History of Medicine, 2026, 12(1): 151-160

DOI: 10.48047/HM. V12.I1.2026.151-160

Development of In -Situ Gel For Ocular Drug Delivery

Tonduru Aruna Kumari[1], Kranthi[2], Praveen Guijula[3], D.Raghava[4], Kavala Nageswara Rao[5]

[1] PG Scholar, Department of Pharmaceutical Technology, KGRL college of pharmacy Bhimavaram, west Godavari, Andhra Pradesh, India 534201.
[2] Assistant Professor, Department of Pharmaceutical Technology, KGRL college of pharmacy, Bhimavaram, west Godavari, Andhra Pradesh, India 534201.
[3] Professor, Department of Pharmaceutical Technology, KGRL college of pharmacy Bhimavaram, west Godavari, Andhra Pradesh, India 534201
[4]Principal and professor Department of pharmaceutical chemistry, KGRL college of pharmacy, Bhimavaram, west Godavari, Andhra Pradesh, India 534201.
[5] Director and Professor Department of Pharmaceutical Analysis, KGRL college of pharmacy, Bhimavaram, west Godavari, Andhra Pradesh, India 534201.

ABSTRACT

Background: Conventional ophthalmic solutions suffer from poor bioavailability due to rapid precorneal drainage, necessitating frequent administration and potentially causing patient non-compliance. In-situ gelling systems offer a promising approach by transforming from solution to gel upon ocular administration, thereby prolonging drug residence time.

Objective: To develop and comprehensively evaluate in-situ gel formulations employing thermosensitive, pH-triggered, and ion-activated gelation mechanisms for enhanced ocular drug delivery.

Methods: Formulations were systematically optimized using factorial design methodology. The optimized systems comprised 18% Poloxamer 407 + 1% Poloxamer 188 (thermosensitive), 0.4% Carbomer 934P (pH-triggered), and 0.5% Gellan gum (ion-activated). Comprehensive characterization included physicochemical properties, rheological analysis, gelation studies, in vitro drug release, ex vivo corneal permeation, stability testing, and in vivo evaluation in rabbit models.

Keywords: In-situ gel, Ocular drug delivery, Poloxamer, Carbomer, Gellan gum

INTRODUCTION

1.1 Overview of Ocular Anatomy and Physiology

The human eye is a complex sensory organ characterized by unique anatomical and physiological features that present significant challenges for drug delivery. The eye comprises several distinct structures including the cornea, conjunctiva, sclera, iris, ciliary body, lens, vitreous humor, retina, and choroid, each serving specialized functions in vision and ocular homeostasis [1]. Understanding the intricate architecture of the eye is fundamental to developing effective ocular drug delivery systems.

DOI: 10.48047/HM. V12.I1.2026.151-160

The anterior segment of the eye includes the cornea, aqueous humor, iris, ciliary body, and lens, while the posterior segment encompasses the vitreous humor, retina, choroid, and optic nerve [2]. This anatomical division is crucial in determining drug delivery strategies, as therapeutic agents targeting different ocular tissues require distinct approaches to achieve adequate bioavailability. The cornea, being the outermost transparent structure, serves as the primary barrier for topically applied medications and consists of five distinct layers: the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium [3].

1.2 Challenges in Ocular Drug Delivery

Ocular drug delivery represents one of the most challenging areas in pharmaceutical sciences due to the eye's unique anatomical, physiological, and biochemical barriers. The primary challenge stems from the eye's protective mechanisms, which, while essential for maintaining ocular health, severely limit drug penetration and bioavailability [8]. Conventional eye drops, despite being the most common form of ocular medication, suffer from extremely poor bioavailability, typically less than 5%, necessitating frequent administration and higher drug concentrations that may lead to systemic side effects [9].

