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DESIGN, DEVELOPMENT AND OPTIMIZATION OF TEDIZOLID PHOSPHATE CARBOPOL BASED EMULGEL FOR SKIN DRUG DELIVERY

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ABSTRACT
Background: Tedizolid phosphate (TZP) is effective against Gram-positive pathogens. It is used most widely in skin infections. Currently, there is no development of emulgels with this novel antibiotic molecule. Hence, the current research focused on developing emulgels for effective topical antimicrobial action to overcome disadvantages associated with oral drug delivery. **Methodology:** The drug spectroscopic method was developed using a UV-visible spectrophotometer. The o/w emulsions were prepared and incorporated into a gel base to form an emulgel. The prepared emulgels were subjected to physicochemical, IR spectral, antimicrobial, and biophysical analysis. **Results and Discussion:** Physical examination revealed a clear emulgel texture across all test formulations, with the greatest spreadability and rheology for carbopol 934 compared to HPMCK 15 and sodium CMC bases. The optimized carbopol 934-based EF7 formulation showed 86% in vitro and 73% ex vivo drug release over 12 hours. The FTIR studies clearly indicate no incompatibility among the drug and excipients. All physicochemical parameters confirmed controlled release, and FTIR studies confirmed no incompatibility. The optimized emulgel showed good inhibition of bacterial growth, and pathological studies confirmed the absence of alterations in porcine ear skin structure. **Conclusion:** The results indicate that the optimized formulation is suitable for treating acute skin infections.

INTRODUCTION

The epidermal skin barrier safeguards the body against a variety of daily threats, offering defense against physical damage and the uptake of chemicals and foreign substances. Beyond serving as a physical shield, the epidermis also provides an innate response to prevent the overgrowth of microbes. As the body's largest organ, the skin acts as the initial line of defense against external pathogens and microorganisms [1]. The skin performs numerous protective and regulatory functions, shielding the body from harmful external agents like chemicals, microorganisms, heat & radiation. Additionally, the skin plays a crucial role in regulating body temperature and blood pressure [2]. Transdermal drug delivery is a sophisticated method of administering therapeutics through the skin, allowing the active pharmaceutical ingredient to permeate the dermal layer while bypassing the selective barrier properties of the stratum corneum. This route enables systemic drug action & offers several advantages over traditional methods [3, 4].

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A recent review provides a comprehensive overview of emerging strategies to enhance drug bioavailability via the skin, focusing on overcoming the formidable barrier function of the stratum corneum and optimizing delivery systems for individualized dosing and therapeutic efficacy [5]. Historically, topical formulations such as creams, gels, and ointments have been widely used for treating dermatological conditions. Meanwhile, oral drug delivery remains the most commonly adopted route due to its convenience and high patient compliance. However, oral administration is not without limitations. It is subject to first-pass metabolism, lacks targeted delivery, and often fails to provide controlled release or accommodate high-dose requirements [6, 7]. These drawbacks have prompted the exploration of alternative delivery systems, particularly transdermal and topical approaches, which offer the potential for localized treatment, reduced systemic side effects, and improved pharmacokinetic profiles. As research progresses, innovative technologies such as microneedles, iontophoresis, and laser-assisted delivery are gaining traction for their ability to enhance skin permeability and therapeutic outcomes [8-10].

In recent years, the incidence of skin infections has increased, posing challenges to the effective treatment with conventional solid dosage forms. While semisolid formulations such as creams and ointments offer localized delivery, they often fall short in achieving optimal viscosity, spreadability, patient acceptability, and therapeutic efficacy. Among the available options, gels have emerged as a favorable medium for delivering hydrophobic drugs due to their non-greasy nature and ease of application [11–13]. To overcome the limitations of traditional gels, emulgels have been developed as an innovative hybrid system that combines the properties of emulsions and gels. Emulgels are gelled emulsions, typically of oil-in-water (o/w) or water-in-oil (w/o) type, designed to enhance the delivery of both hydrophilic and lipophilic drugs [14]. The dual-phase nature of emulgels enables improved drug solubilization, enhanced stability, and increased drug-loading capacity, making them suitable for controlled-release applications [15]. Emulgels exhibit several desirable characteristics, including excellent spreadability and ease of application, non-greasy texture and thixotropic behavior, extended shelf life and aesthetic appeal, odorlessness and patient-friendly formulation [16, 17, 18]. These attributes make emulgels a versatile and effective platform for topical drug delivery, particularly in treating localized infections. Given the limitations of single-phase semisolid formulations, the current study aims to develop an emulgel-based system to ensure uniform drug distribution throughout the infected area and maximize therapeutic efficacy.

