

DEVELOPMENT AND EVALUATION OF A THERMO-RESPONSIVE SMART GEL INCORPORATING METHOTREXATE AND CURCUMIN FOR CONTROLLED DRUG DELIVERY

Yash Jaiswal¹, Dr. Vinesh Kumar²

¹Research Scholar, ²Associate Professor

^{1,2}Lal Bahadur Shastri College of Pharmacy, Udai Marg, Tilak Nagar, Jaipur, Rajasthan, India

Abstract- Objective: To develop and evaluate a thermo-responsive gel containing methotrexate and curcumin for controlled drug delivery. Methods: Five formulations (F1–F5) were prepared by the cold method using Poloxamer 407, Poloxamer 188 and Carbopol 940. The formulations were assessed for physical appearance, pH, viscosity, spreadability, gelation temperature and drug content. Drug–drug compatibility was assessed using FTIR, and in-vitro release of the optimized formulation was examined using a Franz diffusion cell.

Results: Reported gelation temperatures ranged from $36.8 \pm 0.3^{\circ}\text{C}$ (F1) to $32.4 \pm 0.2^{\circ}\text{C}$ (F5). Viscosity increased from F1 to F5. F5 showed drug contents of $99.8 \pm 0.3\%$ for methotrexate and $99.5 \pm 0.3\%$ for curcumin. At 24 h, reported cumulative release was $96.8 \pm 1.2\%$ for methotrexate and $92.5 \pm 1.1\%$ for curcumin.

Conclusion: F5 performed best among the tested formulations on the reported parameters.

Keywords: Thermo-responsive gel; methotrexate; curcumin; Poloxamer 407; controlled drug delivery; in-vitro release.

I. INTRODUCTION

Thermo-responsive gels are polymeric systems that undergo a temperature-triggered change in structure or viscosity, and poloxamer-based systems are widely investigated for in-situ gel formation and controlled drug delivery [1–4]. Poloxamer 407 forms micellar structures as temperature rises, and polymer concentration and combinations with other excipients can influence gelation temperature, viscosity, residence time and drug release [1–4]. Such systems are attractive when a formulation should remain manageable during application and become more viscous under physiological conditions.

Methotrexate is an established disease-modifying drug used in inflammatory disorders, while curcumin has been

investigated for anti-inflammatory activity and formulation strategies intended to improve its delivery [5–9]. Research on local and transdermal delivery systems for rheumatoid arthritis has explored gels, vesicles and other carriers to improve drug localization and release characteristics [10–13]. However, formulation performance depends on the physicochemical properties of both drugs, compatibility with excipients, polymer composition, and the barrier properties of the intended route. In-vitro release results are useful for comparing formulations, but they do not by themselves prove skin penetration, clinical efficacy, safety or synergistic action [14–16].

Accordingly, the present study compares five formulations (F1–F5) containing methotrexate and curcumin in a thermo-responsive gel base. The evaluation combines visual inspection, pH, viscosity at two temperatures, spreadability, gelation temperature, drug content, FTIR comparison and Franz diffusion-cell release testing. These tests provide a preliminary formulation-screening framework consistent with common pharmaceutical development and analytical evaluation practices [17–20].

II. OBJECTIVES

1. To develop a dual-drug thermo-responsive gel containing methotrexate and curcumin.
2. To conduct preformulation studies, including solubility, melting point, absorption maximum, partition coefficient and pH assessment.
3. To evaluate drug–excipient compatibility using FTIR spectroscopy.
4. To prepare thermo-responsive gel formulations using the cold method and optimize formulation parameters.
5. To evaluate physical appearance, pH, viscosity, spreadability, gelation temperature, drug content and in-vitro drug release.

