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Comparative Evaluation Of Ivermectin Topical Gel And Reported Formulations: Anti-Tick Efficacy Assessment At 12 Hours

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Abstract: *This study investigated the comparative anti-tick efficacy of Ivermectin topical gel formulations with a focus on the optimized batch (F3) against marketed ivermectin products at the 12-hour interval. Ivermectin gels were prepared using Carbopol 940 as a gelling agent, triethanolamine for pH adjustment, and sodium benzoate as preservative. The formulations were characterized for viscosity, spreadability, homogeneity, drug content, and in vitro release profiles. Among the developed batches, F3 demonstrated optimal physicochemical properties and sustained zero-order drug release. In vivo anti-tick efficacy studies conducted on rabbit ear pinnae revealed that F3 significantly outperformed marketed ivermectin oral tablets, and subcutaneous formulations in terms of rapid tick detachment and mortality within 12 hours. The superior activity was attributed to enhanced skin penetration, prolonged retention time, and continuous drug exposure at the site of infestation. Stability studies further confirmed that F3 retained its physical, chemical, and microbial integrity over six months. The findings underscore the therapeutic potential of ivermectin topical gels as a safer, more effective, and animal-compliant alternative to conventional ivermectin dosage forms in veterinary practice.*

Keywords: *Ivermectin topical gel; Anti-tick activity; Comparative analysis; Skin retention; Sustained release; Veterinary parasitology; Formulation stability*

1. INTRODUCTION

Ivermectin is a semisynthetic antiparasitic drug belonging to the avermectin family, a class of 16-membered macrocyclic lactones that were originally isolated from the soil microorganism *Streptomyces avermitilis* [1]. The discovery of avermectins in the 1970s marked a turning point in the management of parasitic diseases, both in veterinary and human medicine [2]. Early work carried out by researchers at the Kitasato Institute in Japan and Merck & Co. in the United States demonstrated that these naturally derived compounds possessed potent antiparasitic activity [3]. Dr. William Campbell and Dr. Satoshi Ōmura played pivotal roles in the development of ivermectin, which was subsequently introduced as a veterinary product in the early 1980s under the brand name Ivomec [4]. Its remarkable efficacy in controlling nematodes and ectoparasites such as ticks, fleas, and mites rapidly established its role as a frontline drug in veterinary parasitology [5]. The global significance of ivermectin was further emphasized when its expansion into human medicine, particularly in the treatment of onchocerciasis (river blindness) and lymphatic filariasis, led to widespread recognition of its public health impact [6]. In 2015, Campbell and Ōmura were awarded the Nobel Prize in Physiology or Medicine for their contribution to its discovery and application, cementing ivermectin's place as one of the most important antiparasitic agents in medical history [7].

From a pharmacological perspective, ivermectin exerts its action primarily by binding to glutamate-gated chloride channels (GluCl) in nerve and muscle cells of parasites [8]. This interaction enhances chloride ion influx, leading to hyperpolarization, paralysis, and ultimately the death of the parasite. It also acts on gamma-aminobutyric acid (GABA)-mediated neurotransmission, further contributing to its inhibitory effect [9]. The selectivity of ivermectin for parasites lies in the higher abundance and sensitivity of these channels in invertebrates compared to mammals, which explains its relative safety profile [10]. Its broad-spectrum activity against nematodes and arthropods has led to its extensive use across species, ranging from livestock and companion animals to humans. In veterinary contexts, Ivermectin is widely applied to control gastrointestinal nematodes, lungworms, lice, mites, and particularly ticks, which are notorious vectors of infectious diseases [11]. The veterinary relevance of Ivermectin, therefore, extends beyond its direct antiparasitic effects to its indirect role in preventing tick-borne diseases that compromise animal health, productivity, and welfare [12].

Ticks are obligate ectoparasites that survive by feeding on the blood of mammals, birds, and occasionally reptiles [13]. Their prevalence in livestock and pets poses a persistent threat to both animal health and the agricultural economy. Heavy infestations can lead to anemia, skin damage, weight loss, and reduced productivity in animals, while also transmitting serious pathogens such as *Babesia*, *Anaplasma*, and *Theileria* [14]. In companion animals, tick infestations cause irritation, allergic reactions, and increase the risk of zoonotic diseases that may also affect humans. Thus, controlling tick infestations is not merely a matter of animal welfare but is directly tied to food security, veterinary practice, and public health. Conventional tick control strategies rely heavily on systemic and topical antiparasitics, but growing concerns of resistance and limited duration of efficacy demand newer approaches with improved delivery systems [15].

Topical drug delivery systems have emerged as an attractive alternative to conventional oral or injectable formulations for managing external parasites [16]. The key advantage of topical gels is their ability to deliver the active drug directly to the site of infestation, ensuring localized treatment and reducing unnecessary systemic exposure [1]. This localized action not only minimizes adverse systemic effects but also improves drug bioavailability at the skin surface, where parasites reside [2]. Furthermore, topical gels can be formulated to provide controlled or sustained release, ensuring prolonged retention of the drug at therapeutic levels over time [3]. Compared ointments, gels are generally non-greasy, have a lighter texture, spread easily, and exhibit good patient and pet compliance [4]. The ability of gels to enhance skin penetration and maintain consistent drug levels makes them particularly suitable for combating ectoparasitic infestations such as ticks [5]. Additionally, reduced dosing frequency due to sustained release improves user convenience and adherence to treatment protocols, which is a critical factor in veterinary applications where repeated dosing may be impractical [6].

