RESEARCH ARTICLE

Development and *In-Vitro* Characterization of Gentamycin Sulphate Nanoemulgel for Ophthalmic Applications

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ABSTRACT

This work investigates the optimization of nanoemulgel by analyzing their viscosity and spreadability properties. The findings demonstrate a negative association between the concentration of the polymer and the spreadability, while the viscosity rises with an increase in the polymer content. As an example, formulation F1 exhibited a viscosity of 62,035 ± 10 mPa•S and a notable spreadability value of 38 ± 1. In contrast, formulations F3 and F4, which had viscosities of 92,345 ± 9 and 97,654 ± 10 mPa•S, respectively, showed insufficient capacity to spread. The improved formulation, F2, had an ideal viscosity of 66,098 ± 6 mPa•S and outstanding spreadability of 37 ± 1. Carbopol 974 and other gelling agents have a substantial impact on the physical properties of nanoemulgels, such as their texture, ability to stick to surfaces, ability to expand, and how they release drugs. The compatibility between the essential oils and the formulation was confirmed using FTIR analysis, which maintained the individual peaks of the components without any interactions.

The drug content study showed that cinnamon oil had a high incorporation efficiency of 95.20 ± 1.5%, whereas olive oil had an incorporation efficiency of 93.32 ± 2.6%. The entrapment efficiencies were remarkable, averaging 96.23% for cinnamaldehyde and 97.78% for olive oil. In in vitro release tests, Franz diffusion cells demonstrated sustained release characteristics for both oils over a 24-hour period. The nanoemulgel's mucoadhesive strength, quantified at 41.3 N/cm², ensures prolonged adherence to mucosal surfaces, facilitating the efficient administration of medications. The stability trials done over a three-month period at varied temperatures and humidity levels proved the formulation's durability. These experiments did not lead to any significant alterations in the drug release patterns or physical attributes. These results highlight the capability of nanoemulgel that have been tuned for the administration of topical medications.

Keywords: nanoemulgel, Gentamycin Sulphate, *In-Vitro* Characterization, Ophthalmic Applications.

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INTRODUCTION

Nanotechnology offers a potential approach for drug delivery and targeting, with desired functional and beneficial characteristics. It allows for precise targeting of particular sites of action with exceptional therapeutic effectiveness while minimizing side responses.[1] Nanoemulsion (NEs) have significant attributes such as a substantial surface area, efficient trapping of hydrophobic medicines, strong kinetic stability, capacity to solubilize substances, high permeability through the skin, controlled release, and the potential to target specific areas as a drug carrier.[2]. These products have been specifically created to make it easier to apply various active chemicals, such as tamoxifen, curcumin, mupirocin, and naproxen, to the affected area. However, their effectiveness may be limited due to their low thickness, inadequate capacity to stay on the skin's surface, and limited ability to spread. To improve the rheological behaviour and physicochemical qualities of the formulation, it is feasible to include the nanoemulsion in a hydrogel substrate.[3] Emulsions are complex dispersion systems that consist of small droplets scattered throughout a liquid that is not being stirred. Droplets ranging in size from 1 to 100 µm characterised nanoemulsion, which are alternatively called conventional emulsions or colloids.[4] Classification of various emulsion kinds is based on the size of the droplets. Because they are unstable in water, these droplets often float. One and a half parts in the medium is all that's needed for their rapid absorption by surface solid particles and easy spreading.[5] Microemulsions, on the other hand, include a liquid system with droplets ranging in size from 10 to 100 nm. The size and physical characteristics of these droplets are more consistent. As we go closer to the nanoscale, we find that nanoemulsion have a denser texture than their larger Microemulsions because their droplet sizes are 20 to 200 nm.[6] Nanoemulsion gel's discovery was a watershed moment in the history of hydrogenation using nanoemulsion. Mixing nanoemulsion technology with a hydrogel matrix yields a product with exceptional skin penetrating capabilities. To improve the beauty and medicinal uses of conventional emulsions, this novel method integrates the accuracy of nano-sized droplets with the malleability of a gel matrix.[7] This nanoemulsion gel is ideal for delivering a variety of active substances to the skin because of its well-balanced composition, which improves skin penetration. By eliminating the problems with conventional emulsions, this new formulation improves stability, controlled release, and bioavailability.

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Utilization of nanoemulsion gel in the cosmetics and pharmaceutical sectors exemplifies the ongoing pursuit of efficient delivery technologies that meet the complex demands of modern formulations.[8] The development of pharmaceutical and cosmetic formulations has made great strides with the move from nanoemulsion to nanoemulgel. To make the change, a hybrid structure that combines nanotechnology's advantages with an emulgel system's adaptability must be developed. By improving the formulation's delivery, stability, and application properties, this modification provides a cutting-edge solution to the problems caused by conventional delivery techniques. Oil droplets distributed in water on a nanometer scale form nanoemulsion.[9]

Their capacity to make hydrophobic compounds more soluble and increase their bioavailability has made them famous. Due to its remarkable improvement in medication and active component transportation, nanoemulsion has

