



RECENT INNOVATIONS OF FORMULATION AND EVALUATION FOR CHLORHEXIDINE AS EMULGEL NOVEL DRUG DELIVERY SYSTEMS

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DOI: <https://doi.org/10.5281/zenodo.20557067>



How to cite this Article: Mahmoud Mahyoob Alburyhi^{1*}, Tawfeek A. A. Yahya², Maged Alwan Noman¹, Abdalwali Ahmed Saif¹ (2026). Recent Innovations Of Formulation And Evaluation For Chlorhexidine As Emulgel Novel Drug Delivery Systems. World Journal of Pharmaceutical and Life Sciences, 12(6), 293–313.

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Article Received on 03/05/2026

Article Revised on 23/05/2026

Article Published on 01/06/2026

ABSTRACT

Background: Chlorhexidine is a synthetic cationic bis-biguanide compound used as a topical antiseptic. It is classified as a broad-spectrum antimicrobial agent with potent bactericidal and bacteriostatic activity against Gram-positive and Gram-negative bacteria. Emulgel, combining the hydrophilic properties of gels with the biphasic structure of emulsions, offer enhanced solubility, stability, controlled release, and mucosal penetration. Additionally, Gels further offer ease of application, high spreadability, and good patient acceptability. Additionally, Emulgels further offer ease of application, high spreadability, and good patient acceptability. Clove oil, a natural analgesic, anti-inflammatory, and antimicrobial agent, also improves taste, promoting better compliance. **Methods:** Three formulations of Emulgel were developed using Carbopol 974, Xanthan Gum, and HPMC as gelling agents. Methylparaben and propylparaben served as preservatives, while propylene glycol, glycerin, sucralose, triethanolamine, tween was included as excipients for stability and patient-friendly characteristics and clove oil as a multifunctional additive. Formulations were evaluated for physicochemical properties, viscosity, spreadability, mucoadhesive strength, drug content, swelling index, microbial contamination, and storage stability. A mucosal irritation test was also performed to assess safety and tolerability of the formulations upon application. **Results:** Emulgel formulation F3 exhibited optimal viscosity, spreadability, and mucoadhesive strength among the Emulgel group and was flavored with strawberry for enhanced acceptability. Drug content was found to be 99.05%. Microbial testing confirmed the sterility of key formulations (F1, F2, and F3), and all maintained physical and chemical stability over time. Sensory evaluation revealed improved taste and patient acceptability in clove oil and flavored formulations. **Conclusion:** The optimized Emulgels formulation, containing Chlorhexidine, and clove oil, represents a promising and effective approach for managing oral bacterial infections. It offers antimicrobial activity, enhanced muco-adhesion, and improved sensory qualities, including taste and texture. The inclusion of a tri-polymer base significantly contributes to the rheological performance and stability of the formulation. These attributes support better patient comfort, compliance, and therapeutic outcomes while minimizing systemic side effects and irritation common in oral drug delivery. It was concluded that the best Emulgel Formulation F3 was found to be optimal viscosity, spreadability, percent of drug content 99.05%, and mucoadhesive strength among the Chlorhexidine Emulgels formulations NDDS. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the NDDS (Novel Drug Delivery Systems) product development process.

KEYWORDS: Chlorhexidine, Antimicrobial, NDDS, Formulation, Excipients, Development, Emulgels.

INTRODUCTION

Bacterial Infections^[1-13]

Bacterial infections often result from the accumulation of bacteria due to poor oral hygiene, leading to gum inflammation, plaque formation, and exacerbation of decay issues. For this reason, Chlorhexidine is considered a disinfectant that helps reduce the number of bacteria and cleanse the oral cavities and it's a broad-spectrum biocide. It is effective against Gram-positive bacteria, Gram-negative bacteria and fungi. The bactericidal effect is a result of the binding of this cationic molecule to negatively charged bacterial cell walls. At low concentrations of chlorhexidine, this results in a bacteriostatic effect; at high concentrations, membrane disruption results in cell death.

Chlorhexidine has a broader spectrum of activity and a faster kill rate than other antimicrobials. Chlorhexidine kills by disrupting the cell membrane and the antifungal activity in the Chlorhexidine. The mechanism of action for fungi is very similar to that of bacteria. *Candida* species is the most common of the fungi present in both healthy and affected individuals. Fungi have been found in the infected root canals that have not had any previous endodontic treatment. The fungus uptakes Chlorhexidine in a short amount of time and impairs the integrity of the cell wall and the plasma membrane entering the cytoplasm resulting in leakage of cell contents and cell death. Oral herpes is a common, recurrent condition marked by painful mucosal lesions and risk of secondary bacterial infections. The treatment combines Acyclovir to combat viral infections and Chlorhexidine to manage bacterial infections, comprehensively targeting both causes while maintaining oral health and minimizing complications.

