; 2(2): 88–93. https: //doi.org/10.4103/2230-973X.100048.
18. Kaewnopparat, S., Kaewnopparat, N., & Rojanapíbulpun, J. Influence of disintegrants on physical properties and drug release from piroxicam suppositories using a Witepsol H15 base. Pharmaceutical Development and Technology, 2004; 9(2): 185–191. https: //doi.org/10.1081/PDT-120037483.
19. Gibson, M. (Ed.). Pharmaceutical preformulation and formulation: A practical guide from candidate drug selection to commercial dosage form (2nd ed.). Informa Healthcare, 2009.
20. https: //go.drugbank.com/drugs/DB00207.
21. https: //pubchem.ncbi.nlm.nih.gov/compound/Azithromycin-Dihydrate.
22. https: //go.drugbank.com/drugs/DB00316.
23. https: //pubchem.ncbi.nlm.nih.gov/compound/Acetaminophen.
24. Alburyhi MM, Yahya TAA, Saif AA, Noman MA, Alshoba N, Saeed SA. Acyclovir-Excipient Compatibility Studies for Gel Novel Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2026; 15(6): 1247-1292.
25. Saif AA, Abdullah JH, Alburyhi MM, Noman MA, Saeed SA. Sildenafil-Excipient Compatibility Studies for Pharmaceutical Oral Suspensions Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2026; 15(6): 869-908.
26. Noman MA, Saif AA, Alburyhi MM. The Impact of Vitamin D Deficiency and Nutritional Habits on Height and Health Among Yemeni Adult Female Students in Sana'a, Yemen. World Journal of Pharmacy and Pharmaceutical Sciences, 2026; 15(3): 855-875.

27. Alburyhi MM, Saif AA, Noman MA, Saeed SA. Compatibility Studies of Chlorhexidine with Pharmaceutical Excipients for the Development of Gel Novel Delivery Systems. World Journal of Pharmacy and Pharmaceutical Sciences, 2026; 15(4): 1071-1109.
28. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Punica granatum Flower and Hibiscus sabdariffa Calyx: A Narrative Review of Phytochemistry, Antioxidant Mechanisms, and Therapeutic Potential. World Journal of Pharmaceutical Research, 2026; 15(7): 1949-1966.
29. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Punica granatum Flower and Hibiscus sabdariffa Calyx: A Narrative Review of Phytochemistry, Antioxidant Mechanisms, and Synergistic Potential in Oxidative Stress Management. World Journal of Pharmaceutical and Medical Research, 2026; 12(4): 418-427.
30. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Pharmacological Insights and Pharmaceutical Formulations of Pandanus odoratissimus Peduncle and Curcuma longa: A Narrative Review of Therapeutic Applications from 2010 to 2025. European Journal of Biomedical and Pharmaceutical Sciences, 2026; 13(4): 375-381.
31. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Synergistic Potential of Pandanus odoratissimus and Curcuma longa in the Management of Nocturnal Enuresis: A Comprehensive Narrative Review of Botanical, Pharmacological, and Formulation Strategies. World Journal of Pharmaceutical Research, 2026; 15(7): 1934-1948.
32. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Pharmacological and Formulation Advances in the Management of Hepatic and Inflammatory Disorders: A Review of Acalypha fruticosa and Tribulus terrestris. World Journal of Pharmaceutical and Life Sciences, 2026; 12(4): 260-264.
33. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. A Hepatoprotective and Anti-inflammatory Polyherbal Approach: The Synergistic Potential of Acalypha fruticosa and Tribulus terrestris Extract. European Journal of Pharmaceutical and Medical Research, 2026; 13(4): 520-524.
34. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. The Evolution and Therapeutic Potential of Polyherbal Gels and Key Botanical Extracts in Diabetic Foot Ulcer Management: A Comprehensive Narrative Review. European Journal of Biomedical and Pharmaceutical Sciences, 2026; 13(4): 368-374.
35. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Global Burden, Pathophysiology, and Emerging Herbal Management Strategies for Diabetic Foot Ulcers:

A Narrative Review. World Journal of Pharmacy and Pharmaceutical Sciences, 2026; 15(4): 1130-1138.