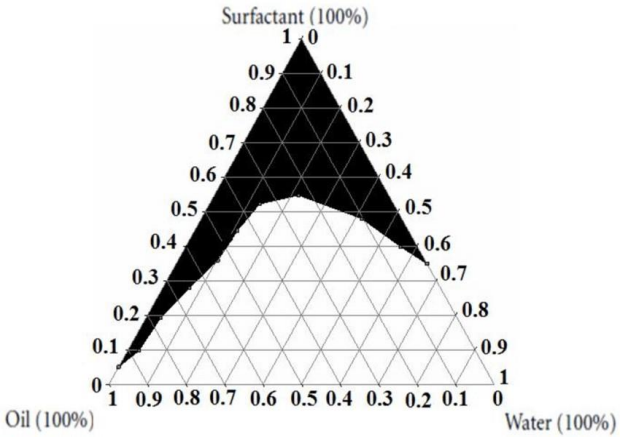

Figure 1: Pseudo-ternary phase diagram

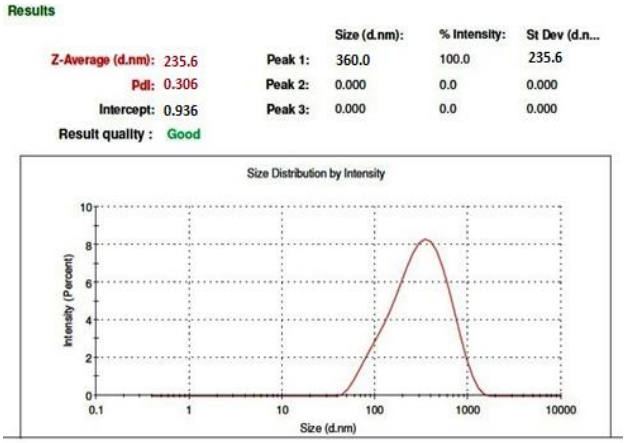

Figure 2: Particle size of nanoemulsion

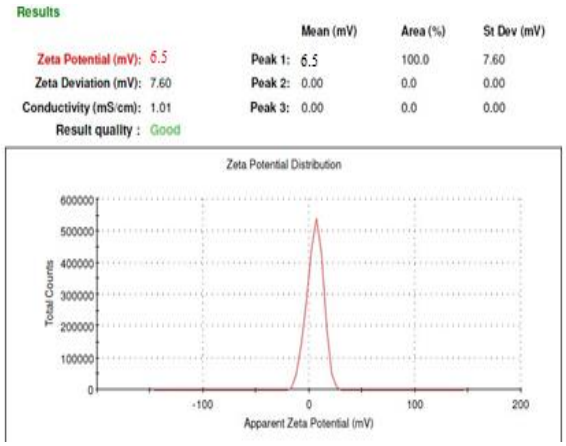

Figure 3: Zeta potential of nanoemulsion

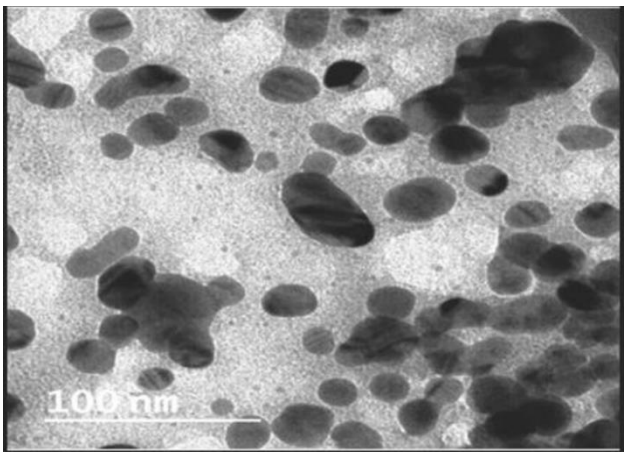

Figure 4: Assessment of Transmission electron microscopy (TEM) of nanoemulsion.

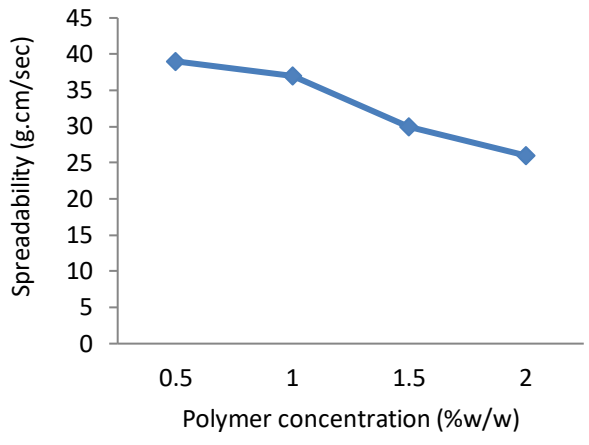

Figure 5: Spreadibility of nanoemulgel

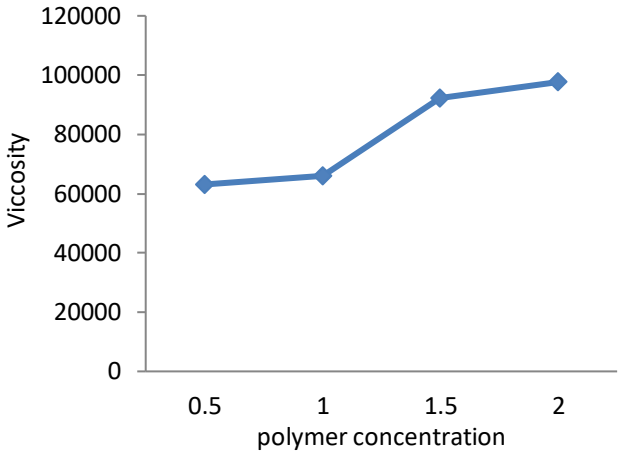

Figure 6: viscosity of nanoemulgel.

become indispensable in the cosmetics and pharmaceutical industries. Improved efficacy and pinpoint accuracy have resulted from this. When it comes to targeted or surface-level medication delivery, for example, nanoemulsion may not be the best choice due to their intrinsic fluidity.[10] The shift from nanoemulsion to nanoemulgel involves integrating nanosized emulsion molecules into a gel matrix, resulting in a gel-like structure. This approach surpasses the limitations of traditional nanoemulsion. The resulting nanoemulgel combines the high solubility of nanoemulsion with the long-lasting properties of gels. This approach produces a formulation that maximizes the beneficial characteristics of both systems, resulting in superior application properties, longer product lifespan, and greater stability. Consequently, the nanoemulgel demonstrates enhanced efficacy and stability for a wide range of medicinal and cosmetic uses.[11] Thorough selection of components, such as gelling agents, co-surfactants, and surfactants, is necessary throughout the formulation process to provide optimal stability and rheological properties. The resulting nanoemulgel may be customized to include a wide variety of active compounds, such as vitamins, antioxidants, prescription medicines, and other bioactive molecules.[12] Nanoemulgel are very advantageous for targeted treatments or transdermal drug delivery due to their enhanced bioavailability, regulated release, and improved drug solubility in pharmaceutical contexts. Nanoemulgel in the cosmetics industry facilitate the efficient dispersion of active hygiene components, resulting in enhanced durability and better absorption. The transition from nanoemulsion to nanoemulgel exemplifies the dynamic nature of formulation science, showcasing the convergence of innovation and practical implementation. This versatile hybrid delivery method has the potential to be used in many applications such as targeted medicine distribution, personalized therapy, and the development of advanced skincare formulae. This represents a notable progress in the ongoing evolution of modern medical and cosmetic technologies.[13]