Pharmaceutical Research Paths^[14-77]

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 needed to prolong the effect, so they operate with controlled delay system.

All of this development through the various methods of administering 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 continuous 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^[78-120]

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.

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

GELS

Gels are defined as semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase.

The word “gel” is derived from “gelatin,” and both “gel” and “jelly” can be drawn back to the Latin gelu for “frost” and gel are, meaning freeze or ‘congeal.’ This origin indicates the essential idea of a liquid setting to a solid-like material that does not flow, but is elastic and retains some liquid characteristics.

Physicochemical Properties of Drug as Gel Dosage Form

The drug should have a molecular weight of less than 400 Daltons, highly acidic or alkaline drugs are not suitable for topical drug delivery, the drug should possess adequate lipophilicity, and ideal pH for drug candidates should range between 5 and 9.

Route of Drug Gel Penetration

Drug molecules come into touch with cellular waste, bacteria, and other substances on the skin's surface, which has an impact on penetration. Three routes connect the administered medication to the living tissue:

Through the hair follicles, sweat ducts, and continuous stratum corneum between the appendages, in that order (hair follicles, sebaceous glands, eccrine, apocrine glands and nails).

Advantages of Gel Formulations

The gel formulation has several key benefits over conventional semisolid dose formulations: Compared to other formulations, gels are simple to manufacture, gel is a sophisticated, non-greasy composition, gels offer fantastic adhesion to the application region, gels are eco-friendly and biocompatible, and be incredibly resilient to stressful situations.

Disadvantages of Gel Formulations

Despite having a number of benefits. Gel formulations can come with certain drawbacks: Gels have a more gradual and persistent effect, the additives or gelators could irritate people, the risk of microbial or fungal assault on gel is increased by the presence of water, the formulation's solvent loss dries to gel, and in some gels, flocculation results in an unstable gel.

Ideal Properties of Topical Gel

The gel ought to be uniform and transparent, when shear or force is applied during the container's shaking, the gel

should break easily, the gel should have an inert composition, the gel must not be sticky, the gel shouldn't ever contact with another component in the formulation,

the gel must be reliable, and the skin or any area where the gel is placed shouldn't be irritated. Types of gels and related data as shown in Tables (6-10).

Table 6: Types of Gels.

Based on Colloidal Phases	a) Inorganic (two-phase system)	b) Organic (single-phase system)
Based on Nature of the Solvent	a) Hydrogels (water- based)	b) Organogels (With a non-aqueous solvent) c) Xerogels
Based on Physical Nature	a) Elastic Gels	b) Rigid Gels
Based on their Rheological Properties	a) Plastic Gel	b) Pseudo-Plastic Gel c) Thixotropic Gel

Table 7: Classification of Gels.

Nature			Cross-linking\Bond		Phase\ Physical Structure		Origin of Materials		Electrical Charge	
Hydrogels	Organogels	Xerogels	Physical Gels\ Reversible	Chemical Gels Irreversible	Single Phase Monophasic	Two Phase Biphasic\ Magma	Natural Origin	Synthetic\ Semi-synthetic	Neutral	Ionic Anionic\ Cationic
Water liquid Phase	An organic or Oil Phase	Solid gel	Elasticity	Viscoelastic	Macromolecules	Mass Thick	Biopolymers	Polymers	Polymer	Network
E.g. Carbopol Gelatin Agar	E.g. Petroleum, Pluronic Lecithin	E.g. Gelatin Acacia dry	E.g. Gelatin Starch	E.g. Carbopol Crosslink PEG hydrogels	E.g. Carbopol gels, Cellulose ethers	E.g. Aluminum Hydroxide gel	E.g. Ager, Alginate, Pectin, Chitosan	E.g. Carbomer Poloxamers Pluronic's	E.g. PEG	E.g. Carbopol, Chitosan

Table 8: Natural Gelling Agent Polymer for Pharmaceutical Formulations.