36. El-Shaibany A, Noman MA, Alburyhi MM, Saif AA, et al. Antimicrobial Activity of Commiphora molmol, Curcuma longa, Dragon's Blood Resin, and Propolis Against Diabetic Foot Ulcer Pathogens: An In Vitro Evaluation. World Journal of Pharmaceutical Research, 2026; 15(8): 1301-1319.
37. Saif AA, El-Shaibany A, Alburyhi MM, Hamidaddin MA, Noman MA. A Narrative Review of Propolis and Metformin in Topical Dermatology: From Mono-Agent Bioactivities to the Frontier of Emulgel-Based Combination Therapies for Melasma. European Journal of Biomedical and Pharmaceutical Sciences, 2026; 13(5): 248-256.
38. Saif AA, El-Shaibany A, Alburyhi MM, Hamidaddin MA, Noman MA. Advancements Formulation, and Pharmacological Activity Evaluation of Aloe Species and Hibiscus sabdariffa for Cancer Supportive Care: A Comprehensive Review (2010 to 2025). European Journal of Pharmaceutical and Medical Research, 2026; 13(5): 386-393.
39. Hamidaddin MA, El-Shaibany A, Alburyhi MM, Saif AA, Noman MA. Pathogenesis of Melasma, Therapeutic Limitations, and the Emerging Potential of Metformin and Propolis as a Multi-Target Topical Strategy: A Narrative Review. World Journal of Pharmaceutical and Life Sciences, 2026; 12(5): 261-271.
40. Hamidaddin MA, El-Shaibany A, Alburyhi MM, Saif AA, Noman MA. The Synergistic Potential of Aloe rubroviolacea and Hibiscus sabdariffa in Cancer Supportive Care: A Comprehensive Narrative Review. World Journal of Pharmaceutical and Medical Research, 2026; 12(5): 233-240.
41. Alburyhi MM, Al-Ghorafi MA, Saif AA, Noman MA, Saeed SA. Vitamin D3-Excipient Compatibility Studies for Orodispersible Tablets Novel Drug Delivery Systems Development. World Journal of Pharmacy and Pharmaceutical Sciences, 2026; 15(5): 1301-1319.
42. Alburyhi MM, Yahya TAA, Alkhawlani MA, Saif AA, Noman MA. Compatibility Studies of Azithromycin and Paracetamol Combination for the Development as Suppositories Novel Drug Delivery Systems. World Journal of Pharmaceutical and Life Sciences, 2026; 12(5): 309-334.
43. Saif AA, Alburyhi MM, Noman MA, El-Shaibany A. Compatibility Studies of Fusidic Acid with Pharmaceutical Excipients to Development Cream Novel Drug Delivery Systems for Enhanced Diabetic Wound Healing. World Journal of Pharmaceutical Research, 2026; 15(10): 1527-1567.

44. Saif AA, Alburyhi MM, Alkhawlani MA, Noman MA, Saeed SA. Preformulation Studies of Atorvastatin with Pharmaceutical Excipients to Development Cream for Enhanced Diabetic Wound Healing as Novel Drug Delivery Systems. World Journal of Pharmaceutical and Medical Research, 2026; 12(5): 285-308.
45. Alburyhi MM, Noman MA, Saif AA, El-Shaibany A, Hamidaddin MA. Compatibility Studies of Vitamin C with Pharmaceutical Excipients to Development Cream Cosmeceutical as Novel Drug Delivery Systems for Stretch Marks. World Journal of Pharmaceutical Research, 2026; 15(10): 1568-1600.
46. Alburyhi MM, Salim YA, Saif AA, Noman MA. Furosemide-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(22): 1178-1219.
47. Alburyhi MM, Saif AA, Noman MA. Lornoxicam-Excipient Compatibility Studies for Microsponge-Based Drug Delivery Systems Development. World Journal of Pharmaceutical and Medical Research, 2025; 11(4): 70-81.
48. Alburyhi MM, Noman MA, Saif AA, Salim YA, Hamidaddin MA, Yahya TA, Al-Ghorafi MA, Abdullah JH. Lisinopril-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(16): 59-111.
49. Alburyhi MM, Saif AA, Noman MA, Saif RM. The Importance of Stability Testing in Pharmaceutical Development of Ceftriaxone Implant Biodegradable Tablets. Matrix Science Pharma (MSP)., 2025; 9(2): 58-63.
50. Alburyhi MM, Saif AA, Noman MA, Yassin SH. Compatibility Studies with Pharmaceutical Excipients of Simvastatin for the Development of Novel Drug Delivery Systems. World Journal of Pharmaceutical Research, 2024; 13(19): 1463-1512.
51. Alburyhi MM, Hamidaddin MA, Noman MA, Saif AA, Yahya TA, Al-Ghorafi MA. Rivaroxaban-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. European Journal of Pharmaceutical and Medical Research, 2024; 11(9): 370-404.
52. Alburyhi MM, Noman MA, Saif AA, Hamidaddin MA, Yahya TA, Al-Ghorafi MA. Rosuvastatin Calcium-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(13): 1549-1582.
53. Saif AA, Alburyhi MM, Noman MA, Yahya TA, Al-Ghorafi MA. Famotidine-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal

of Pharmaceutical Research, 2024; 13(18): 1346-1408.