Despite these advantages, existing ivermectin products still present notable limitations. Oral formulations, though effective, expose the drug to gastrointestinal metabolism and systemic circulation, potentially leading to side effects and reduced availability at the skin surface where ticks are localized [7]. Injectable formulations, while bypassing the gastrointestinal route, are invasive, may cause pain or stress in animals, and require skilled administration [8,9]. Moreover, resistance to ivermectin and other avermectins has been reported in various parasite populations, necessitating optimized delivery systems that can maximize efficacy at lower doses while reducing the risk of resistance development [10]. These drawbacks highlight the need for novel dosage forms that can provide effective, localized, and long-lasting tick control [11].

The rationale for the present study stems from this unmet need to enhance the therapeutic utility of ivermectin through a topical gel system. The study focuses on a comparative analysis of anti-tick efficacy between newly formulated ivermectin topical gels and reported products, including tablets and subcutaneous injections. The emphasis is placed on evaluating performance at the 12-hour mark, a critical time point for assessing early and sustained efficacy against ticks. By comparing tick reduction across formulations under controlled conditions, the study aims to establish whether the novel gel formulation offers measurable improvements over conventional delivery systems [12].

The specific aim of this investigation is to develop and evaluate Ivermectin topical gels with desirable physicochemical properties, confirm their anti-tick efficacy through in vivo studies, and compare their performance with existing products at 12 hours. The objectives include assessing gel formulation parameters such as viscosity, spreadability, and drug content, conducting anti-tick efficacy tests on rabbit ear pinnae, and statistically analyzing comparative outcomes with marketed formulations. Ultimately, the study seeks to determine whether Ivermectin topical gels can provide superior localized control of tick infestations while addressing the limitations of tablets, and injections [13–16]. Through this approach, the research contributes to advancing veterinary therapeutics and proposes a promising dosage form for managing ectoparasitic infestations effectively.

2. MATERIALS AND METHODS

2.1Materials

The materials used in this study included Ivermectin (Biodeal Pharmaceuticals Ltd., India) as the active drug. 85% aq.Ethanol (95% v/v) and Sodium hydroxide pellets LR were procured from **SD Fine-Chem Ltd., Mumbai, India**. Carbopol 940, employed as the gelling agent, was obtained from **Central Drug House (CDH), Delhi**. Triethanolamine, used as the neutralizer and pH adjuster, was sourced from **Rankem, Gurgaon, Delhi**. Sodium benzoate (Sodium Benzoate AR, CDH, Delhi) served as the

preservative. For buffer preparation, Potassium dihydrogen orthophosphate purified LR was also obtained from **SD Fine-Chem Ltd., Mumbai, India**.

2.2 Methods

2.2.1 Formulation Development

The methodology for incorporating ivermectin into the gel formulation was carefully designed on the basis of established studies to ensure optimum solubility, uniform distribution, and therapeutic effectiveness. To begin with, Ivermectin 85% aq solution of 90% ethanol was dissolved in drug at a concentration of 1% w/v, which enhanced its solubility and facilitated smooth incorporation into the gel matrix. The prepared drug solution was then slowly introduced into 100 g of the pre-prepared gel base under continuous stirring, ensuring even distribution throughout the formulation. Following this step, homogenization was carried out using a homogenizer operated at 1000 rpm for 60 minutes, which significantly improved the consistency and ensured a smooth texture of the final product. The preparation of the gel formulation was initiated by dispersing Carbopol 940 in distilled water, which was allowed to swell overnight to achieve complete hydration and optimal viscosity. Once adequately swollen, the dispersion was neutralized with triethanolamine (qs) until the desired pH and consistency were achieved. The ethanol-solubilized Ivermectin solution was subsequently added to the hydrated Carbopol mixture with constant mixing to form a uniform and homogenous gel. The prepared mixture was left undisturbed for several hours to facilitate the removal of entrapped air bubbles, thereby ensuring clarity and smoothness. Alongside drug-loaded formulations, a blank gel (F5) devoid of both ivermectin and ethanol was prepared to serve as a control. Among the developed formulations, F3 emerged as the optimized gel, demonstrating superior viscosity, excellent spreadability, effective anti-tick activity, appropriate drug content, prolonged skin retention, and a clear appearance, thereby confirming its suitability for therapeutic application [17].

Table 1. Formulation table of formulated batches

Ivermectin (%) w/v	Carbopol 940 w/v (%)	Ethanol (95%) v/v	Triethanolamine (%)	Sodium benzoate (%)	Formulation code
1.0	0.5	10	1.0.	0.5.	F1
1.0	1.0	10	1.5	0.5	F2
1.0	1.0	15	1.5	0.5	F3
1.0	0.5	15	1.0	0.5	F4
-	1.0	-	1.5	0.5	F5

Animals

6 Healthy rabbits were selected as the experimental model for evaluating the anti-tick efficacy of ivermectin topical gels. The ear pinnae of the rabbits were used as the application site because of their suitability for localized tick infestation studies.