Polymer Name	Chemical Nature	Pharmaceutical Application
Alginic acid	A naturally occurring, edible polysaccharide found in brown algae is alginic acid, often known as algin.	Stabilize oil-in-water emulsions as well as thicken and suspend a variety of pastes, creams, and gels.
Arginine	an amino acid that aids in the body's protein synthesis.	Immune system function, hormone production, wound healing, ammonia removal from the body, and cell division.
Chitosan	One of the most prevalent natural polysaccharides is chitin.	Antibacterial activity, non-toxicity, simplicity of modification, and biodegradability, chitosan is a bioactive polymer with a wide range of uses.
Carrageenan	Repeating galactose units, 3,6 anhydrogalactose (3,6-AG), and alternating (1-) and (1-4) glycosidic linkages joined by sulfated and non-sulfated sugars	Soft and Hard Gel Hand lotions, shampoos, emulsions, dressings, antacid gels, topical bases, suppository bases, contraceptive gels, and controlled-release tablets
Dextran	α -D-1,6-glucose-linked Glucan	Spheres or implants made of hydrogel
Guar gum	Guar gum can be a cost-effective alternative because of its good viscosity and spreadability.	Gelling and emulsifying agent
Gelatin	Combination of Polypeptide Chains of Glycine, Proline, and Hydroxyproline from Purified Protein Fractions	Gelling agents is gelatin. Film Formation/Rapid Dissolution
Hemicellulose	(Mannans/Xyloglucans/Xylans)/ 1,4-Linked Dglycans/Xyloglucans	Agent for Forming Film
Hyaluronic acid	N-Acetyl glucosamine, Glucuronic Acid, and Polyanionic Polysaccharide	Eye gel, prolonged drug release, intra articular injections, and artificial insemination
Hydroxyethyl Cellulose	Closure Ethers	Tablet Film Forming, Binders, Coating Agents, Emulsifying Agents, and Stabilizing Agents
Inulin	Glucofructan oligomer mixture, polysaccharide, and polymers that have been derivatized using succinic and methacrylic anhydrides	Methylated inulin hydrogels and film formers
Pectin	Anionic Polysaccharide -1, 4 Linked D-galacturonic Acid	Tablets (Directly Compressed, Sustained-Release, Gel Bead, Injection, Oral Film, Colon-Drug

		Delivery System, Transdermal Patch)
Sodium Alginate	D-Mannuronic acid and L guluronic acid in homopolymers, as well as D-Mannuronic acid and L-guluronic acid connected by - or -1,4 glycosidic linkages	Tablet binders, Tablet Disintegrants, Colloidal Preparation, Thickening, Stabilizing, Suspending, Gel Producing, Emulsion Stabilizing, and Biopolymer Film
Agar	Agarobiose (D galactose/Agarpectin) is also known as agarose and agarpectin.	Gelling suppositories, suspending agents, emulsifying agents, laxatives, bacterial cultures.
Albumin	Plasma protein is made up of three homologous domains and has 585 amino acids in human serum albumin (I,II,III))	Gene delivery, injection, creation of nanoparticles, and medication administration (based on peptide or protein).

Table 9: Semi-synthetic Polymers.

Polymer Name	Properties
Hydroxypropyl methylcellulose	Film development and prolonged product wear
Hydroxyethyl cellulose	Rheological control and simplicity of use
Polyacrylic-acid	Prolonged shelf life of the product
Polyamides	Extended product wear, improved product shelf life, rheological control, and simplicity of application
Cellulose – Derivatives	Solution viscosity and surface performance
Cellulose acetates	Topologies of thermoplastic films and heat resistance
Cellulose nitrates	Biodegradation, hydrolysis, and oxidation
Chitosan	Anti-inflammatory antioxidant, antifungal, and antimicrobial
Collagen	Serve as a fibroblast's compass.
Gelatin	Uses water to create thermally reversible gels
Pectin	Used as a gelling ingredient in food, especially in jams and jellies.
Liven	Animal-free components for proteins
Silk	Wholesome protein fibre
Nitrocellulose	Film development and prolonged product wear
Acrylate-copolymers	Upgraded product design

Table 10: Synthetic Polymers and Biomedical Applications

Polymer Name	Biomedical Application
Poly(ether urethanes)	Heart valves, blood contacting equipment, coatings, and vascular grafts.
Carbopol 934	Suitable for usage in lotions and creams as a rheology modifier
Polyphosphazenes	Controlled medication distribution through implants and in tumor-bearing animals
Carbopol 940	In gel preparations, carbopol 940 is frequently employed as a gelling agent.
Carbopol 941	It is possible to create low-viscosity lotions and gels with high clarity using the carbopol 941 NF polymer.
Carbomer	Used to increase the biological availability of medicines and regulate their release.
Poly (vinyl)alcohol (PVA)	Suitable for vascular cell culture, tissue mimicry, and vascular implanting
Poly(ethylene glycol) (PEG)	Hydrogel, or as an antifouling coating on catheters
Polyurethane	Materials that are frequently utilized to make blood contacting devices like heart valves or synthetic veins and arteries
Poloxamers	Poloxamers are an advantageous option in pharmaceutical technology and the biomedical field.
Poly(caprolactone diol) (PCL)	Diol for making polyurethane
Polyvinylchloride (PVC)	Blood bags and blood tubes
Poly(carbonate) (PC)	Biodegradable polyester for containers and dialysis membranes

Emulgels

Emulgel drugs in brief, Emulgel is a combination of emulsion and gel. Despite the numerous advantages of gels, one significant disadvantage is the delivery of hydrophobic medications. As a result, an emulsion-based solution is being used to overcome this limitation, allowing even hydrophobic therapeutic moieties to benefit from the unique properties of the gel.