For successful incorporation into emulgel delivery systems, drugs should meet certain physicochemical and pharmacokinetic criteria that enhance topical penetration, stability, and patient compliance. Key attributes include hydrophobic character, low molecular weight, Short biological half-life, ability to maintain therapeutic levels for longer periods, appropriate partition coefficient, and high skin permeability [19-20]. In line with these guidelines, the current study selected a novel oxazolidinone derivative of TZP. It is a next-generation oxazolidinone antibiotic that shows potent activity against Gram-positive pathogens. Despite its clinical success in oral and intravenous forms for treating acute bacterial skin and skin structure infections, no commercially available topical emulgel formulation of TZP. The physicochemical properties of TZP, such as log P (4), pKa (1.8 and 6.5), and molecular weight (450.3 g/mol), are most suitable to formulate it for skin drug delivery in the form of emulgel.

MATERIALS AND METHODS

Materials

TZP was procured from Simson Pharma Pvt Ltd., Mumbai. The liquid paraffin and Tween 80 were obtained from Sigma-Aldrich, India. Carbopol 934 was obtained as a gift sample from Ashland India Pvt Ltd., Ireland. The propylene glycol, sodium carboxymethyl cellulose, and hydroxypropyl methylcellulose K15M were procured from Standard Reagents Pvt Ltd., Hyderabad.

Method of Preparation

The formulation of emulgel involves a two-step process, combining emulsion formation with gel base preparation to create a stable and effective semisolid dosage form.

STEP 1: Preparation of o/w primary emulsion

The oil phase, typically composed of liquid paraffin, Tween 80 (a non-ionic surfactant), and propylene glycol (a co-solvent and humectant), is prepared. Simultaneously, the aqueous phase is formulated using distilled water. The oil and aqueous phases are combined under continuous stirring, usually with a mechanical or magnetic stirrer, to form a stable emulsion. The pH of the emulsion is adjusted to the desired level (typically between 5.5 and 6.5 for skin compatibility) using sodium hydroxide or triethanolamine.

STEP 2: Preparation of gel base

A polymeric gel base is prepared by dissolving suitable gelling agents such as sodium carboxymethyl cellulose (Na CMC), carbopol 934, and hydroxypropyl methylcellulose (HPMC K15M). These polymers are dispersed in distilled water under continuous stirring until a homogeneous gel is formed. The gel base is then gradually mixed with the prepared emulsion to form the final emulgel**,** ensuring uniform consistency and stability [21, 22, 23]. The compositions of various emulgels are shown in Table 1, and the preparation procedure is shown in Figure 1.

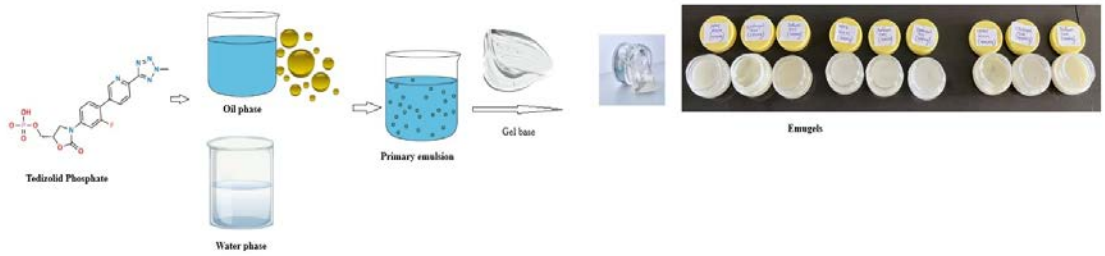

Figure 1: Preparation illustration of Emulgel

Table 1: Composition of different formulation batches

Ingredients	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8	EF9
TZP (mg)	100	100	100	100	100	100	100	100	100
Na CMC (mg)	200	300	400	-	-	-	-	-	-
HPMCK15 (mg)	-	-	-	200	300	400	-	-	-
Carbopol 934 (mg)	-	-	-	-	-	-	200	300	400
Liquid paraffin (ml)	3	4	5	3	4	5	3	4	5
Tween 80 (ml)	6	7	8	6	7	8	6	7	8
Propylene glycol (ml)	6	6	6	6	6	6	6	6	6
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

ASSESSMENT METHODS OF EMULGELS

UV-spectrophotometric method

UV spectrophotometric methods have been reported for estimating TZP. Calibration curves were plotted in phosphate buffer pH 6.8 using the UV-1800 spectrophotometer (Shimadzu) at 230 nm. Linearity was observed over the concentration range of 1–20 µg/ml, with a regression coefficient of 0.9960 in a pH 6.8 phosphate buffer [22, 23].

Physical assessment

The color, appearance, and consistency of the prepared emulgel formulations were examined visually [20].