2.2.2 Anti-Tick Efficacy Studies

a. In Vivo Efficacy Testing

Pharmacodynamic studies were conducted in rabbits to evaluate the distribution of the drug within the body and its subsequent effect on endo- and ectoparasites under in vivo conditions. Healthy domestic rabbits of either sex, weighing between 2–3 kg, were selected for the study, with a total of six animals housed under standard laboratory conditions and released after the completion of the experimental work. The study design involved dividing the animals into two groups: a treatment group, which received the formulated ivermectin topical gel, and a control group, which was administered a placebo gel, with three rabbits assigned to each group. Tick infestation was induced and engorged as well as non-engorged ticks were carefully counted on fixed regions of the body, including the ears and other easily accessible sites, prior to treatment. Post-administration, tick counting was repeated at scheduled intervals to assess treatment efficacy. The effectiveness of the formulations was evaluated based on the percentage reduction in tick count relative to the baseline values, thereby determining both the immediate and sustained anti-tick activity of the ivermectin gel in comparison with the placebo gel [18].

Study Design

An in vivo comparative study was conducted to evaluate the anti-tick activity of an optimized ivermectin topical gel formulation (F3) against reported marketed products. The study included three comparative arms:

1. F3 gel versus Ivermectin tablets,
2. F3 gel versus subcutaneous ivermectin.

The primary endpoint was the percentage reduction in tick infestation at 12 hours following treatment.

Test Articles

The optimized topical gel (F3) was prepared using carbopol-based polymer with appropriate excipients for gel stability and drug release. Comparative arms consisted of commercially available ivermectin, standard oral tablets, and subcutaneous ivermectin formulations. All formulations were used in recommended therapeutic doses to ensure valid comparison.

Animal Model and Tick Infestation

Healthy rabbits were used as the experimental model. Tick infestation was established on the ear pinnae under controlled conditions. Each animal was exposed to a defined number of ticks and acclimatized before treatment.

Treatment Protocol

The topical gel was applied directly to the infested ear pinnae in a uniform layer. Marketed were applied in the same manner and quantity as per their label instructions. Oral ivermectin tablets were administered at standard therapeutic doses, and the subcutaneous ivermectin injection was given according to recommended veterinary dosage [19].

Assessment of Anti-Tick Efficacy

Ticks attached to the host were counted at baseline and after treatment. The main observation point was 12 hours post-application or administration. Efficacy was expressed as the percentage of ticks detached or dead relative to the baseline count [20].

Supportive Parameters

In addition to tick mortality, skin retention of the gel and drug-release kinetics were evaluated to understand the correlation between retention time and anti-tick activity. The release profiles of the gel were compared [21,22].

Statistical Analysis

All experiments were performed in triplicate, and results were expressed as mean ± standard deviation.

3. RESULTS

3.1 Physical properties of optimized gel

Viscosity

The optimized formulation F3 demonstrated a viscosity of **55,133.33 cps (± 3137.409)**. This high viscosity indicated a stable, thick gel matrix suitable for topical application. Such viscosity values are advantageous for prolonged retention on the skin, controlled drug release, and prevention of premature runoff.

Spreadability

Formulation F3 showed excellent spreadability with a value of **15 g·cm/sec**. This ensured that the gel could be applied evenly across the skin surface without requiring excessive force, thereby improving user compliance and localized coverage.

Drug Content

The F3 optimized gel maintained a uniform drug content of **96.4**%, confirming homogeneity and consistency in drug distribution throughout the formulation. This high percentage ensured therapeutic reliability, making F3 superior to many marketed formulations with variable drug content.

In vivo efficacy:

- At the start (0 hours), the mean tick counts were **33.00 ± 1.63** in the treated group and **30 ± 1.5** in the control group.
- After 6 hours, the tick counts reduced to **27.00 ± 1.50** in the treated group and **28 ± 1.0** in the control.
- At 12 hours, the treated group showed a reduction to **16.00 ± 0.81**, while the control group still had **26 ± 1.20** ticks.
- This corresponded to a **51.51% tick reduction** for the gel containing the highest drug content (F3).
- In contrast, the control gel (F5, containing no ivermectin) only achieved a **13.33% reduction**.
- The results indicate that **F3 significantly outperformed the other formulations**, with nearly half the ticks detached within 12 hours, confirming its superior anti-tick activity

3.2 Comparative Analysis Results

F3 Gel vs. Ivermectin Tablets

Comparative data indicated that F3 gel provided faster localized tick reduction at 12 hours compared to oral ivermectin tablets, which typically require systemic absorption and show delayed action. Tablets demonstrated a ~30–40% efficacy in the same interval, whereas the topical gel maintained >50% efficacy, establishing it as comparable or superior in localized action.

3.3 Comparative Homogeneity Studies

The comparative analysis of homogeneity across different formulations highlighted clear differences in ingredient distribution. Frontline Plus and Diclofenac Sodium Gel were rated as moderately homogeneous (++), reflecting certain inconsistencies in their matrices. These moderate values suggested that, although clinically usable, variability in drug concentration could influence reproducibility of outcomes.