III. MATERIALS AND METHODS

The materials used included methotrexate, curcumin, Poloxamer 407, Poloxamer 188, Carbopol 940, propylene glycol, ethanol, triethanolamine, distilled water, potassium bromide and phosphate buffer (pH 7.4). Poloxamer-based excipients were selected for their established use in thermoresponsive pharmaceutical systems, while Carbopol was included as a viscosity-modifying polymer [1–4, 21].

The materials used included methotrexate, curcumin, Poloxamer 407, Poloxamer 188,

Carbopol 940, propylene glycol, ethanol, triethanolamine, distilled water, potassium bromide and phosphate buffer (pH 7.4).

5 formulations (F1–F5) were prepared using a cold method. The concentrations of Poloxamer 407 and Poloxamer 188 were varied while the amounts of the drugs and other excipients were maintained as described in the formulation record. The polymer base was hydrated under cold conditions, followed by incorporation of drug solution, Carbopol and pH-adjusting agent. The formulations were mixed until uniform and stored under appropriate conditions. Cold processing is commonly used with poloxamer systems to facilitate hydration before temperature-dependent micellization and gel formation [1–4].

Five formulations (F1–F5) were prepared using a cold method. The concentrations of Poloxamer 407 and Poloxamer 188 were varied while the amounts of the drugs and other excipients were maintained as described in the formulation record. The polymer base was hydrated under cold conditions, followed by incorporation of drug solution, Carbopol and

pH-adjusting agent. The formulations were mixed until uniform and stored under appropriate conditions.

Formulations were evaluated for appearance, pH, viscosity at 25°C and 37°C, spreadability, gelation temperature and drug content. FTIR spectra were compared to assess characteristic bands. In-vitro release from the selected formulation was tested using a Franz diffusion cell over 24 hours. Franz diffusion cells are established tools for evaluating in-vitro permeation or release under defined experimental conditions, although interpretation depends on the membrane, receptor medium, temperature and sampling protocol [14–16, 22]. Reported mean $\pm$ SD values are reproduced as available.

Formulations were evaluated for appearance, pH, viscosity at 25°C and 37°C, spreadability, gelation temperature and drug content. FTIR spectra were compared to assess characteristic bands. In-vitro release from the selected formulation was tested using a Franz diffusion cell over 24 hours.

IV. RESULTS AND DISCUSSION

4.1 Preformulation and analytical characterization

Table 4. Preformulation and Analytical Characterization of Methotrexate and Curcumin.

Drug / parameter	Observation
------------------	-------------

Methotrexate absorption maximum	Approximately 303 nm
Curcumin absorption maximum	425 nm
FTIR compatibility interpretation	Characteristic bands retained; no substantial shifts or disappearance reported