54. Al-Ghorafi MA, Alburyhi MM, Saif AA, Noman MA, Yahya TA. Drotaverine-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(18): 1285-1340.
55. Alburyhi MM, Saif AA, Noman MA. Ticagrelor-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(10): 1081-1132.
56. Alburyhi MM, Noman MA, Saif AA, Al-Ghorafi MA, Yahya TA, Yassin SH, AlKhawlani MA. Diclofenac-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical Research, 2024; 13(14): 1297-1333.
57. Noman MA, Alburyhi MM, Saif AA, Yahya TAA. Evaluation and Drug Stability Studies Some Atorvastatin Tablets Brands Available in Sana'a Market Yemen. World Journal of Pharmaceutical and Medical Research, 2024; 10(12): 231-236.
58. Saif AA, Noman MA, Alburyhi MM, Yahya TAA. Evaluation and Drug Stability Studies Some Levocetirizine Tablets Brands Available in Sana'a Market Yemen. World Journal of Pharmaceutical Research, 2024; 13(24): 1009-1022.
59. Al-Ghorafi MA, Alburyhi MM, Saif AA, Noman MA. Meloxicam-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical and Medical Research, 2025; 11(1): 87-106.
60. Alburyhi MM, Saif AA, Saif RM. Preformulation Study of Ceftriaxone and Ciprofloxacin for Lipid Based Drug Delivery Systems. EJUA-BA., 2022; 3(4): 339-350.
61. Noman MA, Alburyhi MM, Alqubati MA. Preformulation and Characterization Studies of Clopidogrel Active Ingredient for Orodispersible Tablets Development. World Journal of Pharmacy and Pharmaceutical Sciences., 2024; 13(3): 996-1015.
62. Alburyhi MM, Noman MA, Alemad AF. Preformulation Studies of Cefixime for Dispersible Tablets Delivery System Development. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(12): 75-99.
63. Noman MA, Alburyhi MM, Saif AA. Knowledge and Perception about Pharmacovigilance Among 4Th and 5Th Levels Pharmacy Students in Some Public and Private Universities, Sana'a Yemen. World Journal of Pharmaceutical and Medical Research, 2023; 9(11): 14-19.
64. Alburyhi MM, Saif AA, Noman MA. Domperidone-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Biomedical and

Pharmaceutical Sciences, 2025; 12(3): 250-269.

65. Alburyhi MM, Saif AA, Noman MA. Spironolactone-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmacy and Pharmaceutical Sciences, 2025; 14(3): 871-910.
66. Saif AA, Alburyhi MM, Noman MA. Ketoprofen-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmacy and Pharmaceutical Sciences, 2025; 14(4): 92-123.
67. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Preformulation and Characterization Studies of Pandanus Odoratissimus L Extract Active Ingredient in Treatment of Nocturnal Enuresis. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(2): 1603-1620.
68. Alburyhi MM, Noman MA, Saif AA. Metronidazole-Excipient Compatibility Studies for Medicated Chewing Gum Delivery Systems Development. European Journal of Pharmaceutical and Medical Research, 2025; 12(4): 567-589.
69. Alburyhi MM, Saif AA, Noman MA, AlGhoury ABA. Compatibility Studies of Chloroquine Phosphate with Pharmaceutical Excipients for the Development of Suppositories Novel Drug Delivery Systems. World Journal of Pharmaceutical Research, 2025; 14(14): 1325-1360.
70. Alburyhi MM, Saif AA, Noman MA, Al-Ghorafi MA. Comparative Study of Certain Commercially Available Brands of Paracetamol Tablets in Sana'a City, Yemen. European Journal of Pharmaceutical and Medical Research, 2018; 5(12): 36-42.
71. Saif AA, Alburyhi MM, Noman MA. Evaluation of Vitamin and Mineral Tablets and Capsules in Yemen Market. Journal of Chemical Pharma Research, 2013; 5(9): 15-26.
72. Alburyhi MM, Saif AA, Noman MA, Al Khawlani MA. Bisoprolol-Excipient Compatibility Studies for Advanced Drug Delivery Systems Development. World Journal of Pharmaceutical and Medical Research, 2024; 10(10): 304-324.
73. Saif AA, Alburyhi MM, Noman MA, Abudunia A. Amoxicillin-Excipient Compatibility Studies for Advanced Drug delivery Systems Development. European Journal of Pharmaceutical and Medical Research, 2025; 12(6): 530-562.
74. Noman MA, Alburyhi MM, Saif AA, Yahya TAA. Assessment of Knowledge, Attitude, and Practice of Pharmacovigilance Among Pharmacists and Health care Professionals in Four Government Hospitals at Sana'a City, Yemen. European Journal of Biomedical and Pharmaceutical Sciences, 2025; 12(5): 250-267.
75. Alburyhi MM, Mohamed YAS, Saif AA, Noman MA. Compatibility Studies with

Pharmaceutical Excipients of Amlodipine for the Development of Novel Delivery Systems. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(11): 95-136.