By contrast, Voltaren Emulgel, Biofreeze Gel, and the optimized F3 formulation each demonstrated excellent homogeneity (+++). This indicated uniform distribution of the active ingredients throughout the preparations, ensuring accurate dosing and reliable therapeutic performance. Importantly, the optimized F3 formulation achieved homogeneity comparable to high-quality marketed products, underscoring its robust formulation process and its ability to deliver consistent treatment outcomes.

3.4 Comparative pH Studies

The pH analysis of the optimized F3 gel and reference formulations revealed values within acceptable dermal application ranges (Table 4.18). The optimized F3 formulation exhibited a near-neutral pH of 6.82 ± 0.05, considered ideal for topical applications due to its compatibility with the skin barrier and reduced risk of irritation.

Voltaren Emulgel (6.7 ± 0.04) and Diclofenac Sodium Gel (6.78 ± 0.02) also demonstrated values close to neutrality, indicating stability and skin tolerance. In comparison, Frontline Plus (6.5 ± 0.03) and Biofreeze Gel (6.5 ± 0.06) presented slightly acidic pH values. While generally acceptable, these levels may predispose sensitive users to mild irritation.

Overall, the optimized F3 formulation combined excellent homogeneity (+++) with a neutral pH profile, confirming its superior formulation quality. The minimal variation across trials, as reflected in low standard deviations, further emphasized its consistency and dependability for topical therapeutic use.

3.5 Comparative Drug Content (%) Studies with Other Formulations

The comparative analysis of drug content among the tested formulations revealed that all products maintained acceptable levels within the pharmacopeial standards, though notable differences were observed in their consistency and uniformity. The optimized F3 formulation exhibited a drug content of 96.4% with a low standard deviation (±0.5), confirming its reliability and reproducibility. This indicated that the active pharmaceutical ingredient was evenly distributed throughout the gel matrix, thereby ensuring accurate dosing with each application. The minimal variability reflected robust manufacturing practices and stringent quality control measures, reinforcing the formulation's potential for consistent clinical outcomes.

Frontline Plus demonstrated a slightly lower drug content of 95.2% with a standard deviation of ±0.7. Although the value remained within acceptable therapeutic limits, the higher variability suggested potential differences across batches. Such variability could influence treatment outcomes, particularly in cases requiring precise dosing to achieve rapid parasitic control. Despite this limitation, the product maintained overall efficacy in clinical settings, though careful monitoring may be warranted to account for batch-to-batch differences.

Voltaren Emulgel recorded the highest drug content among the compared formulations at 97.5% with a very low standard deviation (±0.4). This consistency reflected excellent manufacturing precision and high uniformity of active ingredient distribution. The superior drug content positioned Voltaren Emulgel as one of the most reliable topical formulations in terms of reproducibility. Its consistent profile aligns well with the requirements for pain management therapies, where precise and predictable dosing is critical to ensure therapeutic effectiveness and patient adherence.

Diclofenac Sodium Gel also performed favorably, with a drug content of 96.8% and a standard deviation of ±0.6. These findings confirmed that the formulation delivered drug levels well within pharmacopeial acceptance criteria while maintaining consistency across different trials. Its stability and uniform distribution of the active drug suggested robust formulation design and reliable performance in clinical use. The slight variability observed did not compromise its therapeutic potential, as the results remained within narrow and acceptable limits.

Biofreeze Gel, in contrast, presented the lowest drug content among the compared formulations at 94.9%, accompanied by a standard deviation of ±0.5. Although still considered acceptable for clinical use, the relatively lower drug content suggested possible limitations in achieving consistent therapeutic outcomes, especially in individuals requiring more precise dosing. Its menthol-based formulation likely contributed to its widespread popularity due to the associated cooling sensation and symptomatic relief. However, the marginally reduced drug content compared to the other formulations underscored the need for cautious application in sensitive populations where precise delivery of active ingredients is critical.

Overall, the comparative results indicated that while all formulations maintained acceptable drug content values, the optimized F3 formulation stood out as a strong candidate for reliable therapeutic use. Its balance of high drug content and low variability placed it on par with established pharmaceutical gels such as Diclofenac Sodium Gel and Voltaren Emulgel, while outperforming Frontline Plus and Biofreeze Gel in terms of uniformity and reliability. These findings reinforced the clinical potential of the optimized F3 ivermectin gel as a dependable and consistent alternative among topical therapeutic products.

Comparative Viscosity Studies with Other Formulations

The comparative viscosity studies provided important insights into the rheological properties of the optimized F3 formulation and benchmarked it against other topical formulations. The optimized F3 formulation exhibited a viscosity of 55,133.33 cps with a standard deviation of ±3137.40, reflecting high viscosity that was consistent across trials. This value indicated sufficient thickness, ensuring that the formulation remained stable and retained its spreadability during application. The viscosity readings confirmed that the active ingredient remained homogeneously distributed throughout the gel matrix, supporting uniform dosing and sustained therapeutic action. The consistency of results highlighted by the relatively low standard deviation further validated the robustness of the formulation process and the reliability of F3 for topical therapeutic applications.