Droplet size of emulgel and polydispersity index (PDI)

Measurement of droplet size and PDI in emulgel formulations is typically performed using light-scattering techniques such as dynamic light scattering (DLS), which yields an intensity-weighted hydrodynamic diameter and a dimensionless PDI that describes the breadth of the size distribution. Sample preparation, including appropriate dilution to avoid multiple scattering, equilibration at a controlled temperature, and removal of dust or air bubbles, is critical for obtaining reproducible results. Measurements are usually repeated on independent aliquots to report the mean size and standard deviation. The PDI value provides a quick indicator of sample homogeneity [16].

Zeta Potential

Measurement of zeta potential for emulgel formulations is commonly performed by electrophoretic light-scattering instruments that determine particle or droplet electrophoretic mobility and convert it to zeta potential using a zeta sizer [19].

Rheological studies

The rheological behavior of the prepared emulgels was evaluated to determine their flow characteristics and consistency, which are critical for ensuring ease of application and product stability. Measurements were carried out using a viscometer with spindle 7 (Brookfield Engineering Laboratories), and viscosity values were recorded at varying shear rates from 100 to 500 rpm for 30 min. The prepared emulgel offers good flow for a longer period. The assembly was connected to a thermostatically controlled circulating water bath maintained at 25ºC. The viscosity of the formulation was determined by placing it in a beaker fitted with a thermostatic jacket. The spindle was allowed to move freely into the emulgel, and the reading was noted [21].

Measurement of pH

The pH of each prepared emulgel was measured using a digital pH meter. Before use, the pH meter must be calibrated with a standard buffer solution. After dissolving 1 g of the formulation in distilled water to form a homogeneous suspension, the suspension is set aside for 2 hours. The pH is measured two hours after the glass electrode has been dipped into the suspension [23].

Spreadability

Good spreadability is one of the requirements for an emulgel to meet the ideal quantities. It is a term used to describe the size of the area that the gel spreads easily when applied to the skin or affected area. The spreading value of a formulation also affects its therapeutic efficacy. The time in seconds it takes for two slides to separate from emulgel and move between each other when subjected to a specific load is known as spreadability [24].

In vitro drug release studies

A modified Franz diffusion (FD) cell was used for in vitro drug-release experiments. The dialysis membrane, which was positioned between the FD cell's donor and receptor compartments, was coated with the formulation. A phosphate buffer at pH 7.4 was used as the dissolution medium. The water jacket was circulated to keep the cell's temperature at 37ºC. A magnetic bead was used to continuously stir the solution while the entire assembly was held on a magnetic stirrer. As a control, a comparable blank set was executed concurrently. At appropriate intervals, the sample (5 mL) was removed and replaced with equal volumes of fresh dissolving medium. Spectrophotometric analysis of the samples was performed at 254 nm, and the cumulative percentage of drug release was computed [25, 26].

Ex vivo drug release study through diffusion

Porcine ear skin is widely used *ex vivo* as a practical surrogate for human skin to study topical drug bioavailability, permeation, and dermal absorption. The skin was obtained from Minerva Pork Shop in Bhoiguda, Secunderabad; the study was conducted in accordance with institutional ethical guidelines, as the institution holds CPCSEA approval (1657/PO/Re/12/CPCSEA). It enables multiple replicates, avoids human subject approval, and permits evaluation of irritating or toxic compounds while maintaining similar barrier characteristics for procedures such as sequential tape-stripping of the stratum corneum [26]. Mount skin with the stratum corneum facing the donor compartment and the dermal side toward the receptor compartment; check for leaks and air bubbles. Fill with an appropriate medium while stirring; maintain the temperature at approximately skin-surface conditions to mimic physiological conditions. Skin was used in a modified Franz diffusion cell to conduct an *ex vivo* drug release study of specific formulations. With the dorsal side facing up, a piece of skin (2 x 2 cm^2) was cut and inserted into the gap between the FD cell's donor and receptor compartments. The dissolution medium was phosphate buffer at pH 6.8. The water jacket kept the cell temperature steady at 32 ± 5 °C. A magnetic bead continuously stirred the solution while the entire assembly was held on a magnetic stirrer. At the same time, a comparable blank set was run. At appropriate intervals, the samples were removed and replaced with equal volumes of fresh dissolving medium. Spectrophotometric analysis was performed on the samples at 254 nm [26].

Kinetics of both in vitro and ex vivo

The dissolution rate profiles were established by measuring the amount of active ingredient released in *in vitro* and *ex vivo* release studies of the formulations. To identify the mathematical model that best describes the release profiles of the active substance, the equations for the zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models were utilized in Excel® [27].