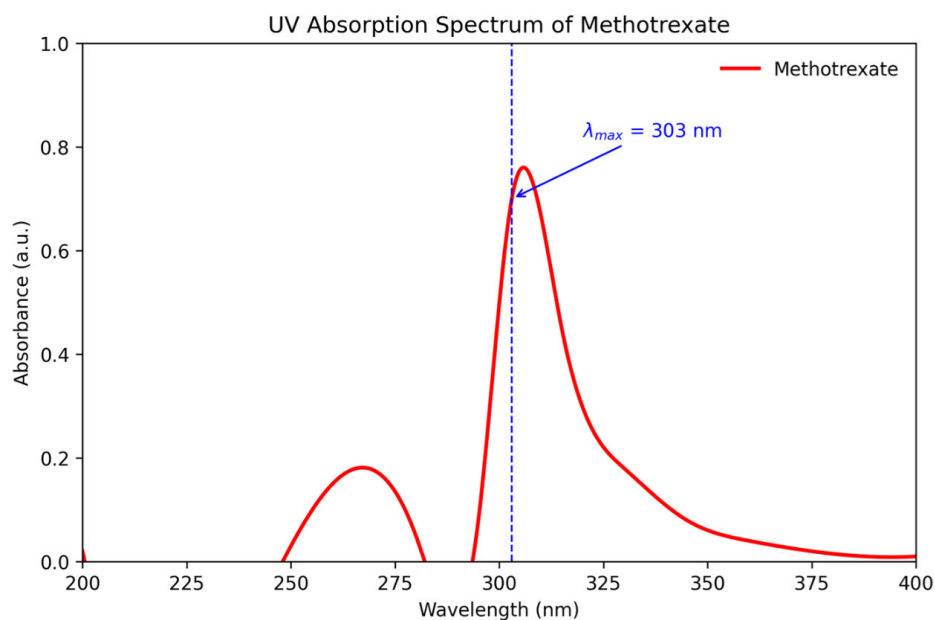


Figure 1. UV–Visible Absorption Spectrum of Methotrexate.

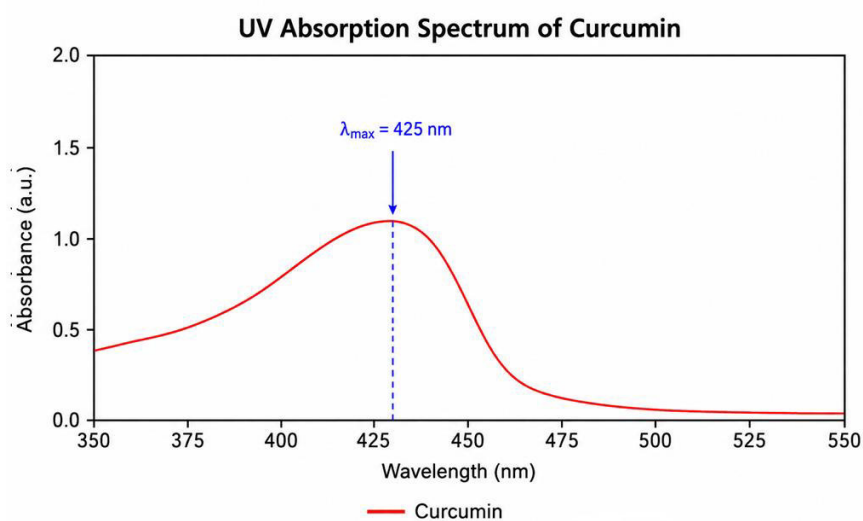
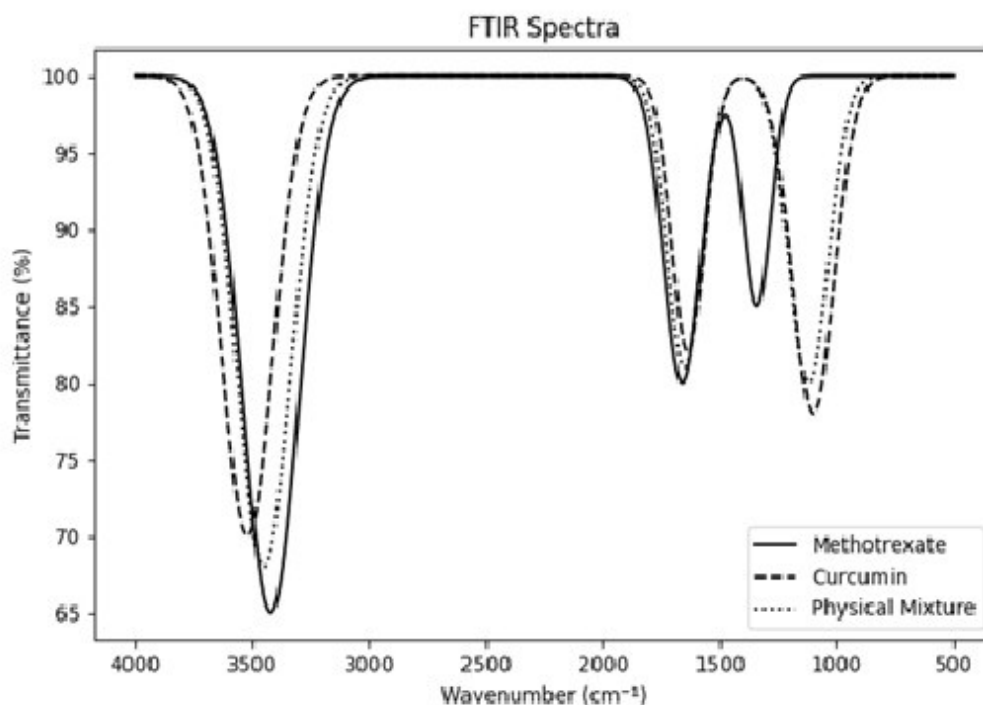