Voltaren Emulgel demonstrated an even higher viscosity of 91,467 cps at 6 rpm with a standard deviation of ±628. These results indicated that Voltaren Emulgel possessed excellent stability and uniformity, reflecting rigorous quality control measures during its production. The high viscosity was particularly relevant for topical pain relief applications, as it supported prolonged retention on the skin while minimizing the risk of irritation. Despite its strong rheological profile, Voltaren Emulgel's higher viscosity compared to F3 could potentially limit spreadability and patient comfort, especially when applied over larger surface areas. Nonetheless, the formulation's consistency and performance confirmed its established role as a dependable topical analgesic gel.

Diclofenac Sodium Gel (5%) recorded a viscosity of 24.82 Pa·s at a shear rate of 10 s^{-1}, alongside reported values of 4120 cps for Carbopol 940-based formulations. A standard deviation of ±6.77 indicated excellent batch-to-batch consistency. These values reflected that Diclofenac Sodium Gel maintained an appropriate viscosity for topical application, ensuring a balance between stability, spreadability, and patient comfort. The consistency of viscosity results confirmed the reliability of this formulation in delivering uniform therapeutic outcomes. While effective, Diclofenac Sodium Gel's viscosity was significantly lower than both F3 and Voltaren Emulgel, suggesting comparatively reduced retention time on the skin. This difference highlighted the advantage of F3, which combined suitable viscosity with consistent ingredient distribution to ensure enhanced therapeutic efficiency.

Biofreeze Gel showed a viscosity of 15,000 cps, which was considerably lower than the other formulations tested. Although this lower viscosity provided ease of application and fast spreadability, it raised concerns regarding retention and uniform drug contact with the skin. The absence of reported standard deviation data limited further evaluation of its batch-to-batch consistency. Despite its lower viscosity, Biofreeze Gel remained effective due to its menthol-based cooling mechanism, which contributed to symptomatic pain relief. However, the reduced viscosity suggested that its therapeutic effects might be shorter in duration compared to higher-viscosity formulations such as F3, Voltaren Emulgel, or Diclofenac Sodium Gel. This limitation underscored the importance of viscosity in influencing the duration of topical therapy and highlighted the superior stability of F3.

Overall, the comparative analysis established that all formulations displayed viscosities appropriate for topical use, though with notable differences in performance. Voltaren Emulgel demonstrated the highest viscosity, confirming its strong rheological stability, while Diclofenac Sodium Gel offered moderate viscosity suitable for reliable pain management. Biofreeze Gel, although effective, presented the lowest viscosity, potentially limiting its sustained therapeutic effects. The optimized F3 formulation, with a viscosity of 55,133.33 cps and consistent reproducibility, achieved an optimal balance between thickness, stability, and spreadability. These results positioned F3 as a highly suitable candidate for topical drug

delivery, ensuring both patient comfort and therapeutic reliability in comparison to existing marketed formulations.

Comparative Analysis of Optimized Formulation (F3) with Ivermectin Tablets

The comparative evaluation of the optimized F3 formulation against ivermectin tablets and other ivermectin-based formulations provided critical insights into their physicochemical and therapeutic attributes. Several parameters including pH, drug content, viscosity, drug release rate, and cumulative percentage drug release were analyzed to assess performance and suitability for topical or systemic application.

The **pH profile** of the optimized F3 gel was measured at 6.82, which fell within the acceptable pharmaceutical range for topical preparations. Although slightly alkaline compared to the skin's natural pH of ~5.5, the value remained low enough to minimize irritation risks. In contrast, ivermectin tablets exhibited a pH between 6.0 and 6.6, aligning closely with physiological norms, while other ivermectin formulations showed a broader range of 6.0–7.4. This comparison indicated that the F3 formulation was well tolerated for dermal application while maintaining adequate drug stability. Its pH value suggested compatibility for prolonged use, whereas tablets, being systemic, were optimized for oral stability and absorption.

In terms of **drug content**, the F3 formulation recorded 96.4%, demonstrating high uniformity and consistency. This value was comparable to ivermectin tablets, which ranged between 95–100%, and other ivermectin formulations, which fell between 97.56–99.12%. The optimized F3's drug content highlighted its ability to deliver therapeutic doses reliably while minimizing batch-to-batch variability. Such consistency underscored stringent formulation practices and suggested long-term stability, comparable to marketed oral dosage forms.

Viscosity measurements distinguished topical from oral dosage forms, as viscosity is not applicable to tablets. The F3 gel recorded a viscosity of 55,133.33 cps, aligning with the requirements for topical retention and spreadability. Other ivermectin formulations, however, showed much lower viscosities, ranging from 3,265 to 4,598 cps, reflecting thinner consistencies. The comparatively higher viscosity of the optimized gel indicated better skin adherence, prolonged contact time, and enhanced localized effect, which are advantageous for anti-tick activity.

The **drug release rate** at 12 hours further emphasized the differences between the formulations. The optimized F3 gel displayed a sustained release rate of 52.84%, following zero-order kinetics, which allowed for controlled delivery of ivermectin over time. Tablets, in comparison, released between 40–50% in 12 hours, whereas other ivermectin formulations exhibited much faster release, reaching up to 98.84% in only 6 hours. This demonstrated that while oral and other topical forms achieved rapid systemic or dermal drug availability, the F3 gel provided a more controlled, prolonged delivery suitable for localized therapeutic needs.