Nanoemulgel is a formulation that combines emulgel systems with nanotechnology, resulting in a distinctive product with both medical and cosmetic properties. This innovative hybrid structure combines the advantageous properties of nanosized emulsion droplets with the flexibility of a gel matrix, resulting in a sophisticated delivery method that effectively resolves many limitations associated with traditional formulations. Nanoemulgel is a state-of-the-art breakthrough in the field of formulation science, with significant potential to revolutionize cosmetics and drug delivery.[14] The primary objective of nanoemulgel is to address significant challenges associated with the delivery of pharmaceutical or cosmetic compounds, particularly those that have limited bioavailability and solubility. An effective strategy to enhance the uptake of hydrophobic and poorly soluble compounds involves incorporating nanoemulsion, which

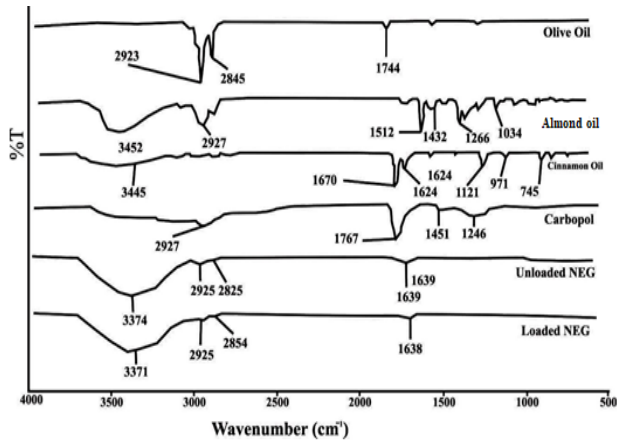

Figure 7: FTIR spectra of nanoemulgel

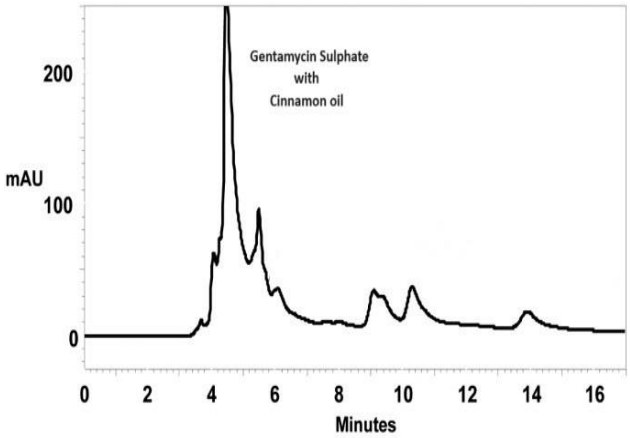

Figure 8: HPLC Spectrum of Gentamycin Sulphate Nanoemulgel with Cinnamon Oil

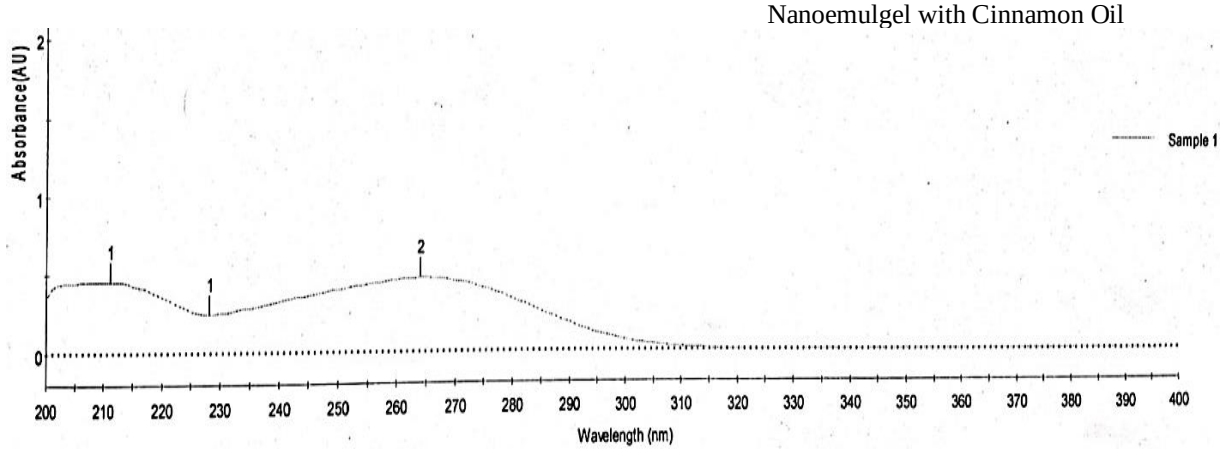

Figure 9: UV Spectrum of Gentamycin Sulphate Nanoemulgel with Cinnamon Oil

Table 1: Ingredients use in formation of nanoemulgel.

Ingredients (% w/w)	F1	F2	F3	F4
CP 974 (%)	1	1.5	2	2.5
Essential oil	0.5	0.5	0.5	0.5
Methyl paraben	0.02	0.02	0.02	0.02
Propyl Paraben	0	0	0	0
Triethanolamine	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.

Table 2: Assessment of particle size, zeta potintial and PDI of nanoemulsion.

Formulation code	Particle size	Zeta potintial	PDI
F1	153.4±0.5	-19.56±2	0.312±0.056
F2	235.6 ± 0.7	-18±4	0.270±0.014
F3	275.1±1.5	-13.0±6	0.280±0.076
F4	320.6±1.4	-11±7	0.080±0.0675