Emulgel can deliver both hydrophilic and lipophilic drugs due to the presence of both aqueous and non-aqueous phases. In recent years, they have been used as a control release formulation. These are biphasic systems that have better drug loading capacity and better stability. Emulgel has several good properties, such as good spreadability, greaseless, thixotropic, good shelf life, odorless, and a pleasant appearance over the conventional topical formulation. Emulgel has both gel and emulsion properties and functions as a dual control release system.

Advantage of Emulgels

Using water/oil/water emulsions, hydrophobic drugs can be quickly implemented into the gel base. Improved stability and load capacity. Easy for production and a low-cost mechanism. Avoid sonication. The first metabolism is avoided. Avoid gastrointestinal incompatibility. Target drug delivery on the body. Improved patient compliance. Improved patient acceptability and suitability for self-medication. Ability to easily terminate medication.

Disadvantage of Emulgels

The drug and/or excipients can lead to skin irritation in people with contact dermatitis. Some medications have low permeability through the skin. Possibility of allergenic reactions. Larger-particle-size drugs are not easily incorporated into the skin.

Rationale of Emulgel as a Topical Drug Delivery System

Topical preparations like cream, ointment have many limitations like less spreading coefficient, less penetration through stratum corneum, less patient compliance due to stickiness or need to apply with rubbing etc. Similarly, gels have the limitation of delivering hydrophobic drugs. Here

Emulgel could be prepared from selected oil on the term of solubility study of antimicrobial agent in them and emulsifier, so problem of solubility of drug can be almost overcome hence drug can be made available in solubilized form in Emulgel, which can penetrate stratum corneum for drug action at viable soft tissue of skin. Emulgel could provide benefits of both emulsion and gel. Emulgel increases drug deposition over to the skin. However, emulsion has more bioavailability than Emulgel but there is problem of stability and it has less patient compliance, as well. Topically used Emulgel has various advantages over to ointment and gels.

In the present study, it was proposed to formulated Chlorhexidine Emulgels of the safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the formulation with commonly different excipients using for development formulations of Chlorhexidine Emulgels NDDS for topical application.

MATERIALS AND METHODS

Chlorhexidine and all raw materials used in the formulation including active pharmaceutical ingredients (APIs), excipients, and analytical reagents were obtained as a gift sample from (Global Pharma Pharmaceutical Industry Company - Yemen). As shown in Table 11.

Table 11: List of Materials Used.

No.	Name of Materials
1	Chlorhexidine
2	Clove Oil
3	Carbopol
4	Xanthan Gum
5	Methylparaben
6	Propylparaben
7	Glycerin
8	Propylene Glycol
9	Tween 80
10	HPMC
11	Sucralose
12	Triethanolamine

Equipment

All equipment used are listed in
Table Error! No text of specified style in document.

Table Error! No text of specified style in document.: List of Instruments.

NO.	Instruments
1	Chamber 40 °C
2	UV-VIS Spectrophotometer
3	Sc Chemtech Ultrasonic Bath
4	pH Meter
5	Brookfield Viscometer
6	Magnetic Stirrer
7	Electronic Balance
8	Digital Thermostatic Water Bath

Formulation and Evaluation of Chlorhexidine Emulgels^[78-173]

Optimization and Development of Chlorhexidine Emulgels

The Emulgels was developed by integrating an oil-in-water emulsion into a Carbopol-based hydrogel matrix, creating a stable, mucoadhesive system for topical drug delivery. The comprehensive formulation process progressed through four critical stages: Emulgels base formation, active ingredient incorporation, and final

system optimization, with specific variations implemented across different formulations (F1-F3), detailed composition of each formula as shown in Table 13.

Emulsion Formulation

This step was only included in formulations F1-F3. The foundation of the Emulgel system began with the preparation of an oil-in-water (O/W) emulsion using a hot emulsification method with magnetic stirring. The oil phase containing clove oil and Polysorbate 80 (tween 80) and the aqueous phase (purified water) were each heated to 65 °C. to ensure optimal mixing conditions. The aqueous phase was then carefully introduced dropwise into the oil phase under continuous magnetic stirring for 5 minutes, with mixing extended for an additional 10 minutes to produce a physically stable emulsion characterized by uniform droplet distribution and excellent stability properties.