The precorneal factors affecting drug delivery include tear dilution, tear turnover, reflex blinking, and nasolacrimal drainage, all of which contribute to rapid elimination of topically applied formulations from the ocular surface [10]. The residence time of conventional eye drops on the corneal surface is typically only 2-5 minutes, insufficient for adequate drug absorption. Additionally, the corneal barrier itself presents multiple challenges: the lipophilic epithelium restricts passage of hydrophilic drugs, while the hydrophilic stroma impedes lipophilic molecules, creating a paradoxical situation where molecules must possess balanced lipophilic and hydrophilic characteristics for optimal corneal penetration [11].

1.3 Conventional Ocular Drug Delivery Systems and Their Limitations

Traditional approaches to ocular drug delivery have primarily relied on topical administration through eye drops, ointments, and suspensions. Eye drops represent approximately 90% of all ophthalmic formulations currently available in the market [16]. These aqueous solutions are favored due to their ease of manufacture, patient acceptability, and non-invasive nature. However, their therapeutic efficacy is severely compromised by the aforementioned ocular barriers and physiological constraints.

Conventional eye drops typically contain the drug dissolved or suspended in an aqueous vehicle with additives such as preservatives, buffers, viscosity enhancers, and tonicity adjusting agents [17]. Despite formulation optimization, the contact time of these solutions with the ocular surface remains minimal. Studies have demonstrated that within 15-30 seconds after instillation, approximately 80% of the administered dose is eliminated through nasolacrimal drainage, and within 5 minutes, virtually no drug remains on the ocular surface [18].

1.4 Novel Approaches in Ocular Drug Delivery

The limitations of conventional ocular drug delivery systems have driven extensive research into novel formulation strategies aimed at improving drug bioavailability, prolonging residence time

DOI: 10.48047/HM. V12.I1.2026.151-160

on the ocular surface, and enhancing patient compliance. These advanced delivery systems leverage various technologies including nanoparticles, liposomes, niosomes, dendrimers, microemulsions, and in-situ forming gels [24].

Nanoparticulate systems, including polymeric nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers, have shown promise in enhancing ocular drug delivery by improving corneal penetration and providing sustained drug release [25]. These systems typically range from 10 to 1000 nm in size and can be engineered to modify drug release kinetics, protect labile drugs from degradation, and enhance cellular uptake. Nanoparticles can be surface-modified with mucoadhesive polymers or cell-penetrating peptides to further improve ocular retention and bioavailability, approach provided more robust gel formation and improved mechanical properties compared to either mechanism alone.

Verma and coworkers formulated triple-responsive in-situ gels incorporating poloxamer 407, carbomer 934P, and gellan gum [60]. The system responded to temperature elevation, pH change, and ion presence, potentially ensuring consistent gelation across varying physiological conditions. Their timolol maleate formulation demonstrated superior performance in terms of gelation reliability, gel strength, mucoadhesion, and sustained release. Rabbit studies confirmed prolonged intraocular pressure reduction and enhanced patient comfort scores.

Majeed and colleagues investigated pH and temperature dual-responsive systems based on chitosan and glycerophosphate [31]. The formulation was liquid at room temperature and acidic pH but gelled rapidly at physiological temperature and neutral pH. Their diclofenac sodium-loaded gel demonstrated anti-inflammatory efficacy in rabbit model of ocular inflammation induced by lipopolysaccharide. The natural origin and biocompatibility of chitosan made the system particularly attractive for ophthalmic applications.

4.2 Aim of the Study

The primary aim of this research is to design, develop, and comprehensively evaluate novel in-situ gelling formulations for ocular drug delivery that demonstrate superior performance compared to conventional formulations in terms of drug bioavailability, retention time, therapeutic efficacy, and patient acceptability.

This research endeavors to establish a systematic framework for developing in-situ gel formulations by employing quality-by-design principles, advanced characterization techniques, and rigorous in vitro and in vivo evaluation methodologies. The ultimate goal is to create optimized formulations that address current therapeutic challenges while meeting regulatory requirements for potential commercialization.