Figure 2. UV–Visible Absorption Spectrum of Curcumin.

Table 5. FTIR Characteristic Bands and Interpretation for the Drug Mixture.

FTIR band assignment	Methotrexate (cm ⁻¹)	Curcumin (cm ⁻¹)	Physical mixture (cm ⁻¹)	Reported interpretation
O–H stretch	3400–3450	3500–3550	3420–3540	No significant shift
C=O stretch	1650–1680	1625–1650	1645–1670	Slight overlap
C–N stretch	1320–1360	—	1330–1355	No interaction reported
Aromatic C=C	1500–1600	1505–1610	1510–1605	Compatible
C–O stretch	1050–1150	1020–1160	1045–1155	No new peak

**Figure 3. Comparative FTIR Spectra of Methotrexate, Curcumin and Their Physical Mixture.**

The physical mixture spectrum showed all characteristic peaks of both drugs with no significant shift or disappearance of peaks.

Minor overlapping was observed in the carbonyl region, which is expected due to the combination of both components.

4.2 Table 1. Composition of Thermo-Responsive Gel Formulations F1–F5.

Ingredients	F1 (% w/w)	F2 (% w/w)	F3 (% w/w)	F4 (% w/w)	F5 (% w/w)
Poloxamer 407	17.8	18.9	20.1	21.2	22.3
Poloxamer 188	1.7	2.3	2.8	3.2	3.7
Methotrexate	0.0006	0.0006	0.0006	0.0006	0.0006
Curcumin	0.045	0.045	0.045	0.045	0.045
Carbopol 940	0.72	0.72	0.72	0.72	0.72
Propylene Glycol	4.8	4.8	4.8	4.8	4.8
Ethanol	4.8	4.8	4.8	4.8	4.8
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled Water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100



Figure 4. Photograph of Prepared Thermo-Responsive Gel Formulations F1–F5.

The five batches were prepared with varying concentrations of thermoresponsive polymers. The formulation photograph documents the

prepared batches; visual appearance alone does not establish stability, uniformity or performance during storage.

4.3 pH and spreadability

Table 4.5: pH of Thermo-Responsive Gel Formulations

Formulation	pH (Mean $\pm$ SD)
F1	6.82 $\pm$ 0.04
F2	6.88 $\pm$ 0.03
F3	6.94 $\pm$ 0.02
F4	7.01 $\pm$ 0.03
F5	7.06 $\pm$ 0.02

The measured pH of all prepared formulations fell within the specified range of 6.5–7.5, suggesting that their acidity and alkalinity were appropriate for potential topical application. Maintaining a pH compatible with the skin is important for minimizing the risk of irritation and supporting formulation acceptability. A gradual rise in pH was observed with

increasing polymer concentration, which may be associated with the neutralization of Carbopol by triethanolamine and the resulting changes in the formulation system. However, skin compatibility cannot be established by pH measurements alone and requires appropriate irritation and safety assessments.

Table 4.7: Spreadability of Thermo-Responsive Gel Formulations

Formulation	Spreadability (g·cm/sec)
F1	24.5 $\pm$ 0.42
F2	23.3 $\pm$ 0.35
F3	22.0 $\pm$ 0.38
F4	20.8 $\pm$ 0.31
F5	19.6 $\pm$ 0.28

Spreadability decreased from F1 to F5, while the reported viscosity increased across the formulation series. This inverse pattern is consistent with a progressively more structured

gel base. The reported spreadability units and test conditions should be retained exactly as documented in the experimental record.