Stability studies

Stability testing was performed to assess the optimized formulation's ability to maintain its physicochemical and therapeutic properties throughout the intended shelf life. The study was designed in accordance with the guidelines issued by the International Conference on Harmonization (ICH) and the World Health Organization (WHO). The optimized formulation was stored in amber-colored containers to minimize light exposure and placed under two controlled conditions: refrigerated storage at 4°C and accelerated storage at 25±2°C/75±5% relative humidity. The samples were maintained for three months, with aliquots withdrawn at predetermined intervals of 1, 2, and 3 months [28].

Biophysical study of porcine skin after ex vivo studies

Porcine skin was selected as a model to evaluate the pathological response due to its close structural and physiological resemblance to human skin. After *ex vivo* treatment, skin samples were carefully prepared and subjected to histopathological examination to assess any alterations in tissue

morphology. Skin sections were fixed, embedded, and stained using standard histological techniques. Microscopic evaluation focused on the epidermal and dermal layers, assessing parameters including cellular integrity, inflammatory infiltrates, changes in collagen fibers, and overall tissue architecture. The analysis revealed that the treated porcine skin maintained normal histological features, with intact epidermal layers and well-organized dermal structures [29, 30].

FTIR

Fourier Transform Infrared (FTIR) spectroscopy was employed to investigate possible interactions between the drug and excipients in the optimized formulations. The technique provides information on the functional groups present and helps to confirm the chemical integrity of the components. Spectra of the pure drug, individual excipients, and the final formulations were recorded and compared. Characteristic absorption peaks corresponding to the drug's functional groups were identified and monitored for significant shifts, disappearance, or the appearance of new peaks in the formulation spectra. Such changes would indicate potential chemical interactions or incompatibilities. The analysis revealed that the major functional group peaks of the drug remained intact in the formulation, suggesting that no undesirable chemical interactions occurred during preparation. The excipients showed their typical absorption bands, and the overall spectral profile confirmed the compatibility of the drug with the selected excipients [31].

Anti-microbial activity

The antimicrobial efficacy of the optimized formulation was evaluated against representative Gram-positive and Gram-negative bacterial strains to determine its broad-spectrum potential. Standard agar diffusion methods were employed, where the formulation was introduced into wells or discs placed on inoculated agar plates. Following incubation, the diameter of the inhibition zones was measured to assess the extent of bacterial growth suppression. The study included Gram-positive organisms, such as *Bacillus subtilis*, and Gram-negative organisms, such as *Escherichia coli*, to provide a comparative assessment of activity across different bacterial classes.

The optimized formulation exhibited clear inhibitory zones against both categories, indicating that the active compound retained its antimicrobial properties after formulation. The results confirmed that the formulation effectively reduced microbial growth, with activity observed against both Gram-positive and Gram-negative strains, thereby supporting its therapeutic relevance [32].

RESULTS AND DISCUSSION

The TP-containing emulgels were formulated successfully. The basic and detailed technical assessments are shown below.

Physical assessment

The optimized emulgel formulations underwent a series of physical evaluations to assess their quality, stability, and suitability for topical application. Visual inspection confirmed that all samples exhibited a smooth, homogeneous appearance without signs of phase separation, grittiness, or precipitation. The formulations were consistent in color and texture, indicating uniform dispersion of the drug and excipients. This result is due to uniform mixing and good compatibility between the drug and excipients.

Droplet size of emulgel and polydispersity index (PDI)

The mean globule size of all the prepared emulgels was found to be in the range of 148.2±0.4 nm to 354.1±1.1 nm, and the PDI was found to be in the range of 0.187±0.1 to 0.464 ±0.7. Compared with all gelling agents, the carbopol system showed superior results. The results showed that the smaller globule size of the emulgel was obtained due to the desirable concentration of gelling agent, i.e., carbopol, in the emulgel system. The decrease in globule size can be attributed to uniform mixing of the emulsion with the internal phase in the gel system, which significantly enhances drug transport through the skin. Moreover, the small globule size of the emulgel droplets also affects the percutaneous absorption of the drug. The higher the PDI, the lower the uniformity of globule size in the formulation.

Zeta potential

The zeta potential of all test emulgels ranged from -4.6±1.2 mV to -19.1±0.9 mV. Compared with all test gelling agents in emulgels, carbopol carbopol-based emulgel showed a superior result. The smaller-sized emulgel shows higher zeta potential, whereas the larger-sized emulgel shows low ZP. The emulgels with low droplet size are usually more stable compared with emulgels with larger droplet size because larger droplets are more susceptible to aggregation or coalescence.