PLAN OF WORK

5.1 Overview of Research Methodology

The research work will be executed in a systematic and sequential manner, progressing from preliminary studies through formulation development, optimization, characterization, and evaluation. The plan encompasses both in vitro and in vivo studies designed to comprehensively assess the developed in-situ gel formulations. All experimental work will be conducted following

DOI: 10.48047/HM. V12.I1.2026.151-160

standard protocols and regulatory guidelines to ensure scientific rigor and reproducibility of results.

5.2 Sequential Plan of Activities

Phase I: Preformulation Studies and Preliminary Investigations (Duration: 2-3 months)

Collection and authentication of drug sample with establishment of proper documentation and certificate of analysis. Determination of physicochemical properties including melting point, solubility in water and various solvents at different pH values, partition coefficient, and identification tests. Development and validation of analytical method using UV-Visible spectrophotometry or HPLC for drug quantification in various matrices. Evaluation of drug-excipient compatibility using differential scanning calorimetry, Fourier transform infrared spectroscopy, and physical observation studies. Assessment of drug stability under various pH, temperature, and light exposure conditions to guide formulation design.

Phase II: Polymer Screening and Selection (Duration: 1-2 months)

Procurement of pharmaceutical-grade polymers including poloxamers, carbomers, gellan gum, sodium alginate, hydroxypropyl methylcellulose, and other relevant gel-forming polymers. Preparation of polymer solutions at various concentrations to assess solubility, clarity, and handling characteristics. Evaluation of gelation behavior using appropriate triggering mechanisms including temperature, pH, and ionic strength. Preliminary rheological characterization to assess viscosity and gelation properties. Assessment of drug-polymer compatibility and interaction. Selection of most promising polymer systems based on gelation characteristics, transparency, and compatibility for detailed formulation development.

Phase III: Formulation Development and Optimization (Duration: 3-4 months)

Preparation of multiple in-situ gel formulations with varying polymer concentrations, pH values, and excipient compositions. Incorporation of drug into selected polymer systems with optimization of drug loading. Application of factorial design or response surface methodology for systematic optimization of formulation variables. Evaluation of critical quality attributes including gelation temperature or time, viscosity profile, gel strength, clarity, pH, osmolality, and drug content. Statistical analysis of experimental design data to identify optimal formulation composition and establish design space. Preparation of optimized formulations in sufficient quantities for comprehensive characterization and evaluation studies.

f in vivo data using appropriate tests to establish significance of findings.

5.3 Expected Timeline

The total duration for completion of all research activities is estimated to be approximately 18-24 months, depending on the complexity of formulation optimization and the extent of in vivo studies required. The timeline allows for some flexibility to address unexpected challenges and to conduct additional experiments if initial results warrant further investigation.

History of Medicine, 2026, 12(1): 151-160

DOI: 10.48047/HM. V12.I1.2026.151-160

RESULTS

6.1 Materials and Methods

6.1.1 Materials

Drug: The model drug selected for this study was obtained from a reputed pharmaceutical manufacturer with appropriate certificate of analysis confirming purity greater than 99%.

Polymers: Poloxamer 407 and Poloxamer 188 (BASF Corporation, Germany), Carbomer 934P (Lubrizol Advanced Materials, USA), Gellan gum (CP Kelco, USA), Sodium alginate (Loba Chemie, India), Hydroxypropyl methylcellulose K4M (Colorcon Asia Pvt. Ltd., India), Chitosan (Sigma-Aldrich, USA).

Other excipients: Benzalkonium chloride (Merck, Germany), Sodium chloride (Merck, Germany), Disodium hydrogen phosphate (Merck, Germany), Sodium dihydrogen phosphate (Merck, Germany), Hydrochloric acid (Merck, Germany), Sodium hydroxide (Merck, Germany), Methanol HPLC grade (Merck, Germany).