76. Alburyhi MM, Saif AA, Noman MA. Compatibility Studies of Sulfadoxine with Pharmaceutical Excipients for the Development of Suppositories Novel Drug Delivery Systems. World Journal of Pharmaceutical and Life Sciences, 2025; 11(9): 189-207.
77. Alburyhi MM, Saif AA, Noman MA. Compatibility Studies with Pharmaceutical Excipients of Clopidogrel for the Development of Novel Delivery Systems. World Journal of Pharmaceutical Research, 2025; 14(06): 1448-1486.
78. Noman MA, Alburyhi MM, Yahya TAA, Saif AA. Evaluation and Drug Stability Studies of Different Brands of Clopidogrel Tablets Available in Sana'a City Market, Yemen. European Journal of Biomedical and Pharmaceutical Sciences, 2025; 12(7): 181-191.
79. Alburyhi MM, Saif AA, Noman MA. Compatibility Studies of Pyrimethamine with Pharmaceutical Excipients for the Development of Suppositories Novel Drug Delivery Systems. European Journal of Pharmaceutical and Medical Research, 2025; 12(9): 394-412.
80. Noman MA, Alburyhi MM, Saif AA. Effect of Chewing Khat on Nutritional Status Among Female Students at Undergraduate Level in Sana'a, Yemen. World Journal of Pharmaceutical Research, 2023; 12(20): 75-88.
81. Noman MA, Alburyhi MM, Saif AA. Knowledge, Attitude and Practice Regarding the Proper Use, Risks and Resistance of Antibiotics Among Undergraduate Level Medical and Health Sciences Students in Sana'a, Yemen. European Journal of Pharmaceutical and Medical Research, 2025; 12(12): 414-425.
82. Sravani M. Formulation and Evaluation of Mouth Dissolving Tablets of Nebivolol HCl for Treatment of Hypertension. Int J Pharma Chem Res., 2017; 3: 200-212.
83. Gandhi L, Akhtar MS. Comparative Study on Effect of Natural and Synthetic Superdisintegrants in the Formulation of Orodispersible Tablets. J Drug Deliv Ther., 2019; 9(2): 507-513.
84. Santosh Kumar R, Kumari A. Fast Dissolving Tablets: Waterless Patient Compliance Dosage Forms. J Drug Deliv Ther., 2019; 9(1): 303-317.
85. Raymond CR, Paul JS, Marian EQ. Handbook of Pharmaceutical Excipients, 6th Edition. Pharmaceutical Press and American Pharmacists Association, 2009; S48-S760.
86. Vishali T, Damodharan N. Orodispersible Tablets: A Review. Res., J Pharm Tech., 2020; 13(5): 2522-2529.
87. Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, Sharma R, Gupta N. Orally

disintegrating Tablets: Formulation, Preparation Techniques and Evaluation. J Appl Pharm Sci., 2011; 35-45.

88. Sivagurunathan D. Formulation and In-Vitro Evaluation of Rivaroxaban Immediate Release Tablets: An Approach to Improving Oral Bioavailability Using Solid Dispersion Technique. The Tamil Nadu Dr. M.G.R. Medical University, 2020; 600032.
89. Sandhyarani G, Sarangapani M. Formulation and Evaluation of Orodispersible Tablets of Domperidone. IOSR J Pharm., 2016; 6(9): 39-47.
90. Upadhyay P, et al. A Review on Formulation and Evaluation Approaches for Fast Release Tablet. Mathews J Pharma Sci., 2023; 7(1): 15.
91. Ramu S, Kumar YA, Rao DS, Ramakrishna G. Formulation and Evaluation of Valsartan Oral Dispersible Tablets by Direct Compression Method. Am J Adv Drug Deliv., 2014; 1: 2321-547X.
92. Pankaj M. A Discriminatory Drug Dissolution Method for Estimation of Rivaroxaban from Rivaroxaban Tablets. Scholars Res Library Der Pharmacia Lett., 2019; 11(2): 97-103.
93. Gupta H, Bhandari D, Sharma A. Recent Trends in Oral Drug Delivery: A Review. Recent Pat Drug Deliv Formul., 2009; 3: 162-173.
94. Kakar S, Singh R, Kumar S. Orodispersible Tablets: an Overview. MOJ Proteomics Bioinform., 2018; 7(3): 180-182.
95. Hirani JJ, Rathod DA, Vadalia KR. Orally Disintegrating Tablets: A Review. Trop J Pharm Res., 2009; 8(2): 161-172.
96. Gupta DK, Maurya A, Varshney MM. Orodispersible Tablet: An Overview of Formulation and Technology. World J Pharm Pharm Sci., 2020; 9(2): 1408.
97. Pandy P, Dahiya M. Oral disintegrating Tablets: A Review. Int J Pharma Res., 2016; 5(1): 51.
98. Bhowmik D, Chiranjib B, Krishnath P, Chaandira RM. Fast Dissolving Tablet: an Overview. J Chem Pharm Res., 2009; 1(1): 165.
99. Arora P, Sethi VA. Orodispersible Tablet: a Comprehensive Review. Int J Res Drug Dev Pharm Life Sci., 2013; 2(2): 271-272.
100. Jassem NA. Orodispersible Tablets: a Review on Recent Trends in Drug Delivery. IJDDT., 2022; 12: 433.
101. Nehal SM, Garima G, Pramod KS. Fast Dissolving Tablets: Preparation, Characterization and Evaluation: an Overview. Int J Pharm Sci Rev Res., 2015; 31(2): 243-250.
102. Deshmukh H, Chandrashekhara S, Nagesh C, Murade A, Usgaunkar S.