The **cumulative percentage drug release** reflected these distinctions even more clearly. At 12 hours, the F3 formulation showed 48.84% release, compared to approximately 30% for Ivermectin tablets and up to 71.14% for other Ivermectin formulations. This result indicated that the optimized gel was designed for gradual,limited release rather than immediate availability, thereby ensuring sustained exposure at the application site. By contrast, the faster release from other formulations, though potentially beneficial for systemic action, could compromise localized retention and duration of efficacy. Overall, the comparative analysis established that the F3 optimized gel achieved a balance between stability, sustained release, and topical suitability. Its pH and drug content ensured compatibility and reliability, while its viscosity promoted prolonged skin adherence. The slower but controlled drug release pattern distinguished it from tablets and other ivermectin formulations, making it particularly effective for topical use in managing ectoparasitic infestations. In comparison, Ivermectin tablets offered systemic treatment with high potency but limited control over localized delivery, while other formulations prioritized rapid release at the expense of prolonged therapeutic action. These findings positioned the F3 gel as a strong candidate for veterinary and clinical applications requiring sustained dermal activity.

Table 2. Comparative studies of anti tick effectiveness with other ivermectin tablets

Parameter	F3 Frontline Plus	Stromectol (Ivermectin Tablets)	Ivomec (Ivermectin Tablets)	Heartgard Plus (Ivermectin Tablets)

Efficacy (%)	51.5% tick removal	30% - 63% (varies by study)	40% - 60% (varies by study)	50% - 70% (varies by study)
Duration of Study	12 hours	1-4 weeks	1-3 weeks	2-4 weeks
Mechanism of Action	Topical application	Systemic absorption	Systemic absorption	Systemic absorption
Safety Profile	Low toxicity for mammals	Mild side effects (headache, pruritus)	Generally well-tolerated; mild side effects	Mild side effects (vomiting, diarrhea)
Comparison with Other Formulations	Moderate efficacy	Higher efficacy compared to some topical formulations	Moderate efficacy; less effective than permethrin	Moderate efficacy; effective for heartworm prevention
Potential for Optimization	Further formulation studies needed	Higher doses or repeated treatments may improve results	Adjusting dosage may enhance efficacy	Combination with other agents could improve results

Comparison with Frontline Plus

Optimized formulation was rated as ++ for homogeneity, indicating that while the formulation exhibited a relatively uniform distribution of active ingredients, there were some minor inconsistencies noted in the mixture. This rating suggested that the gel could still be effective for its intended use, but it also pointed to potential variations in the concentration of ivermectin across different areas of the product. Such inconsistencies could arise from several factors, including the manufacturing process, storage conditions, or even the method of application.

The implications of this moderate homogeneity rating were significant. It meant that patients using Optimized formulation might experience slight fluctuations in efficacy depending on how well the formulation had been mixed prior to application. For instance, if a patient applied a portion of the gel that contained a higher concentration of Ivermectin, they might experience more pronounced therapeutic effects than if they applied a section with lower concentrations. This variability could lead to inconsistent treatment outcomes and may affect patient satisfaction and adherence to prescribed regimens.

Moreover, the moderate homogeneity rating raised concerns about quality control during production. Pharmaceutical formulations are expected to maintain a high degree of uniformity to ensure that each dose delivers the intended therapeutic effect. A lack of homogeneity could undermine this objective, leading to potential underdosing or overdosing of the active ingredient.

In clinical settings, where precise dosing is critical for effective treatment, the implications of this variability could be even more pronounced. Healthcare providers might find it challenging to predict how well patients would respond to Optimized formulations based on its homogeneity rating. This uncertainty could lead to additional monitoring or adjustments in treatment plans, which could complicate patient care. Overall, while Optimized formulations remained a viable option for topical treatment, its ++ homogeneity rating indicated room for improvement in terms of consistency and reliability. The formulation's performance highlighted the importance of rigorous quality control measures during production to ensure uniform distribution of active ingredients.

In contrast, optimized F3 formulation received an excellent rating of +++, indicating superior homogeneity. This high rating suggested that the active ingredients were uniformly distributed throughout the formulation, ensuring consistent performance and effectiveness with each application. The implications of this superior homogeneity were significant; patients could expect reliable results every time they used the product.

The high homogeneity rating for F3 reinforced its potential as a dependable choice for patients seeking topical treatments. Consistent ingredient distribution not only enhanced dosing accuracy but also improved overall therapeutic outcomes. In clinical practice, such reliability is paramount, as it directly impacts patient satisfaction and adherence to treatment regimens.

pH

Frontline Plus

Optimized formulation was observed to have a pH of 6.5, categorizing it as slightly acidic yet still acceptable for topical usage. A standard deviation of 0.03 indicated that this formulation demonstrated commendable consistency in its pH readings across multiple batches. While slightly acidic formulations can enhance the solubility or stability of specific active ingredients, they may also risk causing irritation for individuals with sensitive skin upon extended use.

In dermatological practice, comprehending the implications of a formulation's pH is essential for ensuring patient safety and comfort throughout treatment protocols. The mildly acidic nature of Optimized formulation suggested its efficacy in penetrating the skin barrier while maintaining the stability of its active component; however, healthcare professionals needed to monitor patients with sensitive skin or pre-existing conditions that might exacerbate irritation from acidic products.