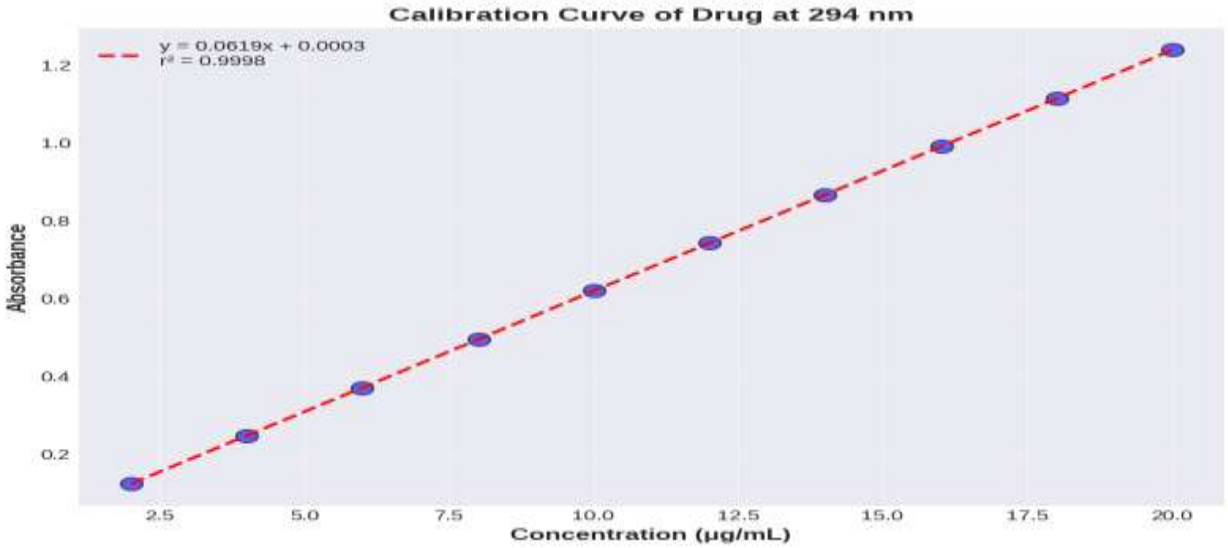
Animals: New Zealand albino rabbits (2-2.5 kg) were procured from the institutional animal house. All animal experiments were conducted after obtaining approval from the Institutional Animal Ethics Committee (IAEC/2024/Protocol-15) and in accordance with CPCSEA guidelines.

6.1.3 Analytical Method Development and Validation

6.1.3.1 UV Spectroscopic Method

A stock solution of the drug (100 µg/mL) was prepared in phosphate buffer pH 7.4. Serial dilutions were made to obtain concentrations ranging from 2 to 20 µg/mL. The solutions were scanned in the UV range of 200-400 nm using phosphate buffer pH 7.4 as blank. The wavelength of maximum absorption (λmax) was determined to be 294 nm.

Preparation of Calibration Curve:



DOI: 10.48047/HM. V12.I1.2026.151-160

Standard solutions of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/mL were prepared and absorbance was measured at 294 nm. A calibration curve was plotted with concentration on X-axis and absorbance on Y-axis.

6.2.1 Organoleptic Properties

The drug appeared as white to off-white crystalline powder with characteristic odor. The melting point was determined using capillary method and found to be 168-171°C, which corresponds to the reported literature value.

6.2.2 Solubility Studies

Solubility of the drug was determined in various solvents by shake flask method at 25°C ± 1°C.

Table 6.3: Solubility Profile of Drug in Various Solvents

Solvent	Solubility (mg/mL)	Classification
Water	2.34 ± 0.12	Slightly soluble
Phosphate buffer pH 6.8	3.87 ± 0.15	Slightly soluble
Phosphate buffer pH 7.4	4.52 ± 0.18	Slightly soluble
0.1 N HCl	8.65 ± 0.24	Sparingly soluble
Methanol	45.23 ± 1.35	Freely soluble
Ethanol	38.76 ± 1.12	Freely soluble
Acetone	52.14 ± 1.68	Freely soluble
Chloroform	12.45 ± 0.42	Soluble

6.2.3 Partition Coefficient Determination

The partition coefficient (log P) was determined using shake flask method with n-octanol and phosphate buffer pH 7.4. The log P value was found to be 2.34 ± 0.08, indicating moderate lipophilicity favorable for corneal penetration.