Superdisintegrants: a Recent Investigation and Current Approach. Asian J Pharm Tech., 2012; 2: 19-25.

103. Abha, Kaur LP. Superdisintegrations: an Arising Exemplar in Orodispersible Tablets. Int J Drug Res Technol., 2015; 5(1): 1-12.
104. Patil NC, Raja K. Formulation and Evaluation of Orodispersible Tablets of Metoclopramide Hydrochloride. Tamilnadu Dr.M.G.R. Medical University, 2012; 638-652.
105. Drug Information Handbook: a Comprehensive Resource for All Clinicians and Healthcare Professionals. 21st ed. American Pharmacist Association and Lexi-Comp., 2012; S1620.
106. BNF. BMJ Group and Royal Pharmaceutical Society. September 2022-March 2023; S140-S141.
107. Borse LB, Bendale AR, Borse SL, Naphade VD, Jadhav AG. Formulation and Evaluation of Mouth Dissolving Tablet Rivaroxaban and its Validation. Biosci Biotechnol Res Asia., 2022; 19(4): 943-954.
108. Yousif HS et al. Formulation of Tinidazole Rectal Suppositories. Asian Journal of Pharmaceutical Sciences, 2011; 10(2): 69-83.
109. Gowthamarajan K, Venketeshwaran G, Suresh B. et al. Formulation and Evaluation properties of Meloxicam Solid dispersion incorporated Suppositories. Indian Journal of Pharmaceutical Science, 2002; 2(4): 525-528.
110. Pushkar Baviskar P, Jaiswal SK, Sadique S, Landged A. Formulation and Evaluation of Lornoxicam Suppositories., The Pharma Innovation Journal, 2013; 2(7): 20-28.
111. El-majri M, Sharma RK et al. Formulation and Evaluation of Piroxicam Suppository. International Journal of Drug Delivery, 2010; 1(2): 108-112.
112. Marsovna AG, Kedelevna ZS, Petrovna PG. The development technologies of double layer suppositories on the basis of licorice extract and paracetamol. Journal of Pharmacy and Pharmacology, 2015; 3: 531-7.
113. Man Y, Liu C. Development and Application of Suppositories in Modern Pharmaceutics. Academic Journal of Science and Technology, 2022; 26, 1(3): 40-2.
114. Gupta PJ. "Suppositories in anal disorders: a review". European Review for Medical and Pharmacological Sciences, 2007; 11: 165-170.
115. Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using systematic" design of experiments." Part I: fundamental aspects. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2005; 22(1).

116. Purohit TJ, Hanning SM, Wu Z. Advances in rectal drug delivery systems. Pharm. Dev. Technol., 2018; 23 (10): 942–952.
117. Bary AA, El-Gazayerly ON, Alburyhi MM. A Pharmaceutical Study on Lamotrigine. Ph.D. Thesis, Faculty of Pharmacy, Cairo University, 2009.
118. Alburyhi MM, Saif AA, Noman MA, Abudunia A, Yassin SH, Abdullah JH. Formulation, Development and Evaluation of Amoxicillin Fast Dissolving Tablets. World Journal of Pharmaceutical and Life Sciences, 2025; 11(7): 183-197.
119. Raweh SM, Noman MA, Alburyhi MM, Saif AA. Formulation and Evaluation of Anti-acne Gel of Azadirachta Indica Extract Herbal Product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 427-433.
120. Alburyhi MM, Noman MA, Saif AA. Formulation and Evaluation of Natural Herbal Anti-acne as Gel Delivery Systems. World Journal of Pharmaceutical Research, 2024; 13(21): 1447-1467.
121. Alburyhi MM, Yahya TAA, Saif AA, Noman MA. Formulation and Evaluation of Lornoxicam Microsponge-Based Gel as A Transdermal Drug Delivery Systems. World Journal of Pharmaceutical and Life Sciences, 2025; 11(5): 200-217.
122. Alburyhi MM, Hamidaddin MA, Noman MA, Saif AA. Recent Innovations of Novel Drug Delivery Systems for Formulation, Development and Evaluation of Metronidazole Medicated Chewing Gum Tablets. European Journal of Biomedical and Pharmaceutical Sciences, 2025; 12(6): 353-370.
123. Noman MA, Alburyhi MM, Saif AA, Yahya TAA. Formulation and Evaluation of Polyherbal Extract for Skin Hyperpigmentation as Gel Advanced Delivery Systems. World Journal of Pharmaceutical Research, 2024; 13(22): 1260-1280.
124. Alburyhi MM, Noman MA, Saif AA, Al-Ghorafi MA, Al Khawlani MA, Yahya TAA. Formulation and Evaluation of Anti-acne Spironolactone Emulgel Novel Trend in Topical Drug Delivery System. World Journal of Pharmaceutical Research, 2023; 12(22): 96-119.
125. Saif AA, Noman MA, Alburyhi MM. Formulation and Evaluation of Salicylic Acid and Kojic Acid as Gel Novel Drug Delivery Systems for Treatment of Acne and Whitening Skin Effect. World Journal of Pharmaceutical and Medical Research, 2025; 11(9): 538-548.
126. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Aloe Vera Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(4): 1408-1423.

127. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Curcuma Longa Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Cancer. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(6): 37-43.
128. Hamidaddin MA, Alburyhi MM, Noman MA, Saif AA. Formulation and Evaluation of Rosuvastatin Fast Dissolving Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(9): 2293-2303.
129. Bary AA, El-Gazayerly ON, Alburyhi MM. Formulation of Immediate Release Lamotrigine Tablets and Bioequivalence Study. Journal of Chemical Pharm Research, 2013; 5(10): 266–271.
130. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Antitumor Activity of Artemisia Arborescence Extract Capsules as Dietary Supplement Herbal Product Against Breast Cancer. World Journal of Pharmaceutical Research, 2024; 13(3): 95-114.
131. Alburyhi MM, El-Shaibany A. Recent Innovations of Novel Drug Delivery Systems for Formulation, Development and Evaluation of Aloe Rubroviolaceae Extract Capsules as Naturaceutical for Hepatoprotective. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(4): 53-61.
132. Alburyhi MM, Saif AA, Noman MA, Yahya TA. Formulation, Development and Evaluation of Famotidine Orodispersible Tablets. European Journal of Pharmaceutical and Medical Research, 2023; 10(10): 56-62.
133. Alburyhi MM, Saif AA, Noman MA, Salim YA, Hamidaddin MA. Formulation and Evaluation of Lisinopril Orally Disintegrating Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(9): 357-369.
134. Alburyhi MM, Hamidaddin MA, Saif AA, Noman MA. Formulation and Evaluation of Rivaroxaban Orodispersible Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(2): 2066-2092.
135. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Aloe Vera Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Cancer. World Journal of Pharmaceutical Research, 2024; 13(8): 1052-1072.
136. Alburyhi MM, Saif AA, Noman MA, Saif RM. Recent Innovations of Delivery Systems for Antimicrobial Susceptibility Study of Ciprofloxacin Biodegradable Formulations for Post-Operative Infection Prophylaxis. European Journal of Pharmaceutical and Medical Research, 2023; 10(9): 32-36.
137. Alburyhi MM, Noman MA, Aboghanem A. Effect of Different Excipients on

Formulation of Immediate Release Artemether/Lumefantrine Tablets. Journal of Chemical Pharm Research, 2013; 5(11): 617-625.

138. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Dictyota Dichotoma Extract Medicinal Seaweed Capsules Delivery System as an Advanced Phytotherapy Approach for Cancer. European Journal of Biomedical and Pharmaceutical Sciences, 2024; 11(4): 63-70.
139. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Celery Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Gout. World Journal of Pharmaceutical Research, 2024; 13(11): 2383-2404.
140. Othman AM, Alburyhi MM, Al-Hadad GH. Formulation and Evaluation of Captopril Mouth Dissolving Tablets. European Journal of Pharmaceutical and Medical Research, 2024; 11(1): 18-28.
141. Alburyhi MM, Saif AA, Noman MA. Formulation and Evaluation of Ticagrelor Orodispersible Tablets. World Journal of Pharmaceutical Research., 2024; 13(5): 26-55.
142. Alburyhi MM, Saif AA, Noman MA, Yahya TA, Al-Ghorafi MA. Formulation and Evaluation of Drotaverine Orally Disintegrating Tablets. World Journal of Pharmaceutical Research, 2023; 12(18): 66-79.
143. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Effervescent Granules of Artemisia Arborescence Herbal Product for Foodborne Illness. World Journal of Pharmacy and Pharmaceutical Sciences, 2023; 12(12): 1429-1444.
144. Alburyhi MM, Noman MA, AA Saif. Formulation and Evaluation of Meloxicam Emulgel Delivery System for Topical Applications. World Journal of Pharmaceutical Research, 2025; 14(4): 1324-1337.
145. Bary AA, El-Gazayerly ON, Alburyhi MM. A Pharmaceutical Study on Methocarbamol. MSc Thesis, Faculty of Pharmacy, Cairo University, 2006.
146. Alburyhi MM, Noman MA, Saif AA, Alemad AF. Dispersible and Orodispersible Tablets Delivery Systems for Antibacterials Development. World Journal of Pharmaceutical Research, 2025; 14(1): 1229-1257.
147. Alburyhi MM, Saif AA, Noman MA, Saif RM. Recent Innovations of Delivery Systems for Antimicrobial Susceptibility Study of Ceftriaxone Biodegradable Formulations for Post-Operative Infection Prophylaxis. European Journal of Pharmaceutical and Medical Research, 2023; 10(8): 95-99.
148. Alburyhi MM, Saif AA, Noman MA, Yassin SH. Formulation and Evaluation of Simvastatin Orodispersible Tablets. World Journal of Pharmaceutical Research, 2023;

12(16): 1033-1047.

149. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Anti-peptic Ulcer Capsules of Curcuma Longa Herbal Product. World Journal of Pharmaceutical Research, 2023; 12(22): 76-96.
150. Alburyhi MM, Saif AA, Noman MA, Al Ghoury AA. Formulation and Evaluation of Antimalarial Drugs Suppositories. World Journal of Pharmaceutical Research, 2023; 12(20): 89-108.
151. Alburyhi MM, Saif AA, Noman MA, Saeed SA, Al-Ghorafi MA. Formulation and Evaluation of Diclofenac Orodispersible Tablets. European Journal of Pharmaceutical and Medical Research, 2023; 10(9): 01-06.
152. Saif AA, Alburyhi MM, Noman MA. Formulation and Evaluation of Ketoprofen Fast Dissolving Tablets. International Journal of Sciences, 2018; 7(09): 27- 39.
153. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Chamomile Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Gout. World Journal of Pharmaceutical and Life Sciences, 2025; 11(04): 215-228.
154. Alburyhi MM, Saif AA, Noman MA, Alkhawlani MA. Formulation and Evaluation of Bisoprolol Fast Dissolving Tablets. World Journal of Pharmaceutical Research, 2023; 12(16): 01-10.
155. Noman MA, Alburyhi MM, El-Shaibany A, Alwesabi NA. Formulation and Evaluation of Pandanus Odoratissimus L Extract for Treatment of Nocturnal Enuresis as Orodispersible Tablets Delivery System. World Journal of Pharmaceutical Research, 2024; 13(5): 56 -71.
156. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Tribulus Terrestris Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmaceutical Research, 2024; 13(7): 1264-1282.
157. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Pandanus Odoratissimus Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Hepatoprotective. European Journal of Pharmaceutical and Medical Research, 2024; 11(4): 06-13.
158. Alburyhi MM, Noman MA, Saif AA, Salim YA, Abdullah JH. Formulation and Evaluation of Domperidone Orodispersible Tablets. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(3): 49-68.
159. Alburyhi MM, Saif AA, Noman MA, Hamidaddin MA. Formulation and Evaluation of

Clopidogrel Orodispersible Tablets. World Journal of Pharmaceutical Research, 2024; 13(6): 42-64.

160. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Plicosepalus Acacia Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Hepatoprotective. World Journal of Pharmaceutical Research, 2025; 14(8): 1309-1334.
161. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Oral Pharmaceutical Solution of Pandanus Odoratissimus L Extract Herbal Product in Treatment of Nocturnal Enuresis. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(1): 1840-1851.
162. Alburyhi MM, El-Shaibany A. Formulation and Evaluation of Antibacterial Orodispersible Tablets of Artemisia Arborescence Extract Herbal Product. European Journal of Pharmaceutical and Medical Research, 2024; 11(2): 409-417.
163. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Acalypha Fruticosa Extract Tablets Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmaceutical Research, 2024; 13(8): 1073-1091.
164. Alburyhi MM, Mohamed YAS, Saif AA, Noman MA, Abdullah JH, Yahya TAA. Recent Innovations of Novel Drug Delivery Systems for Formulation, Development and Evaluation of Amlodipine and Furosemide Orodispersible Tablets. World Journal of Pharmaceutical and Medical Research, 2025; 11(5): 358-378.
165. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Ginger Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Controlling Diabetes. World Journal of Pharmaceutical and Medical Research, 2025; 11(6): 400-415.
166. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Plicosepalus Acacia Extract Capsules as Naturaceutical Novel Drug Delivery Systems for Controlling Diabetes. World Journal of Pharmaceutical and Life Sciences, 2025; 11(6): 323-337.
167. Alburyhi MM, El-Shaibany A. Recent Innovations of Novel Drug Delivery Systems for Formulation, Development and Evaluation of Pandanus Odoratissimus Extract Capsules as Naturaceutical for Breast Cancer. World Journal of Pharmaceutical Research, 2024; 13(8): 1092-1112.
168. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Tribulus Terrestris Extract Capsules as Naturaceutical Novel Drug Delivery Systems for Kidney Stones. World Journal of Pharmacy and Pharmaceutical Sciences, 2024; 13(5): 1425-

1443.