refers to emulsion droplets that are very small in size. This improves the solubility of medicines, facilitating its passage through biological barriers such as mucosal membranes or the skin.[15] The merging of nanoemulsion into a gel matrix represents the combining of nanosized droplets' exceptional solublization and encapsulating properties with the stability of gels. Due to its unique physicochemical properties, the resulting nanoemulgel offers many advantages, including prolonged stability, ease of application, and the potential to deliver cosmetic or medicinal ingredients in a precise and controlled manner.[16] The cosmetics industry has acknowledged the significant potential of nanoemulgel to bring about dramatic changes. These formulations improve the penetration of active compounds such as vitamins, antioxidants, and anti-aging agents into the skin by enclosing them in nanosized droplets. This leads to more favorable cosmetic outcomes. Nanoemulgel are very desirable in cosmetic formulations because of their excellent spreadability and non-greasy characteristics. It is crucial to carefully choose gelling agents, co-surfactants, and surfactants in order to create nanoemulgel that possess ideal rheological qualities and stability. The intricate design of the encapsulation system guarantees accurate regulation of the release kinetics of drugs, resulting in prolonged and consistent therapeutic benefits. The area of nanoemulgel is now gaining speed due to ongoing research, providing novel prospects for the advancement of personalized drug delivery, focused therapies, and improved hygiene products. The combination of nanotechnology with emulgel systems in nanoemulgel signifies a significant change in formulation science, offering the possibility of improving medicinal outcomes and aesthetic benefits in many applications.[17] Gentamicin, a potent aminoglycoside antibiotic, was first extracted from Micromonospora purpurea in 1963. It is often recommended due to its low cost, easy availability, and wide range of medicinal uses. Gentamicin is a very beneficial therapy choice for many bacterial infections, especially those caused by Pseudomonas aeruginosa, since it has exceptional efficacy against severe gram-negative infections. [18] It is crucial to highlight that when combined with betalactam antibiotics, it demonstrates a synergistic impact that streamlines the treatment of complicated diseases, minimizes negative effects, and simplifies dose modifications. The possibility of experiencing serious harmful consequences, such as kidney damage and hearing loss, may limit the utilization of Gentamycin, despite its track record of effectiveness in certain therapy scenarios.[19] Micromonospora purpurea, actinomycetes, produces gentamicin sulphate, which is a water-soluble antibiotic belonging to the aminoglycoside class. As an aminoglycoside antibiotic, it is effective in preventing or treating a wide range of bacterial infections. Gentamicin suppresses the growth and replication of bacteria by blocking bacterial protein synthesis. This technique is efficacious in treating infections caused by a diverse range of gram-negative and some gram-positive bacteria.[20] Topical Gentamycin, an antibiotic, is often used to treat bacterial skin infections, including impetigo and folliculitis. Additionally, it is used to address infections that result from dermatological conditions including psoriasis or dermatitis, as well as contaminated scars, ulcers, or wounds. Topical Gentamycin may not be suitable for treating any of the stated illnesses, since its effectiveness depends on the particular bacteria responsible for the sickness. Due to bacterial resistance, the efficacy of topical Gentamycin may be reduced in some geographical areas. [21]

MATERIASL AND METHOD

Prior to developing a dosage form, it is crucial to carry out Preformulation research on the drug and its excipients. This step is crucial because it sets the groundwork for the creation of formulations that have the necessary stability, drug release characteristics, and other important properties. The purpose of Preformulation studies is to analyses the substance sample and determines its identity by examining its particular physicochemical features. These studies include analyzing the physical and chemical properties of solids, confirming their identity, and assessing how well the medicine interacts with the other substances in the formulation.[22]

Table 3: Assessment of colour, consistency, Homogeneity, pH, viscosity and spreadability of nanoemulgel.

Formulation code	Parameters					
	Colour	Consistency	Homogeneity	pH	Viscosity	Spreadability
F1	White	Good	Excellent	6.7	63087±11	39±2
F2	White	Good	Excellent	6.8	66098±6	37±1
F3	White	Good	Excellent	6.7	92345±9	30±3
F4	White	Good	Excellent	6.9	97654±10	26±3

Table 4: drug content examination of nanoemulgel

Formulation	Ingredients	Drug content release profile (%)
Nanoemulgel	Cinnamon oil	95.20±1.5%
Nanoemulgel	Olive oil	93.32±2.6%

Table 5: Entrapment Efficiency of nanoemulgel

Formulation	Ingredients	Entrapment Efficiency (%)
Nanoemulgel	Cinnamon oil	96.23%
Nanoemulgel	Olive oil	97.78%.

Optimization of nanoemulsion

A pseudo-ternary phase diagram is created to analyses the phase behaviour of the different components in the formulation. At summary, a blend (Smix) was created by blending 100 milliliters of excipient (Tween 80) and co-excipients (Span 80) at a ratio of 4:1. Smix was hired to create sixteen unique oil blends, all of which consisted only of olive oil. The volume ratios of these combinations varied from 1:8 to 8:1, including ratios such as 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, and 8:1. A solution containing a blend of olive oil and Smix was subjected to titration using deionized water. An ocular examination was conducted to record the outcomes after the addition of 5% of the aqueous phase to the oily and Smix combination. The phase diagram used axes to indicate the continuous phase, oil phase, and Smix, enabling the plotting of the respective percentages of water, oil, and Smix. A selection of formulations was made from each phase diagram, taking into account parameters such as the minimum surfactant concentration and the ease of dissolving the 3% essential oil concentration. The oil concentration was calculated using the phase diagram, which offered the possibilities of 5%, 10%, 15%, and 20%.[23]

Formulation of nanoemulsion

The nanoemulsion were prepared by blending a mixture comprising 3% w/w essential oil with different concentrations of olive oil (5%, 10%, 15%, and 20%) using a vortex mixer and following the correct Smix ratios. After the essential oil and olive oil were combined, water was added to the mixture. The mixture was then stirred vigorously to form a stable emulsion. This process ensured the production of nanoemulsion with different oil concentrations for further analysis and formulation.[24]

Globule size distribution

The glob dimension of the nanoemulsion preparation was determined using a Zetasizer 1000 HS instrument (Malvern Instrument, Worcestershire, UK). The light scattering was recorded at a temperature of 25◦C and a trickle angle of 90◦.[25]

Stability of nanoemulsion

Kinetic stability

The centrifugation method was used to evaluate the kinetic stability of the formulation. The mixture is imperiled to centrifugation at a temperature of 25 ◦C aimed at a period of fifteen minutes, with rotation speeds of 1000, 2000, and 3000 revolutions per minute (rpms). In order to assess the kinetic stability of the formulation, we observed the visual characteristics of the emulsion and recorded any phase separation both earlier and later the centrifugation process.[26]

Table 6: In-vitro release study of nanoemulgel.