Formulation of Chlorhexidine Emulgels

The hydrogel base formulation followed a meticulous polymer hydration protocol with formulation-specific variations. The standard preparation involved initially dispersing xanthan gum in glycerin to create a homogeneous, lump-free mixture, though this step was omitted in formulations F1, F2 and F3. Concurrently, Carbopol 974 was hydrated in purified water maintained at 70°C in a water bath. In formulation F3, hydroxypropyl methylcellulose (HPMC) was prepared using a hot hydration method to ensure complete dispersion and eliminate entrapped air bubbles. Specifically, approximately one-third of the purified water was heated to around 70 - 75°C, and HPMC powder was gradually added under continuous stirring to this hot purified water. This process allowed the polymer to disperse fully without forming lumps or foam, as HPMC does not dissolve at this temperature but forms a uniform suspension. After complete dispersion, the remaining water at room temperature (20-25°C) was added, and the mixture was stirred for about 30 minutes until a clear, bubble-free gel was obtained. The cooled HPMC solution was then incorporated into the hydrated Carbopol dispersion. These prepared components were then systematically integrated, with both the xanthan-

glycerin mixture (where applicable) and HPMC dispersion (F3) being incorporated into the hydrated Carbopol solution. The complete polymer system underwent thorough mixing for 10 minutes to ensure complete hydration and bubble elimination.

Final Emulgel Formation and Drug Incorporation

In formulations F1 to F3, the preformed oil-in-water (O/W) emulsion was incorporated into the prepared gel base to form the Emulgel system. The emulsion was added gradually to the gel base under continuous magnetic stirring at approximately 500 rpm. After complete addition, stirring was continued for an additional 5 minutes to ensure uniform distribution of oil droplets within the polymeric matrix. Subsequently, the system was allowed to cool to ambient temperature (25 °C).

The active pharmaceutical components were introduced through a carefully orchestrated addition process. Chlorhexidine was first dissolved in purified water, while methylparaben and propylparaben were dissolved in propylene glycol and subsequently combined with the Chlorhexidine solution along with sucralose for taste modification. This comprehensive mixture of active ingredient, preservatives, and sweetener was then simultaneously introduced into the gel-emulsion matrix under moderate stirring over a precisely controlled 5-minute period. To guarantee complete and uniform distribution of all components throughout the polymer network, mixing continued for an additional 10 minutes, ensuring homogeneous drug dispersion in the final preparation.

Final System Optimization

The completed Emulgel formulation underwent critical final adjustments to achieve optimal performance characteristics. The pH was carefully titrated using triethanolamine (TEA) to reach the target range of 6.8-7.0, a crucial step that simultaneously optimized formulation stability and skin compatibility. This pH adjustment, combined with the carefully engineered polymer-emulsion matrix, resulted in a robust topical delivery system exhibiting excellent mucoadhesive properties for effective therapeutic application.

Table 13: Composition (% w/w) of Chlorhexidine Emulgel Formulations.

Ingredients	Formulation Code		
	F1	F2	F3
Chlorhexidine	1	1	1
Clove Oil	0.76	0.76	0.76
Carbopol 974	1	1	1
Xanthan Gum	0.5	0.5	0.5
Methylparaben	0.2	0.2	0.2
Propyl paraben	0.02	0.02	0.02
HPMC	-	-	0.2
Glycerin	6	6	6
Propylene Glycol	10	10	10
Tween 80	1	1	1
Sucralose	-	0.04	0.075

Triethanolamine	1.5	1.5	1.5
Purified Water	Q.s	Q.s	Q.s

Evaluation of Chlorhexidine Emulgels

Characterization of Chlorhexidine Emulgels

Macroscopic Evaluation of Formulations

The physical appearance of the Chlorhexidine Emulgels was thoroughly evaluated using various organoleptic properties, including visual observation and sensory perception. The general appearance plays a significant role in consumer acceptance, as it reflects the overall elegance, quality, and uniformity of the formulation.

Physical Appearance

The Assessment Focused on the Following Aspects

Evaluate color, homogeneity, and odor.

Color

The formulation was visually inspected to ensure it exhibited a consistent and uniform color throughout the formulation. Any discoloration or uneven shading could indicate instability or improper mixing of components.

Odor

The formulation was checked for any undesirable or strong odor. A pleasant or neutral scent is important to enhance patient compliance, especially for topical applications. The absence of any foul or medicinal odor was confirmed.

Homogeneity

The formulation was examined for uniformity in texture and composition. A homogeneous formulation should not contain any lumps, grittiness, or particulate matter, and should have a smooth, consistent feel when applied to the skin.