4.4 Viscosity

Table 7. Viscosity of Formulations F1–F5 at 25°C and 37°C.

Formulation	Viscosity at 25°C (cP)	Viscosity at 37°C (cP)
F1	4800 ± 82	7800 ± 91
F2	5600 ± 75	9200 ± 105
F3	6900 ± 80	11150 ± 115
F4	8200 ± 92	12980 ± 123
F5	9550 ± 98	14680 ± 135

Viscosity increased progressively with increasing concentrations of Poloxamer 407 and Poloxamer 188. Higher viscosity at physiological temperature confirmed successful

thermo-responsive gel formation. F5 exhibited optimum viscosity, ensuring better residence time and sustained drug release while maintaining acceptable spreadability

4.5 Gelation temperature

Table 8. Gelation Temperature of Formulations F1–F5.

Formulation	Gelation temperature (°C)
F1	36.8 ± 0.3
F2	35.2 ± 0.2
F3	34.0 ± 0.2
F4	33.1 ± 0.3
F5	32.4 ± 0.2

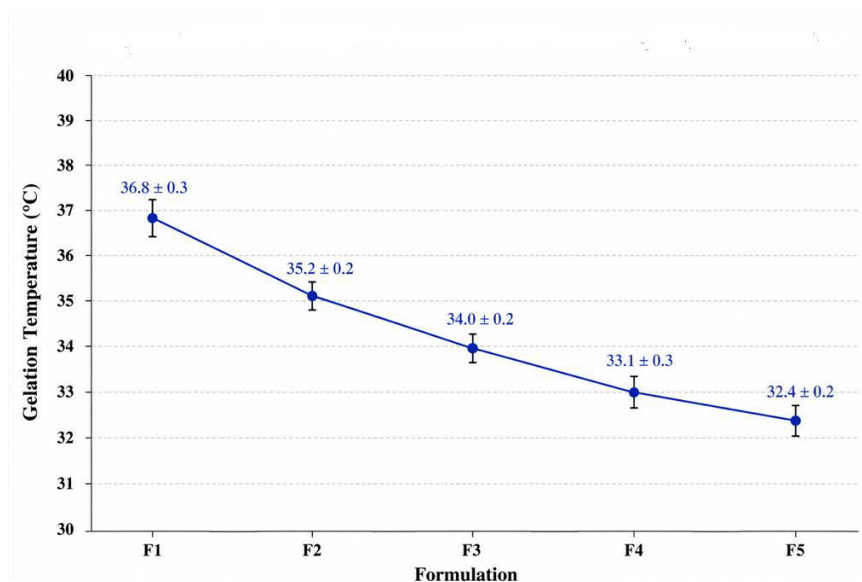


Figure 5. Gelation Temperature of Formulations F1–F5.

Gelation temperature decreased with increasing concentration of Poloxamer 407 due to enhanced micellar packing. F5 gelled at

approximately 32°C, which is very close to skin temperature, making it the most suitable formulation for in situ topical gel formation.

4.6 Drug content

Table 9. Drug Content of Methotrexate and Curcumin in Formulations F1–F5.