Measurement of pH

The pH of emulgel formulations was measured to assess their suitability for topical application and to ensure compatibility with the skin's physiological pH. Formulations prepared with

different gelling agents such as Na CMC, HPMC K15, and Carbopol 934 were analyzed at room temperature using a calibrated digital pH meter. The results indicated that all formulations exhibited pH values within the acceptable dermatological range (6.5), minimizing the risk of irritation upon application. Emulgels containing Na CMC showed slightly higher pH values than those prepared with Carbopol 934, while HPMC K15 formulations maintained intermediate pH values. Importantly, no significant fluctuations in pH were observed during the study period, confirming the stability of the formulations. Overall, the findings demonstrated that the choice of gelling agent influenced the pH profile of the emulgels. Still, all remained within the safe and skin-friendly range, supporting their potential for topical therapeutic use.

Rheological studies

The rheological results indicated that the emulgels exhibited non-Newtonian, shear-thinning behavior, with viscosity decreasing as shear rate increased. This property is desirable for topical formulations, as it allows the gel to spread easily under the mechanical stress of application while maintaining sufficient thickness at rest to ensure retention on the skin surface. Additionally, the formulations showed pseudoplastic flow with no evidence of thixotropy, confirming structural stability during repeated shear cycles. The optimized emulgel demonstrated consistent rheological properties across all test conditions, supporting its suitability for therapeutic use and patient compliance. Figure 2 shows that formulation EF7 exhibited optimal viscosity (1250 cps), which is suitable for spreading the gel for easy topical application. This result may be due to the lower concentration of carbopol 934 and its fluffy, free-flowing nature. On the other hand, the remaining two formulations (EF8 & EF9) of carbopol 934 were also found to have low and acceptable viscosity (1305 & 1350 cps).

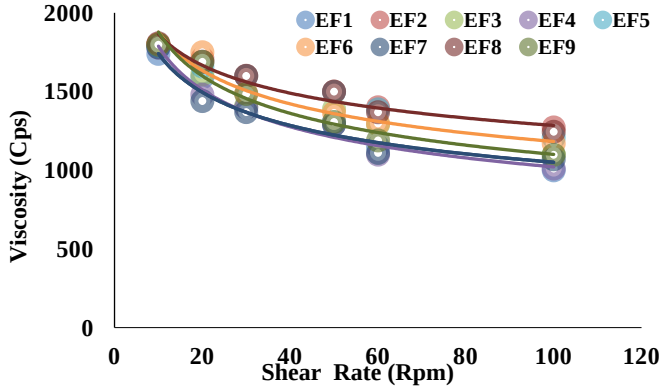

Figure 2: Physical examination of emulgel

Spreadability

Spreadability testing was conducted to assess the ease of application and the uniform distribution of the emulgel formulations across the selected skin surface. Formulations prepared with Na CMC, HPMC K15, and Carbopol 934 were evaluated using the standard slip-and-drag method, in which the time required for the gel to spread under a defined weight was recorded. The results demonstrated noticeable differences among the gelling agents.

Emulgels containing Na CMC exhibited higher spreadability, indicating smoother application and lower shear resistance. Formulations prepared with HPMC K15 showed moderate spreadability, balancing ease of application with adequate consistency. In contrast, Carbopol 934-based emulgels displayed comparatively lower spreadability, reflecting their higher viscosity and stronger gel network. Overall, these findings confirmed that the choice of gelling agent significantly influenced the spreadability of emulgels. While Na CMC provided superior ease of application, Carbopol 934 offered better structural integrity & HPMC K15 maintained intermediate characteristics. These findings highlight the importance of selecting an appropriate polymer depending on the desired balance between patient comfort and formulation stability.

The spreading efficiency and optimum viscosity of the low-concentration Carbopol 934 gel base formulation EF7 are due to its highly cross-linked polymeric structure, which allows it to swell extensively in aqueous systems, forming smooth, stable gels at low concentrations. The Carbopol gels also have better bioadhesive properties and are easy to spread on skin or mucosal surfaces. At the same time, Sodium CMC and HPMC K15 are cellulose derivatives. They are linear or slightly substituted polymers that hydrate to form viscous solutions but lack the extensive cross-linking observed in Carbopol. Sodium CMC and HPMC K15 tend to form more stringy or sticky gels, which can reduce smooth spreading [33, 34].

In vitro drug release studies

The *in vitro* drug-release profile of the prepared emulgels was evaluated to assess the influence of different gelling agents, such as Na CMC, HPMC K15, and Carbopol 934, on the release kinetics of the incorporated drug. The study was conducted using the diffusion technique, with samples withdrawn at predetermined time intervals and analyzed spectrophotometrically. The *in vitro* DR profiles of all test formulations are shown in Figure 3.