Phase Separation

The formulation was checked for any signs of phase separation, such as the separation of oil and aqueous layers. A stable gel should appear as a single, well-blended phase with no visible separation over time.

pH Determination Test

The pH of the oral Emulgel formulations was measured to verify compliance with the physiological pH range of the oral cavity (typically 5.5-7.6), thus reducing potential irritancy. For each formulation, a 0.5 g sample was homogenized in 50 mL of purified water. The mixture was first vortexed for 2 minutes followed by 2 minutes of sonication to achieve complete dispersion of gel components in the aqueous medium. The pH of the resulting homogeneous mixture was then measured in triplicate using a calibrated pH meter, and the mean values were recorded.

Viscosity Test

Measure viscosity using a viscometer to ensure it meets product requirements for topical application.

Stability Studies

A stability study was conducted to evaluate the physical and chemical stability of the optimized formulations under accelerated conditions. The formulations were stored for 3 months in an accelerated stability chamber at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity. This study aimed to ensure that the formulations maintained their intended physical and chemical characteristics throughout the testing period without undergoing undesirable changes. The evaluation focused on monitoring key physical parameters such as changes in color, odor, clarity, phase separation, and overall appearance of the formulation.

Mucoadhesive Evaluation

Mucoadhesive strength of formulations was evaluated using two simple methods. In the first, a simulated mucosal membrane was placed between two glass slides. Equal amounts of each formulation were applied, and the upper slide was pressed gently for one minute. Adhesion was assessed by the resistance felt during vertical separation.

In the second method, a fixed amount of each formulation was placed on membrane-covered glass slides. The slides were then inclined at a 45° angle, and distilled water was gradually dropped onto the samples to simulate saliva. The distance each formulation slid from its original position was measured to estimate mucoadhesive retention.

Spreadability Test

A fixed quantity of each test formulation was uniformly placed on a clean glass slide; a second glass slide was carefully placed on top to sandwich the formulation between the two slides. A standardized weight (50 g) was placed on the upper slide for a fixed duration (1 minute) to ensure even distribution and adhesion of the formulation. The weight was removed, and the time taken for the upper slide to detach completely from the lower slide due to the formulation's viscous flow was recorded in seconds (s).

Good spreadability ensures uniform application over the skin and oral mucosa enhances patient compliance, and supports effective drug penetration.

Rheological Study

The viscosity of the developed formulations was determined using a viscometer apparatus. Measurements were performed using spindle sizes 93 and at 120 rotational speeds (rpm). A sample of the formulation was placed into a beaker, and the spindle was immersed in the sample. Viscosity readings were then recorded to assess the rheological behavior of the Formulations.

Microbiological Contamination Testing

To ensure the microbiological safety of the prepared Emulgels formulations, samples with optimal physical and sensory properties were submitted to a certified local laboratory for evaluation. The testing focused on detecting any microbial contamination that could affect product stability or safety. The presence or absence of viable microorganisms was assessed, and the formulations were classified accordingly as either passing or failing based on standard microbiological criteria.

Drug Content Determination Test

The drug content is determined by UV spectroscopic analysis. The equation used is.

Drug content = (Concentration × Dilution factor × Volume taken) × Conversion factor.

The concentration of Chlorhexidine in the formulation was quantified using UV-Visible Chlorhexidine, adhering to the USP acceptance range for topical formulations. A stock solution was prepared by accurately weighing 10 mg of Chlorhexidine (0.5 mL), was pipetted out in Purified Water solution and the absorbance of this mixture was measured at 254.5 nm. The drug content was calculated against the absorbance of control ACV solution of the same concentration at 254.5 nm.

Swelling Index Test

To determine the swelling index of prepared topical Emulgels, 1gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml purified water. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows

Swelling Index (SW) % = $(W_t - W_0) / W_0 \times 100$

Where, (SW) % = Equilibrium percent swelling, W_t = Weight of swollen gel after time t , W_0 = Original weight of Emulgels at zero time.

Skin and Oral Mucosa Irritant Test

To assess the local tolerance and safety of the formulated Chlorhexidine Emulgels (containing clove oil), standardized irritation testing was performed on healthy adult volunteers. Specific quantity of each formulation was topically administered to three distinct anatomical sites: (1) perioral skin, (2) labial mucosa (inner lip surface), and (3) buccal mucosa (cheek lining). All application sites were subsequently evaluated at predetermined intervals for potential irritant reactions, including erythema, edema, pruritus, burning sensation, or any other adverse local effects.