Time (hrs)	Cinnamon oil NEG	Olive oil NEG	Cinnamon oil (pure form)	Olive oil (pure form)
0	0	0	0	0
1	12.6±0.5	15.8±0.6	25.3±0.7	32.4±0.4
2	19.9±1.8	22.6±1.7	30.7±1.9	38.2±0.9
4	22.4±1.9	28.9±1.2	38.7±1.6	40.3±1.5
6	26.6±0.3	33.7±0.6	40.9±1.7	43.0±2.8
8	34.8±0.5	40.3±1.7	45.8±1.9	46.9±1.7
10	38.7±1.8	49.7±1.7	52.8±1.9	53.9±2.1
12	50.4±1.6	55.7±2.7	60.2±2.8	61.9±1.3
16	65.9±2.1	70.9±0.8	80.9±0.7	85.7±0.3
20	73.3±1.5	80.9±0.7	90.6±0.4	91.7±1.6
24	81.9±2.5	84.8±2.8	96.6±0.8	97.7±1.7

Thermodynamic stability

The thermodynamic stability of the nanoemulsion was determined by using a cooling-heating cycle. The were heformulationld at a temperature of 4 ◦C for a period of 48 hours, later which they are transferred to a temperature of 48 ◦C for an additional 48 hours. Subsequently, the nanoemulsion is observed for some modifications, like phase separation.[27]

Formulation of nanoemulgel

The following step are involve in the prepration of nanoemulgel

Fromulation of gel

The gel foundation was created by mixing purified water with different quantities of the gelling chemical Carbopol 974 (0.5%, 1%, 1.5%, and 2%). The gelling agent was completely dissolved in the liquid by continually swirling it at a temperature of 25°C. An inquiry was carried out to examine the impact of different concentrations on the viscosity and spreadability of the substance. The aim of this examination is to assessment the ideal quantity of Carbopol 974 that would allow the nanoemulgel formulation to attain a balanced state between optimum spreadability and appropriate viscosity(28).

Incorporation of formulated gel into already formulated microemulsion

In order to convert the gel into an emulgel, the nanoemulsion was added gradually and mixed completely with the gel at a temperature of 25°C for around 20 minutes. The pH of the emulgel is modified to match the pH of the buccal cavity after the mixing procedure, ensuring maximum performance and compatibility for applying to the mucosal surface (29).

Optimization of nanoemulgel formulation: The nanoemulgel formulation was adjusted by considering the concentration of the gelling ingredient, viscosity, and spreadability. For optimal formulation, five different formulations were created using different quantities of gelling agents (0.5, 1, 1.5, 2, 2.5%).[30]

Postformulation examination of prepared nanoemulgel:

FTIR examination

The objective of the FTIR study was to identify any incompatibilities between the active components and excipients in the formulation, as previously stated. The nanoemulgel formulations underwent FTIR analysis to ascertain the presence of Carbopol 974, olive oil, and cinnamon essential oil in both loaded and unloaded states. This research aimed to ascertain if there were any chemical interactions or alterations when the components were combined, in order to guarantee the stability and compatibility of the formulation.[31]

Viscosity examination

The conventional approach was used to determine the viscosity of each composition. The viscosity of the nanoemulgel was measured at a temperature of 25 ± 2◦C and a rotational speed of 6 rpm using a Brookfield viscometer equipped with spindle no. 4 (Digital, Labtronics, Panchkula, India).[32]

Physical Appearance

The visual assessment of all the created nanoemulgel formulations was conducted to evaluate their colour, uniformity, texture, and potential phase separation.

pH Examination

The aforementioned method was used to ascertain the pH of nanoemulgel combinations. The pH of the emulgel was determined by immersing the electrode tip into the solution for duration of two minutes, without any dilution, using a pH meter.[33]

Spreadability Examination

The spreadability of the formulations was assessed using a modified method. Two glass slides, each measuring 2.5 cm in width and 7.5 cm in length, were utilised. One slide was stationary and operated by a strand threaded by a pulley that supported a weight, while the other slide was mobile and secured to the wooden board. Subsequently, the concoction was placed between the two plates. During a period of one to two minutes, a 100 g mass was placed on top of the slide, exerting pressure. This pressure facilitated the uniform coating of the material and the release of any trapped air between the slides. Next, in order to provide force to the top slide, the 100 g weight was replaced with a 30 g mass that is connected to the pulley. The results were quantified as the duration it took for a movable slide to cover a distance of 6.5 cm, with measurements recorded in seconds.[33] The spreadability was determined using the latter equation.

$S = M \times L/T$

The weight connected to the higher slide is denoted as M, the length of the glass slides is denoted as L, and the time it takes to separate the slides is denoted as T.

Electron microscopy examination of microemulgel

The dimensions and surface morphology of the inner oil phase in the nanoemulgel were analysed using Field Emission Scanning Electron Microscopy (FE-SEM LEO 1525 ZEISS) at electron high tensions of 5 and 15 kV. Carbon tape with adhesive on both sides was used to attach the material onto inserts and facilitate the application of an 8-nanometer layer of chromium, so simplifying the photographic procedure. The scanning electron microscope (SEM) pictures were taken at scales of 1.00 KX utilising second electron (SE) scanning and in-lens detectors. The median dimension distribution of particles in the interior oily phase of the nanoemulgel was examined utilising SEM photographs and Image J software, yielding precise insights into its structural characteristics.[34]

Mucoadhesive examination

The evaluation of the nanoemulgel mucoadhesive properties was performed utilizing the aforementioned approach. In summary, the buccal mucosa of goats was promptly transported from the slaughterhouse to the laboratory and submerged in a phosphate buffer with a pH of 6.8. Subsequently, one of the equilibrium plates was removed, and a vial containing a solitary slice of buccal mucosa was placed on it. Another section of buccal mucosa was affixed to a vial, which was then fastened to

Table 7: kinetics drug relese study of nanoemulgel

Formulation	Ingredients	Zero order R^2	First order R^2	Higuchi model R^2	Korsmeyer-pappas model R^2	N	Best fit model
Nanoemulgel	Cinnamon oil	0.9646	0.9656	0.9808	0.9907	0.610	Korsmeyer-pappas model
	Olive oil	0.9615	0.9745	0.9876	0.9909	0.622	