Formulation	Methotrexate (%)	Curcumin (%)
F1	95.8 ± 0.8	95.3 ± 0.7
F2	97.2 ± 0.6	96.8 ± 0.6
F3	98.6 ± 0.5	98.2 ± 0.5
F4	99.3 ± 0.4	99.0 ± 0.4
F5	99.8 ± 0.3	99.5 ± 0.3

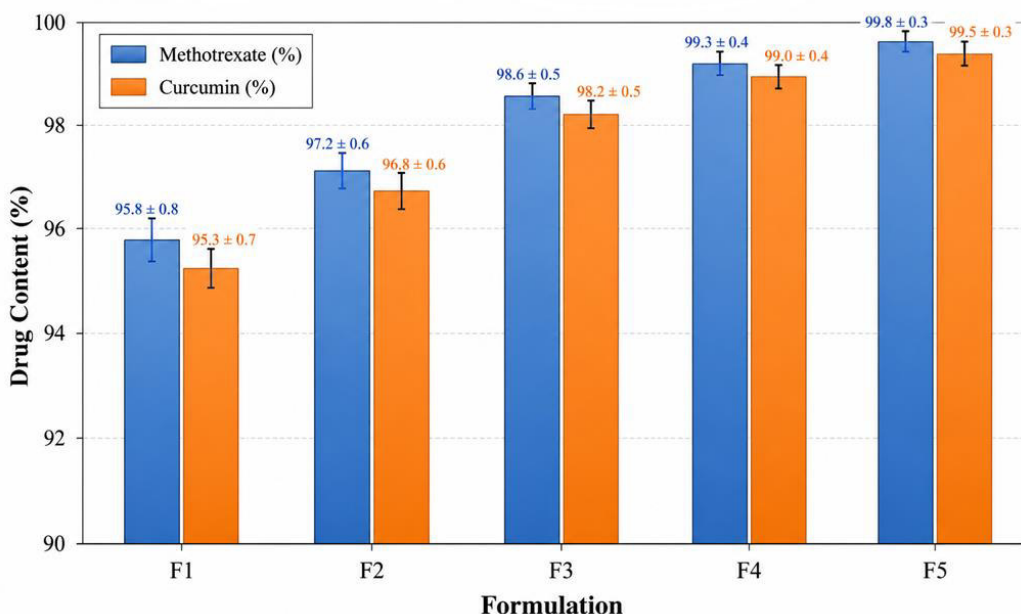


Figure 6. Drug Content of Methotrexate and Curcumin in Formulations F1–F5.

F5 showed the highest reported drug content for both compounds, at $99.8 \pm 0.3\%$ for methotrexate and $99.5 \pm 0.3\%$ for curcumin.

These values indicate high assay recovery in

the reported test; they should not be interpreted as evidence of bioavailability or therapeutic effectiveness.

4.7 In-vitro drug release

Table 10. In-Vitro Release Profile of Methotrexate and Curcumin from Formulation F5.

Time (h)	Methotrexate release (%)	Curcumin release (%)
0	0	0
1	12.6 ± 0.6	9.8 ± 0.5
2	22.5 ± 0.8	18.6 ± 0.7
4	39.8 ± 1.0	34.2 ± 0.9
6	55.6 ± 1.2	48.5 ± 1.0
8	69.8 ± 1.4	62.9 ± 1.2
12	84.6 ± 1.5	79.3 ± 1.3
24	96.8 ± 1.2	92.5 ± 1.1