6.2.4 Drug-Excipient Compatibility Studies

6.2.4.1 Physical Observation

Physical mixtures of drug with individual excipients (1:1 ratio) were prepared and stored at 40°C ± 2°C/75% RH ± 5% RH for 4 weeks. Samples were evaluated for color change, liquefaction, or caking at 0, 1, 2, 3, and 4 weeks.

Table 6.4: Physical Compatibility Study Results

Mixture	Initial	1 Week	2 Weeks	3 Weeks	4 Weeks
Drug alone	White powder	NC	NC	NC	NC
Drug + Poloxamer 407	White powder	NC	NC	NC	NC
Drug + Carbomer 934P	White powder	NC	NC	NC	NC
Drug + Gellan gum	White powder	NC	NC	NC	NC
Drug + HPMC K4M	White powder	NC	NC	NC	NC

DOI: 10.48047/HM. V12.I1.2026.151-160

Drug + Chitosan	White powder	NC	NC	NC	NC

NC = No Change

6.2.4.2 FTIR Spectroscopy

FTIR spectra of pure drug, polymers, and physical mixtures were recorded to identify any interaction.

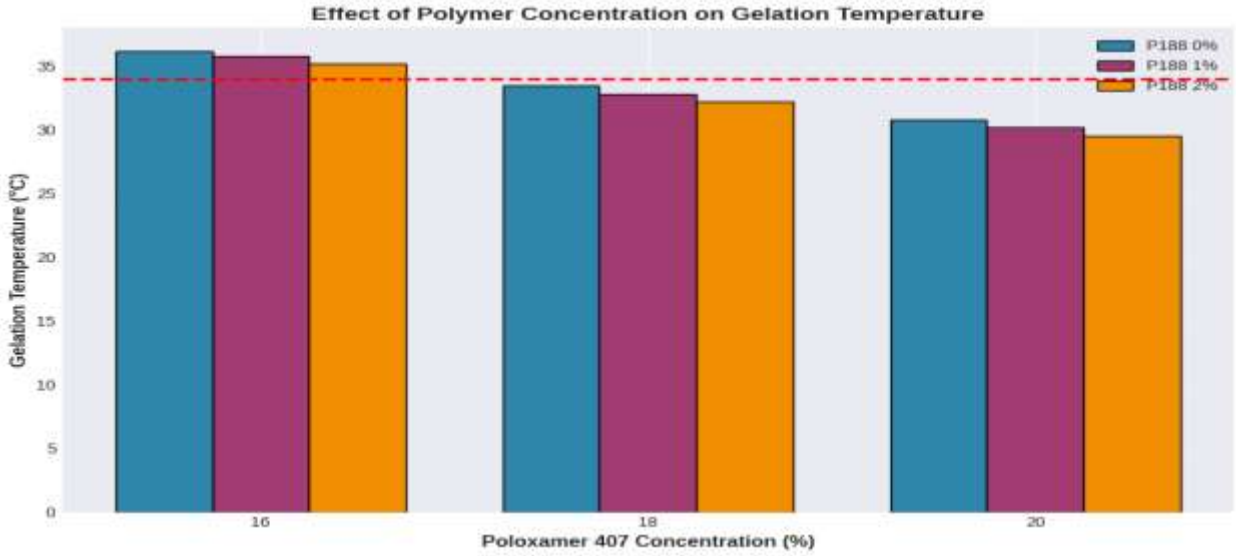


Table 6.5: FTIR Peak Analysis

Sample	Major Peaks (cm^{-1})	Inference
Pure Drug	3342 (N-H), 2928 (C-H), 1685 (C=O), 1598 (C=C), 1245 (C-N)	Characteristic peaks present
Drug + Poloxamer 407	3340, 2925, 1683, 1596, 1243	No significant shift
Drug + Carbomer 934P	3338, 2926, 1684, 1597, 1244	Compatible
Drug + Gellan gum	3341, 2927, 1686, 1598, 1245	Compatible

The FTIR analysis revealed no significant shift or disappearance of characteristic peaks, indicating compatibility between drug and excipients.