Table 8: stability study of nanoemulgel at 4^0C and 25^0 C/60%RH for 90 days

Parameters	Temperature	0 day	30 days	60 days	90 days
Colour and homogeneity	4^0C	White and Homogenous	White and Homogenous	White and Homogenous	White and Homogenous
	25^0C	White and Homogenous	White and Homogenous	White and Homogenous	White and Homogenous
pH	4^0C	6.8±0.2	6.8±0.1	6.6±0.3	6.5±0.4
	25^0C	6.7±0.1	6.7±0.0	6.6±0.2	6.4±0.2
Spreadability (mm)	4^0C	35±0.5	35±0.1	32±0.6	30±0.8
	25^0C	37±0.6	37±0.3	34±0.7	32±0.3
Viscosity (cp)	4^0C	68058±4	66987±3	63987±5	61865±4
	25^0C	66098±6	64345±2	62354±3	60435±2

Values are expressed as mean ± (SD). * $p < 0.05$ compared to nanoemulgel. # $p < 0.05$ compared to nanoemulgel

the tabletop. In order to expel any entrapped air, the nanoemulgel was compressed between the two vials. Subsequently, weights were added to the pan on the other side of the balance until the two vials were separated. The mucoadhesive strength of the nanoemulgel was measured by calculating the weight at which the containers disengaged and using the following calculation to calculate the adhesive force.[16]

$$\text{Mucoadhesive strength} = \frac{\text{weight (grams)} \times \text{Gravitaional acceleration } \left(\frac{m}{s^2}\right)}{\text{Area of the vial opening } (cm^2)}$$

A weight was put to the pan in order to remove it. The gravitational acceleration is 9.8 m/s^2.

Drug content examination

The quantity of essential oils was determined using the UV-Vis spectrophotometric method. The essential oil of olive oil is dilute by ethanol (1:1000) and then homogenized in an ultrasonic chamber. Subsequently, its wavelength was slow at 230 nm. The cinnamon necessary oil was also analysed at a wavelength of 290 nm. Cinnamaldehyde was included as one of the nanoemulgel formulations that used this data. The essential oil concentration was determined using the standard curve.[35]

Encapsulation Efficiency (EE) Examination

The efficacy of nanoemulgel encapsulation has evaluated with a previously described approach, by slight adjustments. This assessment included comparing the measured amount of free necessary oil with the initial quantity of oil that is mixed to the preparation. The encapsulation efficiency was determined by formulating the nanoemulgel with the essential oil, separating the free oil through centrifugation, quantifying the amount of free essential oil using suitable analytical methods, and calculating the encapsulation efficiency by subtracting the measured quantity of free oil from the original quantity. This technology confirmed the efficacy of encapsulating the essential oil inside the nanoemulgel.[36]

$$EE(\%) = [(\text{initial conc. of EO} - \text{free EO})/\text{initial conc. of EO}] \times 100$$

Where EE = encapsulation efficiency, EO = essential oil

Drug release examination

A Franz diffusion cell (Permegear, model 4G01-00-05-05) with a diffusion area of 0.2 cm2 and a capacity of 7 mL for the acceptor compartment was used to calculate the release profile. At 37 ± 1 ◦C for 24 hours, fiber skins (14 kDa, dialysis tubes fiber skin from Sigma-Aldrich, St. Louis, MI, USA) were immersed into receptor liquid. They are then inserted into the receptor and donor compartments. A phosphate buffer solution by a pH of 6.8 is used to mimic the normal circumstances of the body, and samples were taken at predetermined intervals (0.5, 1, 1.5, 2, 4, 8, 12, 16, and 24 hours). A UV spectroscope calibrated to detect eugenol at 230 nm and cinnamon aldehyde at 290 nm was used to examine the collected samples for the presence of cinnamon aldehyde. Plotting the total quantity of essential oil released over time allowed us to quantify the release of cinnamon oil and olive oil through the membrane. For pure essential oils, the same process was used.[37]

RESULTS AND DISCUSSION

Optimization of nanaemulsion

The nanoemulsion was optimised by employing a pseudo-ternary phase diagram. The dispersing medium was distilled water, and the dispersed phase was a blend of Span 80 and Tween 80 (referred to as Smix) combined with olive oil. The stable oil region within the water nanoemulsion in the pseudo-ternary phase diagram is depicted by the darkened area in Figure 1. The precise ratios that produce a stable nanoemulsion formulation are indicated by each point on the phase diagram, which represents a component concentration of 100%.

Assessment of Transmission electron microscopy (TEM)

The nanoemulsion exhibited a mostly round and almost spherical external structure, with a particle size of about 100 nm. The optimised formulation (F2) was characterised using Transmission Electron Microscopy (TEM) pictures, which clearly displayed nanoparticles measuring 100 nm in size, as seen in Figure 4.[38]

Kinetic stbility

To assess the kinetic stability of the improved preparation, it is imperiled to centrifugation at speeds of 1000, 2000, and 3000 rpm. The findings confirmed that the

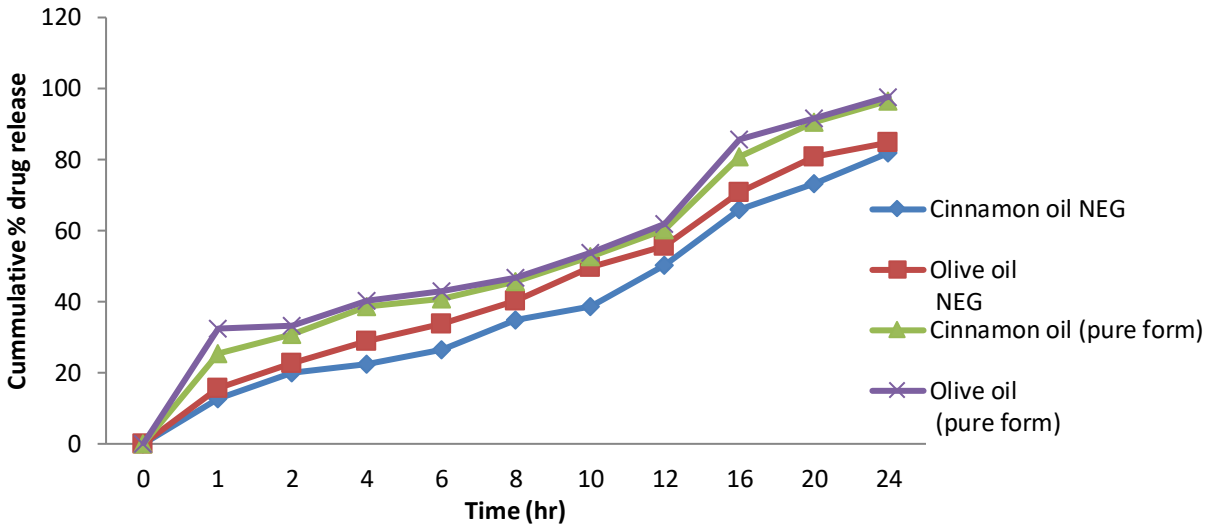

Figure 10: *In-vitro* release study of nanoemulgel.