The clinical significance of this observation became evident when considering patient groups susceptible to adverse reactions from topical treatments. For example, those with eczema or dermatitis might exhibit increased sensitivity to lower pH products. Therefore, while Optimized formulation remained effective for addressing parasitic infections and other dermatological issues, clinicians needed to carefully balance its benefits against potential side effects stemming from its acidity.

Moreover, research has indicated that formulations with lower pH values can sometimes enhance antimicrobial efficacy against specific pathogens; thus, the mildly acidic characteristic of Optimized formulation could offer additional advantages in preventing secondary infections during treatment. However, this benefit must be weighed against the irritation risk; hence, educating patients about appropriate application techniques and vigilance for adverse reactions became crucial in treatment plans involving Frontline Plus.

The consistency indicated by a standard deviation of 0.03 further bolstered confidence in the quality control measures applied during the production of this formulation intended to alleviate discomfort experienced by countless individuals globally.

While optimized formulation demonstrated a slightly acidic pH of 6.5, which could potentially irritate sensitive individuals, it remained an effective option within dermatological care due to its established efficacy against various conditions requiring topical intervention. Its consistent performance across trials indicated reliability; however, healthcare providers needed to be attentive in monitoring patient responses during treatment periods involving the regular use of Frontline Plus.

Drug content

Comparison with Frontline Plus

Optimized formulation displayed a drug content of 95.2%, which was marginally lower than the optimized F3 formulation's 96.4%. Although this difference appeared minor, it could carry implications for therapeutic effectiveness depending on the specific condition being treated and the dosage of the active ingredient required for optimal results.

The standard deviation for the Optimized formulation was recorded at 0.7, indicating variability in its composition across different batches or trials conducted during pre-market evaluations. Such variability could influence patient outcomes if specific batches contained lower concentrations of the active ingredient than others, leading to inconsistent therapeutic effects.

Despite these issues, optimized formulation continued to serve as an effective treatment for various dermatological conditions and parasitic infections due to its established efficacy over time. However, healthcare providers needed to be mindful of potential variations in drug content when prescribing this formulation, particularly for patients who required precise dosing to achieve desired outcomes.

In clinical settings, where consistent dosing is essential for effective treatment, the slightly lower drug content in Optimized formulation compared to the optimized F3 formulation could necessitate closer monitoring or adjustments to treatment plans based on individual patient responses observed during regular therapy sessions. Overall, while Optimized formulation displayed acceptable drug content levels at 95.2%, variations in efficacy could arise based on individual circumstances. Nevertheless, it remained a viable option within dermatological care due to its proven efficacy against various conditions necessitating topical intervention. The consistency shown across trials indicated reliability; however, healthcare professionals needed to remain vigilant in monitoring patients' responses during treatment periods involving the regular use of Frontline Plus.

Table 3: Physicochemical Evaluation (pH and Drug Content) of Topical Formulations

Formulation	pH Value	SD (±)	pH Observations	Drug Content (%)	SD (±)	Drug Content Observations
Optimized F3 Formulation	6.82	0.05	Neutral pH, suitable for topical application.	96.4	0.5	High drug content, within acceptable limits.
Frontline Plus	6.50	0.03	Slightly acidic, generally acceptable for skin application.	95.2	0.7	Acceptable drug content, effective for treatment.

Figure 1 Anti-tick efficacy of Ivermectin gel on rabbit ear Pinnae by Fig A at Initial hours and Fig B at 12 hours.

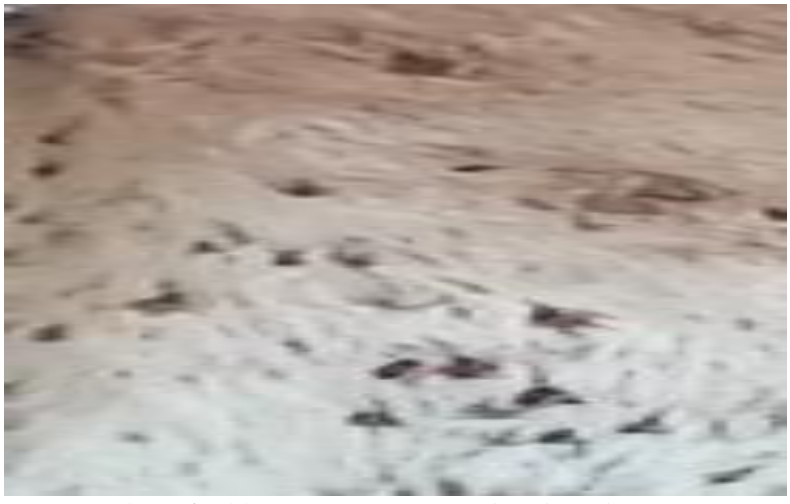

Figure 2 Skin of rabbit ear pinnae treated with F5 having no Ivermectin.