RESULTS AND DISCUSSION

Evaluation of Chlorhexidine Emulgels Formulations

Macroscopic Evaluation of Formulations

All gel formulations (F1-F3) exhibited uniform white coloration and when evaluated 24 hours post-preparation. In contrast, Emulgels formulations displayed uniform off-white coloration with a distinct clove odor at the same evaluation time point. All formulations showed homogeneous distribution without visible aggregates or phase separation, formulations F1, F2, and F3 demonstrated optimal physicochemical characteristics, including: Ideal equilibrium between gel cohesion and bio-adhesion, with smooth, glossy texture free from particulate matter.

pH Determination Test

All formulations demonstrated physiologically acceptable pH values ranging from 6.5 to 6.8 (Table).

Table 14: Mean pH Values of the Gel Formulations.

Formulation Code	F1	F2	F3
Mean pH Value	6.5	6.8	6.8

Swelling Index Test

The results of selected formulations as shown in Table 15.

Table 15: Swelling Index Results of the Optimized Formulations.

Formulation Code	Time (Min)	Initial Weight	Final Weight	Swelling Index%
F2	0	1.5	1.5	60%
	5	1.5	1.7	
	10	1.5	2	
	15	1.5	2.86	
	20	1.5	3.05	
F3	0	1.5	1.5	97.5%
	5	1.5	2.22	
	10	1.5	3	
	15	1.5	3.2	
	20	1.5	3.43	

Rheological Study

The rheological properties of the **Chlorhexidine Emulgels** formulations (F1–F3) were evaluated by measuring their viscosities at 25°C using a viscometer with spindle 93 at 120 rpm. The viscosity values, presented as mean $\pm$ standard deviation of triplicate measurements, are summarized in

Table 16: Viscosity Measurements Results of Gel Formulations (F1–F3).

Formulation Code	Viscosity (cP) Mean $\pm$ SD
F1	13,640 $\pm$ 1268.5
F2	16,293 $\pm$ 165
F3	14,380 $\pm$ 838.6

Skin and Oral Mucosa Irritant Test

The prepared Emulgels formulations were topically administered to the perioral skin, labial mucosa, and buccal mucosa of 20 healthy volunteers.

In two volunteers with known skin sensitivity, mild allergic reactions (grade 1 erythema) were transiently observed within the initial 40 seconds of application of the Emulgels. These reactions resolved spontaneously without intervention and did not recur during subsequent monitoring periods. All other participants exhibited excellent tolerance to both formulations with no irritation.

Spreadability Test

Spreadability of all formulations was measured using the slide-separation method under a 50 g load. The mucoadhesive of Chlorhexidine Emulgels (F1–F3) were generally more cohesive, yielding lower spreadability values between 0.124 and 0.213 mm/s. These differences reflect the balance between ease of application and formulation consistency essential for mucosal delivery.

Among the mucoadhesive Emulgels, F1 demonstrated the less desirable profile, with a spreadability of 213mm/s, combining less flow for uniform coating and adequate viscosity to minimize rapid runoff. In the Emulgel series, F2 (0.124 mm/s) and F3 (0.140 mm/s) provided the optimal compromise between spreadability and structural integrity, suggesting enhanced residence time on oral mucosa without sacrificing patient-friendly application. As shown in Table 17.

Table 17: Spreadability Measurements Results of Gel Formulations (F1–F3).

Formulation Code	Spreadability (mm/sec)
------------------	------------------------

F1	0.213
F2	0.124
F3	0.140

Mucoadhesive Evaluation

The mucoadhesive strength was evaluated using both the slide separation method and the inclined slide method.

Formulations F2 and F3 both demonstrated strong adhesion in the two test methods. In the slide separation method, F3 showed slightly higher resistance than F2, suggesting stronger bonding to the membrane. In the inclined slide test, both formulations exhibited slow movement, with F3 moving more slowly than F2, but the difference between them was not very large.

Microbial Test

All of the Emulgel formulations submitted for microbiological contamination testing met the predefined sterility criteria. No viable microorganisms were detected in any sample, and each formulation was classified as “pass” according to the standard microbiological acceptance limits.

Drug Content Determination Test

All selected formulations (F2 and F3) exhibited drug contents within acceptable range (dose.). The mucoadhesive Chlorhexidine Emulgels (F3) contained 99.05% of the labelled **Chlorhexidine** dose..

Viscosity measurements revealed significant variation among the formulations. Formulation F1 exhibited the lowest viscosity at 13,640 $\pm$ 1268.5 cP, while formulation F2 demonstrated the highest viscosity at 16,293 $\pm$ 165, and formulation F3 demonstrated the highest viscosity at 14,380 $\pm$ 838.6.

Table 16: Viscosity Measurements Results of Gel Formulations (F1–F3).