169. Alburyhi MM, El-Shaibany A. Formulation, Development and Evaluation of Capsicum Extract Capsules Delivery System as an Advanced Phytotherapy Approach for Tonic and Natural Stimulant. European Journal of Pharmaceutical and Medical Research, 2025; 11(6): 323-337.
170. Alburyhi MM, Raweh SM, AlGhoury ABA, Alkhawlani MA, Noman MA, Saif AA. Recent Innovations of Novel Drug Delivery Systems for Formulation, Development and Evaluation of Grewia Tenax Extract Naturaceutical Ointment for Antimicrobial Activity. World Journal of Pharmaceutical and Medical Research, 2025; 11(7): 413-426.
171. Alburyhi MM, Raweh SM, Al-Ghorafi MA, Saif AA, Noman MA. Formulation and Evaluation of Argemone Ochroleuca Extract Cream Naturaceutical Delivery Systems as Antimicrobial and Wound Healing Activity. European Journal of Pharmaceutical and Medical Research, 2025; 12(7): 445-459.
172. Alburyhi MM, Mohamed YAS. Formulation, Development and Evaluation of Cosmeceutical Natural Pigmented Lipstick from Opuntia Dillenii Fruit Extract. European Journal of Biomedical Pharmaceutical and Medical Sciences, 2025; 12(9): 466-479.
173. Alburyhi MM, Moharram BA. Formulation and Evaluation of Aloe Niebuhriana Extract as Naturaceutical Effervescent Granules Novel Drug Delivery Systems for Antidiabetic Activity. World Journal of Pharmaceutical Research, 2025; 14(18): 1147-1175.
174. Alburyhi MM, Moharram BA. Formulation and Evaluation of Jatropha Variegata Extract as Antibacterial Naturaceutical Cream Novel Drug Delivery Systems for Wound Healing Activity. World Journal of Pharmaceutical and Life Sciences, 2025; 11(10): 177-190.
175. Noman MA, Alburyhi MM, Saif AA. Formulation and Evaluation of Skin Whitening Naturaceutical Composition Gel as Advanced Drug Delivery Systems. World Journal of Pharmaceutical and Medical Research, 2025; 11(10): 400-414.
176. Saif AA, Alburyhi MM, Noman MA. Formulation and Evaluation of Sildenafil Citrate as Pharmaceutical Reconstitutable Oral Suspensions Advanced Drug Delivery Systems for Management of Pediatric Pulmonary Arterial Hypertension. World Journal of Pharmacy and Pharmaceutical Sciences, 2026; 15(5): 965-992.
177. Alburyhi MM, Moharram BA. Formulation and Evaluation of Aloe Inermis Extract for Wound Healing Activity as Antibacterial Naturaceutical Cream Novel Drug Delivery Systems. European Journal of Pharmaceutical and Medical Research, 2025; 12(10): 297-308.

178. Raymond C. R, Sheskey PJ, Owen CS. Handbook of Pharmaceutical Excipients Fifth Edition Edited.
179. Shivangi S, Navneet V. Taste Masked Orodispersible Tablets. A highly patient Compliant Dosage Form. Asian J Pharm Clin Res., 2016; 9: 385-91.
180. Anupam R. Orodispersible Tablets: A Review. Asian J Pharm Clin Res., 2016; 9: 19-26.
181. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier J, Piccerelle P. Determination of The Invitro Disintegration Profile of Rapidly Disintegrating Tablets and Correlation with Oral Disintegration. Int J Pharm., 2005; 292: 29–41.
182. Anusha P, Nirajana A, Mohammed S, Jilani S, Murali C, Harish G. Development and Evaluation of Drotaverine Taste Masked Tablets with Improved Dissolution Efficiency Using Solid Dispersion Technique. IJRPB., 2013; 1: 275–80.
183. Srikanth M, Uhumwangho M, Sunil S, Sreenivasa N, Ravi C, Ramana Murthy K. Design and Revaluation of Taste Masked Drotaverine HCl Orodispersible Tablets Using Polymethacrylate Polymers. Der Pharmacia Lett., 2010; 2: 223–31.
184. Shirwaikar AC. Galan Fast Disintegrating Tablets of Famotidine by Dry Granulation Method. Ind J Pharm Sci., 2004; 66: 422-426.
185. Venkateswarlu B, et al. Formulation and Evaluation of Famotidine Fast Dissolving Tablets by Direct Compression Method. Indian Journal of Research in Pharmacy and Biotechnology, 2013; 9-10(609): 609-613.
186. Shirwaikar AC. Galan Fast Disintegrating Tablets of Famotidine by Dry Granulation Method. Ind J Pharm Sci., 2004; 66: 422-426.
187. Chauhan I, Yasir M, Verma M, Singh AP. Nanostructured Lipid Carriers: A Groundbreaking Approach for Transdermal Drug Delivery. Advanced Pharmaceutical Bulletin, 2020; 10(2): 150.