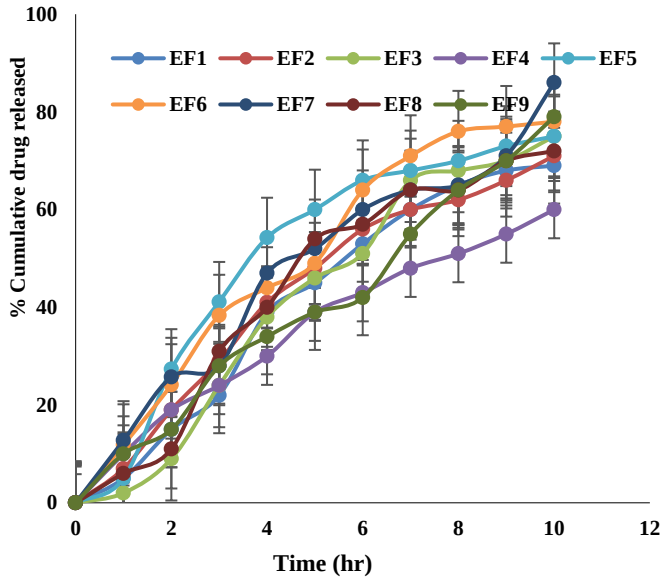

Figure 3: *In vitro* cumulative drug release profiles of all test formulations

Ex vivo drug release study

Ex vivo drug release experiments were conducted using porcine skin as a diffusion membrane to mimic the barrier properties of human skin. Emulgel formulations prepared with Na CMC, HPMC K15, and Carbopol 934 were evaluated to determine the influence of different gelling agents on drug permeation. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically to quantify the amount of drug released. The *ex vivo* findings confirmed that the choice of gelling agent significantly influenced drug-release behavior across biological membranes. Na CMC favored rapid permeation, HPMC K15 provided controlled release, and Carbopol 934 ensured extended retention, highlighting the importance of polymer selection in tailoring emulgel formulations for specific therapeutic needs. The *ex vivo* cumulative drug release profiles of all test formulations are shown in Figure 4. The drug release in vitro (86%) and drug permeation ex vivo (73%) were highest over 12 hrs for carbopol 934 at lower concentrations. This result may be due to swelling in an aqueous environment, which facilitates faster drug diffusion and release. Formulations with Sodium CMC and HPMC K15 showed the lowest drug release because they limit water penetration and form restrictive gel matrices [35, 36].

Kinetics of both in vitro and ex vivo

To understand the release mechanisms of the prepared emulgels, kinetic modeling was applied. In both in vitro and ex vivo, the release pattern followed zero-order kinetics for EF1 to EF9 formulations, as shown by the highest R values. This obtained result may be due to drug release being independent of gelling agent concentration. At optimal concentration, more drug is entrapped in the gel matrix, causing further delay and slower release. Drug release is influenced by the gelling agent and rheological properties [37].

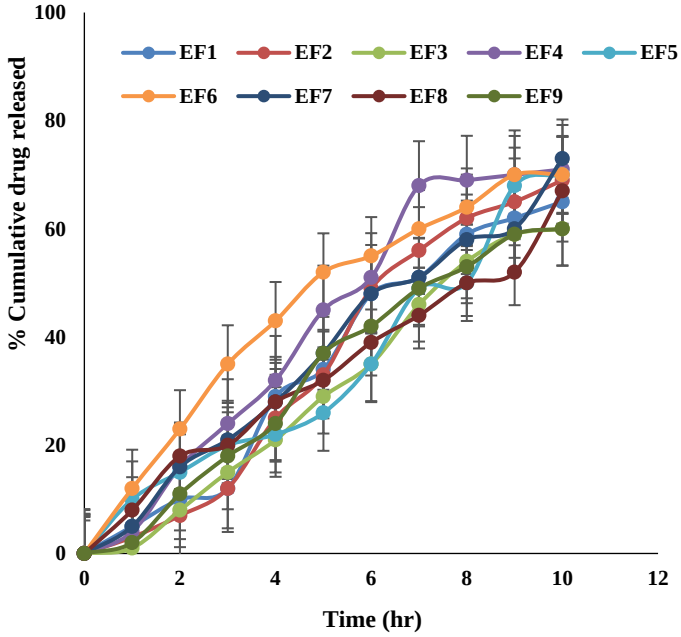

Figure 4: *Ex vivo* cumulative drug release profiles of test formulations

In the in vitro drug release study, among the nine formulations, EF7 showed the highest R value (0.9975) for zero-order kinetics. To determine the drug-release mechanism, formulations were fitted to the Higuchi kinetic model; i.e., a graph plotting the amount of active substance released (Q) against the rate of release (dQ/dt) over a specific time frame was created to identify the most applicable model. The release of hydrophilic drugs from anhydrous gel matrices occurs via a swelling-controlled diffusion process that involves concurrent water absorption and drug desorption. From this, the r value for EF7 was 0.9779, and from the Korsmeyer-Peppas equation, it was 0.9879. The release exponent ‘n’ value was observed as the highest, i.e., 0.38 for EF7, which indicated the Fickian diffusion pattern. The Korsmeyer-Peppas model describes the release of active substances through diffusion and/or relaxation in the polymeric system. From the *ex vivo* release kinetics, the highest r value was obtained for zero-order kinetics of EF7, i.e., 0.9992, and in the mechanism of drug release, it follows Korsmeyer-Peppas by its highest r value, i.e., 0.9866, and the release exponent ‘n’ value