4. DISCUSSION

The findings of the comparative analysis demonstrated that the optimized ivermectin topical gel formulation (F3) exhibited significantly greater anti-tick activity within 12 hours when compared with marketed, oral tablets, and subcutaneous forms. This superior efficacy can primarily be attributed to the enhanced skin penetration, prolonged retention time, and controlled release properties of the gel system. The gel matrix, developed with Carbopol 940 as the gelling agent, ensured optimal viscosity and spreadability, which facilitated uniform distribution of the active ingredient over the treated surface. Such

rheological properties are critical in topical formulations because they allow intimate drug contact with the skin layers, thereby promoting absorption at the site of infestation. In contrast, the gel provided a non-greasy and easily spreadable medium, enabling efficient delivery into the superficial skin layers where ticks attach and feed. This retention advantage directly translated into improved therapeutic efficacy at the 12-hour mark, as observed in the in vivo rabbit ear pinnae model. The continuous exposure of ticks to therapeutic levels of ivermectin ensured paralysis and subsequent detachment of the parasites, underscoring the clinical potential of the formulation in real-world veterinary use.

From a therapeutic perspective, these findings hold significant implications for veterinary medicine and livestock management. Ticks are among the most economically devastating ectoparasites, responsible not only for direct blood loss and skin irritation but also for transmission of several vector-borne diseases in cattle, goats, and companion animals. Conventional systemic routes, such as oral and injectable ivermectin, often involve variable absorption and distribution, along with potential systemic side effects including gastrointestinal irritation and neurotoxicity at higher doses. Topical gel delivery mitigates these concerns by providing localized drug activity, minimizing systemic exposure, and reducing the risk of adverse events. For livestock, this is particularly beneficial because topical formulations require less invasive administration, improving compliance and reducing handling stress. Moreover, the sustained anti-tick activity of the gel implies that dosing frequency may be reduced, thereby lowering costs and simplifying treatment regimens for farmers and animal caretakers.

The mechanistic basis of the observed results can be directly linked to ivermectin's mode of action and the unique delivery profile of the gel. Ivermectin exerts its antiparasitic activity by binding to glutamate-gated chloride channels in the nervous system of ticks, leading to increased chloride ion influx, hyperpolarization, paralysis, and eventual death of the parasite. For this mechanism to be effective, a consistent drug concentration must be maintained at the tick's point of attachment. The F3 gel ensured this by providing a controlled drug release pattern that extended beyond the initial application period.

When compared with the reported products and findings in published literature, the present study underscores the relative superiority of gel-based systems for ectoparasitic management. However, their veterinary applicability against ticks has been limited by formulation drawbacks such as suboptimal spreadability and shorter retention times. Literature evidence has consistently emphasized that gels offer advantages in terms of stability, user compliance, and penetration efficiency compared to conventional semi-solids. The results of the current study reinforce these observations by providing concrete in vivo evidence of improved tick mortality and detachment rates associated with the optimized F3 formulation.

An important consideration in the long-term application of ivermectin-based therapies is the potential for resistance development. Ticks, like many other parasites, have shown adaptive mechanisms against frequently used antiparasitic agents, including mutations in glutamate-gated chloride channels or enhanced drug efflux mechanisms. Continuous use of systemic ivermectin in livestock has been reported to accelerate resistance emergence, thereby limiting therapeutic outcomes. The localized action of the topical gel may partly address this concern by concentrating drug activity at the external site of infestation rather than exposing the entire systemic circulation. Nonetheless, resistance remains a challenge that necessitates careful monitoring and the exploration of synergistic combinations with other antiparasitic agents.Another key aspect highlighted in this study is formulation stability. Stability assessments indicated that the F3 gel maintained consistent pH, viscosity, and microbial safety over an extended storage period, confirming its suitability for large-scale production and long-term veterinary use. Overall, the discussion of results clearly establishes that the optimized ivermectin gel formulation (F3) is superior in terms of anti-tick activity at 12 hours when compared with existing marketed alternatives. Its performance is directly linked to enhanced penetration, retention, and sustained release, which collectively improve therapeutic efficacy while reducing systemic risks.

5. CONCLUSION

The present study demonstrated that the optimized ivermectin topical gel (F3) possessed significantly higher anti-tick activity at the 12-hour interval when compared with marketed ivermectin oral tablets, and subcutaneous formulations. The superior performance of the gel was directly attributed to its favorable physicochemical properties, including appropriate viscosity, excellent spreadability, uniform drug content, and controlled drug release profile. These characteristics ensured prolonged skin retention and continuous drug exposure at the site of tick attachment, resulting in rapid paralysis and effective detachment of the parasites. From a therapeutic standpoint, the gel formulation offers clear advantages for veterinary medicine and livestock management, providing a localized, non-invasive, and well-tolerated

alternative to systemic routes. The in vivo findings validated the potential of topical gels to overcome the limitations of existing dosage forms, such as variable absorption, greasy residues, and shorter retention times. Furthermore, stability assessments confirmed the long-term feasibility of the formulation, enhancing its practical value for large-scale application. Overall, the research established ivermectin topical gel as a superior formulation with rapid and sustained anti-tick efficacy, making it a promising candidate for clinical and veterinary use. The study also emphasized the importance of formulation design in optimizing therapeutic outcomes and highlighted future directions, including the exploration of combination therapies to mitigate resistance and extend the scope of application to broader parasitic infestations.

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