formulation remained stable despite the centrifugal forces, thereby validating its kinetic stability and ensuring its constant functionality in various settings.[39]

Tharmadynamic Stability

The test sample underwent a heating-cooling cycle to assess its thermodynamic stability. Observations revealed that the nanoemulsion exhibited creaming and phase separation after three successive cycles of heating and chilling, indicating clear evidence of thermodynamic instability. Nanoemulsions undergo creaming and phase separation after extended storage as a result of their thermodynamic instability and kinetic stability. The centrifugation method is often used to subject freshly created nanoemulsions to stress conditions in order to determine their kinetic stability. The increased free energy of the colloidal dispersion in a nanoemulsion compared to the individual phase indicates that the nanoemulsion is more potent.[37]

Nanoemulgel examination

The nanoemulgel underwent adjustments depending on their viscosity and spreadability characteristics, revealing a clear relationship between the concentration of the polymer and these features. The spreadability of the nanoemulgel reduced as the concentration of the polymer rose, as seen in Table 3 and Figure 2. Conversely, the viscosity of the nanoemulgel increased dramatically, as shown in Table 3 and Figure 3. It is noteworthy that formulation F1 exhibited a comparatively lower viscosity of 62,035 ± 10 mP a•S, while still reaching a substantial spreadability rate of 38 ± 1. On the other hand, formulations F3 and F4 had very high viscosities of 92,345 ± 9 and 97,654 ± 10 mPa•S, respectively. However, they were found to have poor spreadability. In contrast, Formulation F2 exhibited remarkable spreadability at a temperature of 37 ± 1 degrees Celsius and an ideal viscosity of 66,098 ± 6 millipascal-seconds (mPa•S), indicating that it is a well-rounded formulation with favourable characteristics for real-world use.[40] Ensuring the uniformity of nanoemulgel formulations is crucial and may be achieved by using polymers, namely gelling agents. These compounds have an impact on many physical qualities such as homogeneity, texture, adhesion to biological surfaces, swelling capacity, rheological features, drug release behaviour, ease of extrusion, and dispersion. Carbopol 974 is a synthetic polymer that has a high viscosity ranging from 63,087±11 to 97,654±10 centipoises. It is often used in topical and transdermal formulations due to its ability to produce a transparent gel when mixed with water or hydroalcoholic solutions. The high viscosity of the nanoemulgel enhances its durability and consistency, but it also hampers its spreadability. Our study indicates that higher concentrations of Carbopol 974 enhance the viscosity of the formulation. However, this improvement in viscosity comes at the cost of lower spreadability, since these two parameters exhibit an inverse relationship. In order to enhance the effectiveness of the formulation for application on the skin, it is crucial to achieve a proper equilibrium between viscosity and spreadability.[41]

FTIR

The compatibility of pharmaceuticals and excipients in nanoemulgel formulations has been assessed by the use of Fourier Transform Infrared Spectroscopy (FTIR). The final formulation preserves the distinctive peaks of essential oils and excipients. The FTIR spectra exhibited consistent peaks that correlated with essential functional groups. The stretching of OH groups and fatty acids in olive oil may be noticed at 2923 cm^{-1} and 2845 cm^{-1}, respectively. In addition, the presence of ester C=O, aromatic C=C, and phenolic groups was detected by the observation of peaks. Cinnamon oil exhibits peaks in the OH stretching region at 3452 cm^{-1}, C=O region at 1670 cm^{-1}, C=C region at 1624 cm^{-1}, aromatic C-H region at 745 cm^{-1}, and C-H bending region at 970 cm^{-1}. Carbopol 974 displays clear peaks corresponding to the acrylate backbone, COOH groups, and CH_2 stretching. The lack of significant interaction between the components, as shown by the persistence of these peaks in the formulations, ensures the stability and integrity of the nanoemulgel formulation. This verifies that the essential oils and excipients maintain their unique spectrum properties.[42]

Drug content examination

The research on drug content analysis found that the optimised nanoemulgel formulation contained 95.20±1.5% of cinnamon oil and 93.32±2.6% of olive oil.

Sample Preparation

Weighing: Accurately weigh an appropriate amount of the ophthalmic nanoemulgel containing Gentamycin Sulphate. Typically, 1 g of the nanoemulgel is used for analysis.

Dissolution: Transfer the weighed sample into a 100 mL volumetric flask.

Solubilization: Add 50 mL of phosphate buffer (pH 7.4) to the flask. Sonicate the mixture for 10-15 minutes to ensure complete dissolution of Gentamycin Sulphate in the solvent.

Volume Adjustment: After sonication, allow the solution to cool to room temperature and make up the volume to 100 mL with the same phosphate buffer.

Filtration: Filter the solution through filter paper or a syringe filter (0.45 µm) to remove any undissolved particles.

Standard Preparation

Weighing: Accurately weigh a known amount of pure Gentamycin Sulphate (e.g., 10 mg).

Dissolution: Dissolve the weighed Gentamycin Sulphate in the same solvent used for sample preparation (phosphate buffer, pH 7.4) and transfer it to a 100 mL volumetric flask.

Volume Adjustment: Make up the volume to 100 mL with the solvent.

Dilutions: Prepare a series of standard solutions with known concentrations (e.g., 10 µg/mL, 20 µg/mL, 30 µg/mL) by serially diluting the stock solution.

Measurement:

UV-Vis Spectrophotometry:

Calibration Curve: Measure the absorbance of the standard solutions at the wavelength of maximum absorbance (λmax) for Gentamycin Sulphate, typically around 332 nm.

Sample Measurement: Measure the absorbance of the filtered sample solution.

Concentration Calculation: Determine the concentration of Gentamycin Sulphate in the sample by comparing its absorbance to the calibration curve.

HPLC Analysis:

Setup: Use a suitable column (e.g., C18) and a mobile phase such as water with a small amount of trifluoroacetic acid.