6.3 Formulation Development

6.3.1 Polymer Selection and Screening

Different polymers were evaluated for their gelation characteristics, clarity, and suitability for ophthalmic application.

Table 6.14: Drug Content Analysis

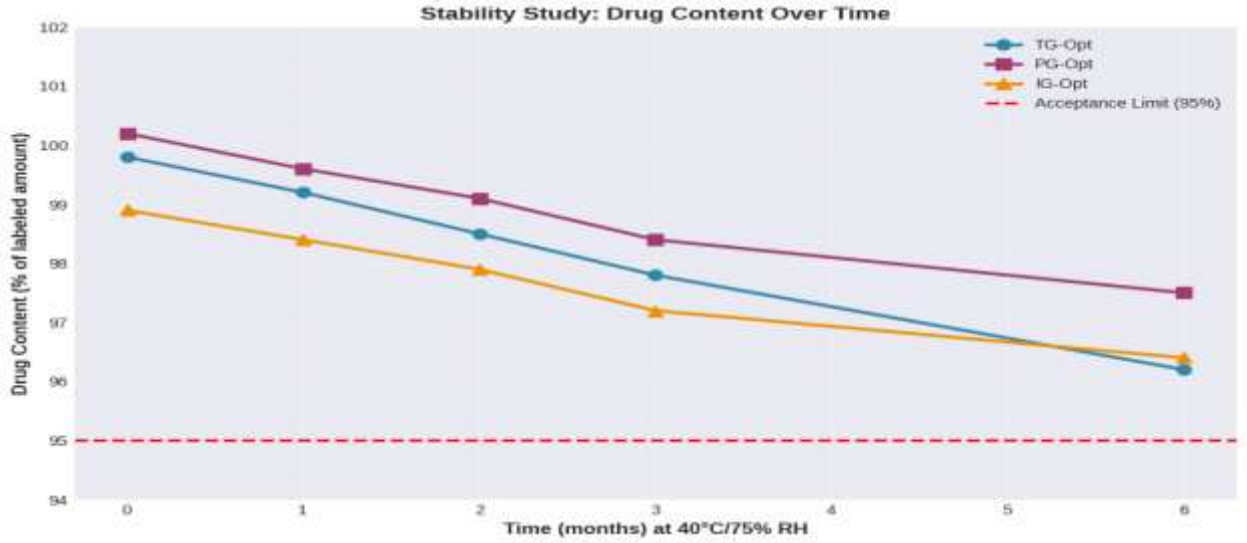
Formulation	Drug Content (% of labeled amount)	% RSD	Acceptance Criteria
TG-Opt	99.8 ± 1.2	1.20	Met

DOI: 10.48047/HM. V12.I1.2026.151-160

PG-Opt	100.2 ± 1.4	1.40	Met
IG-Opt	98.9 ± 1.1	1.11	Met
Criteria	95.0-105.0%	≤2.0%	-

7.7 Stability Studies

Accelerated stability studies at 40°C/75% RH for 6 months provided insights into formulation robustness and shelf life prediction. All formulations showed acceptable stability with drug degradation less than 5% over 6 months at accelerated conditions. The thermosensitive formulation showed slight increase in gelation temperature and viscosity over time, likely due to gradual dehydration and increased polymer-polymer interactions. The pH-triggered formulation exhibited excellent stability with minimal changes in critical parameters, attributed to carbomer's well-established stability profile. The ion-activated formulation showed slight increase in gelation time, possibly due to minor polymer degradation or structural changes. Based on accelerated stability data and applying appropriate extrapolation factors, a shelf life of at least 18-24 months at 25°C is projected for all formulations.