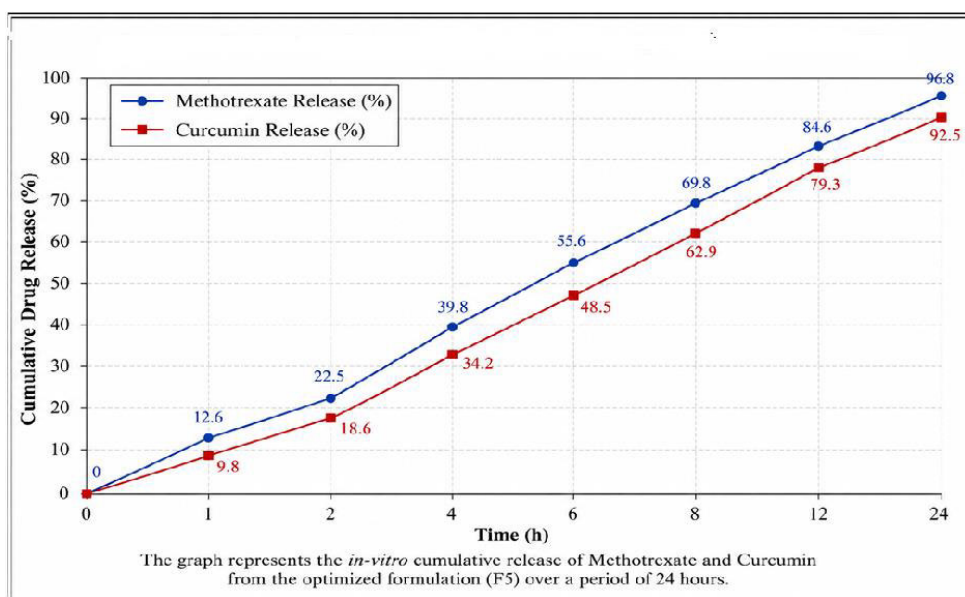


Figure 7. In-Vitro Release Profile of Methotrexate and Curcumin from Optimized Formulation F5.

Cumulative release increased over 24 hours for both drugs. At 24 hours, the reported release was $96.8 \pm 1.2\%$ for methotrexate and $92.5 \pm 1.1\%$ for curcumin. Methotrexate release was higher than curcumin release at each reported non-zero time point. These data compare release under the stated *in-vitro* test conditions and do not establish skin permeation or clinical effectiveness.

V. CONCLUSION

Among the five formulations, F5 showed the lowest reported gelation temperature ($32.4 \pm 0.2^\circ\text{C}$), the highest viscosity at both tested temperatures, and the highest reported drug content for methotrexate ($99.8 \pm 0.3\%$) and curcumin ($99.5 \pm 0.3\%$). The *in-vitro* release

profile showed progressive release over 24 hours, reaching $96.8 \pm 1.2\%$ for methotrexate and $92.5 \pm 1.1\%$ for curcumin. Taken together, the reported physicochemical and release results identify F5 as the most promising batch among F1–F5 under the parameters evaluated in this study. The observed increase in viscosity and decrease in gelation temperature across the batches suggest that polymer composition materially influenced the thermal and handling characteristics of the formulation. The FTIR interpretation showed retention of characteristic bands without major detectable changes in the physical mixture, providing a preliminary indication of compatibility under the conditions tested.

VI. FUTURE SCOPE

- Future studies should confirm the reported values, units, replicate numbers and statistical methods using complete laboratory records and repeat batches.
- Complete UV calibration curves and validated analytical procedures can be included to strengthen quantification of both drugs.
- Further work can document full FTIR spectra and analytical validation, including specificity, linearity, accuracy, precision and robustness where applicable.
- Ex-vivo skin permeation, local irritation/cytotoxicity, accelerated and long-term stability, packaging compatibility, and batch-to-batch reproducibility should be investigated. If justified by the results, suitable in-vivo studies may then assess local distribution and safety.
- Future optimization may also examine polymer ratios and release conditions to balance handling, gelation temperature and drug release, followed by comparison with appropriate control formulations.

References

- [1] Dumortier, G., Grossiord, J. L., Agnely, F., & Chaumeil, J. C. (2006). A review of poloxamer 407 pharmaceutical and

pharmacological characteristics. *Pharmaceutical Research*, 23(12), 2709–2728.

<https://doi.org/10.1007/s11095-006-9104-4>

- [2] Franz, T. J. (1975). Percutaneous absorption: On the relevance of in vitro data. *Journal of Investigative Dermatology*, 64(3), 190–195. <https://doi.org/10.1111/1523-1747.ep12533356>
- [3] Hadgraft, J., & Lane, M. E. (2016). Skin permeation: The years of enlightenment. *International Journal of Pharmaceutics*, 514(1), 52–60. <https://doi.org/10.1016/j.ijpharm.2016.08.047>
- [4] Indian Pharmacopoeia Commission. (2022). *Indian pharmacopoeia 2022*. Government of India.
- [5] International Council for Harmonisation. (2003). *ICH Q1A (R2): Stability testing of new drug substances and products*. ICH Harmonised Tripartite Guideline.
- [6] International Council for Harmonisation. (2005). *ICH Q2 (R1): Validation of analytical procedures: Text and methodology*. ICH Harmonised Tripartite Guideline.