Injection: Inject a known volume (e.g., 20 µL) of the standard solutions and the sample solution into the HPLC system.

Retention Time: Record the retention time and area under the peak for Gentamycin Sulphate in both the standard and sample solutions.

Concentration Calculation: Calculate the drug content in the sample based on the area under the curve (AUC) from the calibration curve.

Calculation

Calculate the drug content in the nanoemulgel sample using the concentration obtained from the calibration curve and the dilution factor.

$$\text{Drug content}(\%) = \frac{\text{Concentration from calibration curve} \times \text{Dilution factor} \times \text{Volume of sample solution (mL)}}{\text{Labeled amount}} \times 100$$

Example

If the sample contains 93.32±2.6% of olive oil and 95.20±1.5% of cinnamon oil, these components do not interfere with the detection of Gentamycin Sulphate. If the concentration of Gentamycin Sulphate from the calibration curve is found to be **0.093 mg/mL**:

$$\text{Drug content}(\%) = \frac{0.093 \times 100}{\text{Labeled amount}} \times 100 = \text{Calculated Drug Content}$$

This procedure ensures that the Drug content of Gentamycin Sulphate in the nanoemulgel is accurately quantified, accounting for the presence of other components in the formulation.

Entrapment Efficiency

The nanoemulgel had an average entrapment effectiveness of 96.23% for cinnamaldehyde, whereas olive oil displayed an usual EE of 97.78%. The homogeneity of the system and the efficiency of drug encapsulation are affected by the drug's solubility in the required viscous phase and its compatibility with other constituents. The process of drug encapsulation is significantly affected by surfactants and Cosurfactants, which help to stabilise the insolubility of the chemical compounds. Elevated surfactant content in nanoemulsion and nanoemulgel results in decreased drug entrapment and diminished particle sizes. In our specific situation, the solubility of the active components increased when the material transitioned from the hydrophobic phase to the aqueous phase, resulting in enhanced solubility. The solubility improvement led to a reduction in the viscosity of the formulation and an enhancement in the diffusion phase during self-assembly. This elucidates the previously reported decrease in the concentration of the active ingredient in the formulation.[43]

Invitro drug release profile

The nanoemulgel drug release profile was analysed via in vitro testing utilising the Franz diffusion cell. A graph illustrating the relationship between the percentage of drug release and the length of the experiment is shown in Figure 9. The continual release of the chemical occurred due to the presence of the necessary oil in the lipid component of the nanoemulgel. The formulation including olive oil essential oil showed a significant release of 73.9% over a 24-hour period, whereas the formulation with cinnamon oil had a virtually equal release profile of 71.2% (Figure 8). In contrast, pure essential oils at a concentration of 100% emitted substances over a period of two hours.[37]

Mechanism of drug release from Cinnamon oil and Olive oil

The medication discharge contrivance from the nanoemulgel is analysed by many kinetic models, such as Zero order, Principal order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. The formulation exhibited a strong adherence to the Korsmeyer-Peppas model, as shown by a high R^2 value of 0.9909. Nevertheless, the study's findings indicated that the formulation failed to effectively control the release of the medication, despite the strong association. This indicates that more optimization is required in order to get the intended release profile.[44]

Mucoadhesive examination

In order to effectively transport medications to mucosal surfaces, it is crucial that the hydrophilic polymer Carbopol 974, which acts as a gelling agent, demonstrates significant mucoadhesive characteristics. The nanoemulgel formulation was evaluated using the modified balancing technique, and it exhibited an impressive mucoadhesive strength of 41.3 N/cm². The strong adhesion of this formulation allows it to stick to the damaged mucosal region, ensuring that the therapeutic substance is released gradually and remains in touch for a long time. The mucoadhesive qualities of Carbopol 974 are a result of its ability to form hydrogen bonds with mucin. This enhances its effectiveness in maintaining the desired concentration of drug at the intended location.[44]

Stability study

When comparing fresh preparations to F2 formulations, stability experiments were conducted under 60% relative humidity at temperatures of 4°C and 25°C over a three-month period. These experiments did not reveal any notable differences in physical characteristics, such as colour, uniformity, pH, dispersion, and viscosity. Moreover, the proportion of medication released from the preserved formulations was similar to that of the fresh formulations ($p < 0.05$). The observed stability is likely due to the addition of a gelling agent to the nanoemulgel, which aligns with Mohamed's study highlighting the crucial function of gelling agents in preserving the stability of preparations. The findings highlight the durability of the F2 formulations over extended periods of usage, showcasing their resilience under the circumstances of the tests.[42-50,52]

CONCLUSION

This inquiry examines the significant impact of polymer content on the capacity of nanoemulgel formulations to spread and their viscosity. An observed correlation was found between higher polymer content and reduced

spreadability, as well as increased viscosity. The suitability of Formulation F1 for topical application was attributed to its remarkable equilibrium between viscosity and spreadability. In contrast, formulations F3 and F4 showed reduced spreadability as a result of their elevated viscosities. The stability of the components of the nanoemulgel was ensured by the use of Fourier Transform Infrared (FTIR) spectroscopy, which confirmed the compatibility of essential oils and excipients. The preservation of bioactive components was seen to be excellent, with a retention rate over 95% for both cinnamon and olive oils, as determined by drug content analysis and entrapment efficacy evaluations. The polymer matrix of the nanoemulgel was determined to be accountable for the prolonged release patterns of both oils in in vitro drug release investigations. The formulation followed the Korsmeyer-Peppas paradigm, indicating a method for regulated drug release. Moreover, the nanoemulgel exhibited significant mucoadhesive characteristics, hence enhancing its capacity for prolonged topical use. The nanoemulgel's physical and chemical characteristics remained unchanged during stability trials lasting three months, even when exposed to different temperature and humidity settings. This confirms its appropriateness for extended usage. The optimised nanoemulgel formulation has the potential to deliver drugs effectively through the skin. It does this by combining prolonged drug release, high drug entrapment efficiency, and desired spreadability.

List of Abbreviation

NE	=	Nanoemulsion
µm	=	micrometre
nm	=	nanometre
Smix	=	Surfactant and co-surfactant mixture
°C	=	degree centigrade
mPa•S	=	millipascal second
SD	=	Standard Daviation
FTIR	=	Fourier Transform Infrared spectroscopy

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