was observed as highest, i.e., 0.35 for EF7, which indicated the Fickian diffusion pattern. Based on the in vitro and ex vivo kinetic results obtained, the release pattern is well correlated with the highest r values from the zero-order and Korsmeyer-Peppas equations.

Stability studies

Stability assessment was conducted for both the control and test formulations over 3 months at 4±2°C and 40±2°C/75±5% RH, as shown in Table 2. For the organoleptic assessment, the emulgel was physically examined for any changes in color, odor, liquefaction, and evidence of microbial growth. The results of the stability study indicated changes in a few formulation parameters relative to their initial values. The EF7 showed greater stability than the other test formulations. The viscosity of the gel structure restricts particle movement in the emulgel. This might be the reason for the greater stability of carbopol 934 gel with lower concentration. In the present study, stability studies demonstrated that this formulation requires refrigerated storage (4±2°C) to maintain its functionality and potential usefulness as a topical formulation.

The stability results indicated that 4±2°C is an essential storage condition for the emulgel due to a clear emulgel for the entire storage period up to three months, without changing its original form at the storage condition 4±2°C. In contrast, at 40±2°C, the clear emulgel EF7 showed turbidity at two and three months of storage. Under these storage conditions, the gelling agent carbopol 934 may form a thick network due to the increased temperature. Hence, this condition is not suitable for storing the emulgel. Stability evaluation of the optimized formulation was conducted in accordance with ICH guidelines. The formulation maintained its physical characteristics, pH, consistency, microbiological quality, and *in vitro* release profile for up to three months under different storage conditions. No significant variations were detected in any test parameter throughout the study period, confirming the stability of the developed TZP emulgel formulation.

Table 2: Stability studies of EF7 formulation

	EF7 (optimized emulgel) at 4±2°C			EF7 (optimized emulgel) at 40±2°C/70±5%RH		
	Initial	2 months	3 months	Initial	2 months	3 months
pH	6.51± 0.5	6.50 ± 1.0	6.54 ± 0.7	6.51± 0.5	6.50 ± 1.0	6.54 ± 0.7
Physical examination	Clear	Clear	Clear	Clear	Turbidity	Turbidity
% Drug release	85.9± 0.2	85.6±0.1	86.0± 0.5	79.9± 0.2	83.6±0.1	80.0± 0.5

Each value represents mean ± s.d

FTIR

FTIR studies were conducted to determine the interactions between functional groups in the used drug and its excipients. These studies showed no major changes in functional groups, indicating no possible interactions with the excipients. No functional group changes were observed with EF7, which may be due to compatibility between the drug and excipients. The spectral wavenumbers and functional groups at their respective vibrations are shown in Table 3.

Anti-microbial activity

The antimicrobial potential of the optimized emulgel (EF7) formulation was evaluated against selected bacterial strains using the agar diffusion method. Clear zones of inhibition were observed around the wells containing the emulgels, indicating effective suppression of microbial growth. The optimized formulations demonstrated significant activity against both Gram-positive and Gram-negative organisms when compared with the standard, i.e., Albucid. The results confirmed that the optimized emulgels exhibited strong antimicrobial activity, thereby validating their therapeutic potential for topical applications. The findings highlight that the formulation not only maintained drug activity but also provided a stable and effective delivery system for combating microbial infections. The results are shown in Table 4.

The formulated emulgel inhibited the growth of both organisms, with a larger zone of inhibition observed for *Staphylococcus aureus* (39.2±0.1 mm) compared to *E. coli* (38.5±0.6mm). This indicates that the sample exhibits stronger antimicrobial activity against *Staphylococcus aureus* than *E. coli*, as the drug acts against Gram-positive bacteria. The zone-of-inhibition results demonstrated that the optimized EF7 emulgel formulation exhibited strong antimicrobial activity against S. aureus and E. coli [33]. Existing literature indicates that when the diameter of the zone of inhibition exceeds 18 mm, formulations are considered highly antimicrobial [38]. Thus, TZP retained its high antimicrobial efficacy even after being formulated into an

emulgel system. The EF7 Carbopol 934 base gel formulation demonstrates excellent skin tolerance, which may be due to its biocompatibility, non-reactivity, gentle rheology, and hydration-supporting properties [39, 40].