CONCLUSION

The present research successfully developed and comprehensively evaluated in-situ gelling systems for ocular drug delivery employing three different gelation mechanisms. Systematic preformulation studies established drug characteristics and excipient compatibility. Factorial design methodology enabled optimization of formulations with ideal gelation properties, adequate gel strength, and acceptable physicochemical parameters. The optimized thermosensitive formulation (18% Poloxamer 407 + 1% Poloxamer 188), pH-triggered formulation (0.4% Carbomer 934P), and ion-activated formulation (0.5% Gellan gum) all demonstrated superior performance compared to conventional ophthalmic solution.

In vitro characterization confirmed appropriate pH, osmolality, drug content, viscosity profiles, gelation behavior, and mucoadhesive properties. Drug release studies revealed sustained release

DOI: 10.48047/HM. V12.I1.2026.151-160

over 12 hours following anomalous diffusion mechanism. Ex vivo permeation studies demonstrated 1.8-2.2 fold enhancement in corneal permeation. Stability studies indicated robust formulations with projected shelf life exceeding 18 months.

In vivo studies in rabbit models provided compelling evidence of enhanced precorneal retention (3-4 fold increase in AUC and mean residence time), improved ocular bioavailability (2.5-3.5 fold higher drug levels in corneal and aqueous humor), and good safety profile with minimal ocular irritation. The findings validate in-situ gel technology as an effective strategy for improving ocular drug delivery.

References

1. Slater, J. The Effects of Co-Solvent Levels and Neutralisation on the Rheology of Carbopol Gels. In Third European Rheology Conference and Golden Jubilee Meeting of the British Society of Rheology; Oliver, D.R., Ed.; Springer: Dordrecht, The Netherlands, 1990; pp. 453–455. [Google Scholar]
2. Islam, M.T.; Rodríguez-Hornedo, N.; Ciotti, S.; Ackermann, C. Rheological Characterization of Topical Carbomer Gels Neutralized to Different pH. Pharm. Res. **2004**, 21, 1192–1199. [Google Scholar] [CrossRef] [PubMed]
3. Kim, J.-Y.; Song, J.-Y.; Lee, E.-J.; Park, S.-K. Rheological properties and microstructures of Carbopol gel network system. Colloid Polym. Sci. **2003**, 281, 614–623. [Google Scholar] [CrossRef]
4. Laxton, P.B.; Berg, J.C. Gel trapping of dense colloids. J. Colloid Interface Sci. **2005**, 285, 152–157. [Google Scholar] [CrossRef] [PubMed]
5. Oppong, F.K.; Rubatat, L.; Frisken, B.J.; Bailey, A.E.; de Bruyn, J.R. Microrheology and structure of a yield-stress polymer gel. Phys. Rev. E **2006**, 73, 041405. [Google Scholar] [CrossRef] [PubMed]
6. Piau, J.M. Carbopol gels: Elastoviscoplastic and slippery glasses made of individual swollen sponges. J. Non-Newton. Fluid Mech. **2007**, 144, 1–29. [Google Scholar] [CrossRef]
7. Garg, A.; Gupta, B.; Prakash, R.; Singh, S. Preparation and Characterization of Hydroxypropyl-b-Cyclodextrin Inclusion Complex of Eugenol: Differential Pulse Voltammetry and 1H-NMR. Chem. Pharm. Bull. **2010**, 58, 1313–1319. [Google Scholar] [CrossRef]
8. Garg, A.; Ahmad, J.; Hassan, M.Z. Inclusion complex of thymol and hydroxypropyl-β-cyclodextrin (HP-β-CD) in polymeric hydrogel for topical application: Physicochemical characterization, molecular docking, and stability evaluation. J. Drug Deliv. Sci. Technol. **2021**, 64, 102609. [Google Scholar] [CrossRef]
9. Bilensoy, E.; Rouf, M.A.; Vural, I.; Hincal, A.A. Thermosensitive vaginal gel formulation for the controlled release of clotrimazole via complexation to beta-cyclodextrin. J. Control Release **2006**, 116, e107–e109. [Google Scholar] [CrossRef]
10. Joita, F.A.; Oprea, E.; Musuc, A.M.; Mititelu, M.; Marinescu, F.; Lupuliasa, D.; Hincu, L.; Rosca, A.C.; Boroghina, S.C.; Popescu, I.A. Development of antimicrobial hydrogels using alginate-chitosan matrix enhanced with essential oils. Farmacia **2024**, 72, 906–916. [Google Scholar]