Formulation Code	Viscosity (cP) Mean $\pm$ SD
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In two volunteers with known skin sensitivity, mild allergic reactions (grade 1 erythema) were transiently observed within the initial 40 seconds of application of the Emulgels. These reactions resolved spontaneously without intervention and did not recur during subsequent monitoring periods. All other participants exhibited excellent tolerance to both formulations with no irritation.

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Spreadability of all formulations was measured using the slide-separation method under a 50 g load. The mucoadhesive of Chlorhexidine Emulgels (F1–F3) were generally more cohesive, yielding lower spreadability values between 0.124 and 0.213 mm/s. These differences reflect the balance between ease of application and formulation consistency essential for mucosal delivery.

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Mucoadhesive Evaluation

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Formulations F2 and F3 both demonstrated strong adhesion in the two test methods. In the slide separation method, F3 showed slightly higher resistance than F2, suggesting stronger bonding to the membrane. In the inclined slide test, both formulations exhibited slow movement, with F3 moving more slowly than F2, but the difference between them was not very large.

Microbial Test

All of the Emulgel formulations submitted for microbiological contamination testing met the predefined sterility criteria. No viable microorganisms were detected in any sample, and each formulation was classified as “pass” according to the standard microbiological acceptance limits.

Drug Content Determination Test

All selected formulations (F2 and F3) exhibited drug contents within acceptable range (dose.). The mucoadhesive Chlorhexidine Emulgels (F3) contained 99.05% of the labelled **Chlorhexidine** dose.

Table 18: Results of Drug Content Test.

Formulation code	F1	F2	F3
Drug content % Chlorhexidine	--	98.7%	99.05%

Stability study of optimized formulation

The evaluation focused on monitoring key physical parameters such as changes in color, odor, clarity, phase separation, and overall appearance as shown in Tables (19, 20). After the 3-month period, no noticeable changes in appearance, odor, or pH were observed, confirming the robustness and stability of the formulations.

Table 19: Result of Stability Study for Optimized Batch F2.

Evaluation Parameter	Initial	After 3 Months
Appearance	Off-White, Smooth Texture	Off-White, Smooth Texture
Odor	Characteristic Clove Oil Aroma	Unchanged Aroma
pH	6.6	6.35

Table 20: Result of Stability Study for Optimized Batch F3.

Evaluation Parameter	Initial	After 3 Months
Appearance	Off-White, Smooth-Glossy Texture	Off-White, Smooth-Glossy Texture
Odor	Characteristic Clove Oil Aroma	Unchanged Aroma
pH	6.8	6.8

DISCUSSION

The formulated Chlorhexidine Emulgels exhibited desirable physical properties. All preparations were macroscopically uniform with no phase separation. The optimized Emulgels (F2 and F3) were off-white with a characteristic clove odor ideal balance between Emulgel cohesion and muco-adhesion. Formulations F2 and F3 achieved although detailed spreadability data are omitted, the high viscosity in F2, and F3 did not prevent uniform application and was considered suitable for topical dosing.

Biological evaluations demonstrated excellent tolerability. When tested on a group of human volunteers, none of the formulations caused any signs of erythema, skin irritation, or adverse reactions. These findings indicate good biocompatibility of all final gels supporting their safety for topical application.

Microbial contamination tests were performed to ensure the formulations were free from microbial growth or contamination. All tested samples showed no signs of microbial presence, confirming that the products were microbiologically safe.

The quantitative drug content assays showed essentially complete entrapment of the actives. The Chlorhexidine Formulations contained in F2 and F3 Emulgel were 98.7% and 99.05% respectively. Such high drug content indicates uniform dispersion and minimal loss during manufacturing. This uniformity is critical for dose accuracy and was expected given the thorough mixing steps. Finally, stability testing of the optimized formulations demonstrated robust stability. Over 3 months during the stability study, the appearance, odor, and pH of the formulations remained essentially unchanged.

CONCLUSION

The optimized Emulgels formulation, containing Chlorhexidine, and clove oil, represents a promising and effective approach for managing oral bacterial infections. It offers antibacterial activity, enhanced muco-adhesion, and improved sensory qualities, including taste and texture. The inclusion of a tri-polymer base significantly contributes to the rheological performance and stability of the formulation. These attributes support better patient comfort, compliance, and therapeutic outcomes while minimizing systemic side effects and irritation common in oral drug delivery. It was concluded that the best Emulgel Formulation F3 was found to be optimal

viscosity, spreadability, percent of drug content 99.05%, and mucoadhesive strength among the Chlorhexidine Emulgels formulations NDDS. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the NDDS (Novel Drug Delivery Systems) product development process.

ACKNOWLEDGEMENT

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

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