Table 3: Components of emulgels and their functional group interactions

Component	Wavenumber (cm^{-1})	Vibration Type	Functional Group
TZP	1746.4	C=O stretching	Carbonyl group
	3256.4	O-H stretching	Hydroxyl group
	1464.1, 1406.8, 1208.4	Bands with C-C, C-O, C-F sigma bonds	-
Carbopol 934	3000−3500	O-H stretching	Hydroxyl group
	1700	C=O stretching	Carboxylic groups
Sodium CMC	3482.81, 3200-3600	O-H stretching	Hydroxyl group
	2897.52, 2904, 3000	C-H stretching	Alkane (CH_2, CH_3)
	1599.7, 1605	C=O asymmetric stretching	Carboxylate (COO^-)
	1414.5, 1425	C-H symmetric stretching	Carboxylate (COO^-) or Alkane (CH_3)
	1029, 1034.62	C-O-C stretching	Ether/Pyranose ring
Propylene Glycol	3700-3000	O-H stretching	Hydroxyl group
	2960-2853	C-H stretching	Alkane (CH)
	1150-1085	C-O stretching	Alcohol
Liquid Paraffin	2955, 2918, 2850	C-H stretching	Alkane (CH_3, CH_2)
	1459, 1465	C-H bending	Alkane (CH_2)
	719-720	CH_2 rocking	Alkane (long chain)
Tween 80	3100-3700	O-H stretching	Hydroxyl group
	1738	C=O stretching	Ester
	1103	C-O stretching	Ether
EF7	1700	C=O stretching	Carbonyl group
	3127.2	O-H stretching	Hydroxyl group
	1342.1, 1506.8, 1200	Bands with C-C, C-O, C-F sigma bonds	-

Table 4: Zone of inhibition of Emulgel compared with std.

Test organism of bacterial strains	Zone of inhibition (mm)	
	Standard (mm) Albucid (10%)	EF7 (optimized formulation)
S. aureus	38.3±0.3	39.2±0.1
E. coli	37.6±0.4	38.5±0.6

Each value represents mean ± s.d

Pathological study of porcine skin after ex vivo

No significant pathological changes, such as necrosis, edema, or abnormal cellular infiltration, were observed. These findings confirmed that the optimized formulation was non-irritant and safe for topical application, supporting its suitability for further therapeutic use. The pathological images of porcine skin after *ex vivo* studies are shown in Figure 5.

Studies on porcine skin confirm that the polymer does not induce irritation or necrosis, reinforcing its role as a preferred gelling agent for safe topical drug delivery systems.

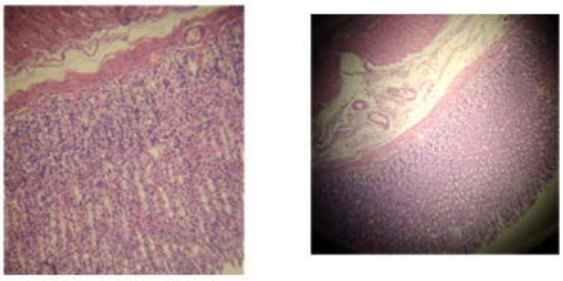

Figure 5: Pathological images of A) plain and B) EF7-treated skin

CONCLUSION

The emulgels were successfully designed and developed for TZP. Only solid dosage forms with TZP are available on the market for oral administration; however, upon oral delivery, they cause severe gastrointestinal issues and cannot be used long term; hence, we aimed to develop a transdermal product to bypass these oral drawbacks. Currently, there is no TZP emulgel

on the market; we focused mainly on improving drug permeation through the skin. The emulgel showed higher permeation than gels and exhibited a high partition coefficient; we previously investigated it, and the current research confirmed these findings. Compared with other gelling agents such as sodium CMC and HPMCK15, carbopol 934 showed superior results across all evaluated parameters. The significant results of physicochemical evaluation, in vitro, ex vivo, and antimicrobial studies proved that the lowest concentration of carbopol 934 is suitable to heal acute skin infections. We succeeded in our plan, achieving desirable results, and we plan to conduct clinical studies in the future to demonstrate its systemic therapeutic efficacy.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Madhavi Nimmathota was involved in the design of the work. Sravani Chokkarapu performed the experimental work. Akshitha Tirumalli performed the analysis. Umamaheshwara Rao Vattikuti interpreted the data and observations. Finally, all authors collectively contributed to the draft and revised it.

DECLARATION OF USE OF AI TOOLS
The authors used ChatGPT to assist with language editing and readability improvement. All content, analysis, and conclusions were reviewed and verified by the authors. The authors take full responsibility for the originality, accuracy, and integrity of the work.

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