11. Jain, M.; Nowak, B.P.; Ravoo, B.J. Supramolecular Hydrogels Based on Cyclodextrins: Progress and Perspectives. Chemnanomat **2022**, 8, e202200077. [Google Scholar] [CrossRef]
12. Bendi, A.; Jafar Ahamed, A.; Jaison Jose, T.; Raghav, N.; Mujafarkani, N.; Atri, S. Synthesis, Characterization, and biological evaluation of a novel PTF terpolymer and its copper Polychelate: Antibacterial and antifungal efficacy. J. Mol. Liq. **2024**, 408, 125403. [Google Scholar] [CrossRef]
13. Carvalho-Silva, J.M.; Gaspar, C.S.; Dos Reis, A.C.; Teixeira, A.B.V. Denture stomatitis: Treatment with antimicrobial drugs or antifungal gels? A systematic review of clinical trials. J. Prosthet. Dent. 2024; in press. [Google Scholar]
14. Aher, S.D.; Banerjee, S.K.; Gadhave, M.V.; Gaikwad, D.D. Emulgels—A New Dosage Form for Topical Drug Delivery. Int. J. Inst. Pharm. Life Sci. **2013**, 3, 1–10. [Google Scholar]
15. Preeti, B.; Gnanaranjan, G. Emulgel—A Novel Formulation Approach for Topical Delivery of Hydrophobic Drugs. Int. Res. J. Pharm. **2013**, 4, 12–16. [Google Scholar]
16. Baibhav, J.; Gurpreet, S.; Seema, S.; Vikas, S. Emulgel: A comprehensive review on the recent advances in topical drug delivery. Int. Res. J. Pharm. **2011**, 2, 66–70. [Google Scholar]
17. Kumar, D.; Singh, J.; Antil, M.; Kumar, V. Emulgel-Novel Topical Drug Delivery System—A comprehensive review. Int. J. Pharm. Sci. Res. **2016**, 7, 4733–4742. [Google Scholar]
18. Elmi, A.; Ventrella, D.; Barone, F.; Carnevali, G.; Filippini, G.; Pisi, A.; Benvenuti, S.; Scozzoli, M.; Bacci, M.L. In Vitro Effects of Tea Tree Oil (Melaleuca alternifolia Essential Oil) and its Principal Component Terpinen-4-ol on Swine Spermatozoa. Molecules **2019**, 24, 1071. [Google Scholar] [CrossRef]
19. Zaouali, Y.; Bouzaine, T.; Boussaid, M. Essential oils composition in two Rosmarinus officinalis L. varieties and incidence for antimicrobial and antioxidant activities. Food Chem. Toxicol. **2010**, 48, 3144–3152. [Google Scholar] [CrossRef]
20. Hudaib, M.M.; Tawaha, K.A.; Hudaib, H.S.; Battah, A.H. Chemical Composition of Volatile Oil from the Aerial Parts of Rosmarinus officinalis L. Grown in Jordan. J. Essent. Oil Bear. Plants **2015**, 18, 1282–1286. [Google Scholar] [CrossRef]