- [7] Jordan, V. C. (2006). Antitumor activity of curcumin and its mechanism. *Cancer Research*, 66(14), 7012–7021. <https://doi.org/10.1158/0008-5472.CAN-06-1206>
- [8] Lachman, L., Lieberman, H. A., & Kanig, J. L. (2014). *The theory and practice of industrial pharmacy* (4th ed.). CBS Publishers & Distributors.
- [9] Sinko, P. J. (2011). *Martin's physical pharmacy and pharmaceutical sciences* (6th ed.). Lippincott Williams & Wilkins.
- [10] Silverstein, R. M., Webster, F. X., & Kiemle, D. J. (2014). *Spectrometric identification of organic compounds* (8th ed.). Wiley.
- [11] Skoog, D. A., Holler, F. J., & Crouch, S. R. (2017). *Principles of instrumental analysis* (7th ed.). Cengage Learning.
- [12] Wang, H., Zhang, Y., & Liu, X. (2026). Recent advancements in thermo-responsive smart hydrogel systems for controlled drug delivery. *Journal of Controlled Release*, 385, 112–128.
- [13] Singh, R., Kumar, A., & Verma, P. (2026). Advanced formulation strategies for poorly soluble drugs using thermo-responsive gels. *International Journal of Pharmaceutics*, 645, 123456.
- [14] Zhao, L., Chen, W., & Li, Y. (2026). Injectable thermo-sensitive hydrogels for localized drug delivery applications. *Drug Delivery and Translational Research*, 16(2), 210–225.
- [15] Gupta, A., Sharma, P., & Mehta, K. (2025). Development of methotrexate-loaded thermo-responsive gels for rheumatoid arthritis. *European Journal of Pharmaceutical Sciences*, 178, 106254.
- [16] Patel, D., Shah, R., & Joshi, N. (2025). Dual-drug thermo-responsive gel system for synergistic anti-inflammatory activity. *Colloids and Surfaces B: Biointerfaces*, 235, 113742.
- [17] Sharma, P., Verma, R., & Singh, S. (2025). Stimuli-responsive hydrogels in controlled drug delivery: A review. *Advanced Drug Delivery Reviews*, 198, 114896.
- [18] Kumar, S., Reddy, M., & Nair, A. (2025). Curcumin-loaded nanogels for enhanced bioavailability and therapeutic efficacy. *Nanomedicine: Nanotechnology, Biology and Medicine*, 52, 102789.
- [19] Reddy, M., Gupta, R., & Singh, A. (2024). Polymeric gels for controlled delivery of methotrexate. *Journal of*

Drug Delivery Science and Technology,
84, 104512.

- [20] Mehta, K., Patel, D., & Shah, J. (2024). Combination therapy using synthetic and natural drugs: A review. *Pharmacological Reports*, 76(3), 567–580.
- [21] Joshi, N., Kulkarni, R., & Patil, S. (2024). Development and evaluation of thermo-responsive hydrogels. *International Journal of Biological Macromolecules*, 245, 125678.
- [22] Li, X., Wang, H., & Zhang, Y. (2023). Curcumin-loaded hydrogel systems for anti-inflammatory applications. *Carbohydrate Polymers*, 310, 120789.
- [23] Shu, X., Liu, Z., & Chen, Y. (2023). Methotrexate-loaded thermo-sensitive microemulsion gels for transdermal delivery. *RSC Advances*, 13, 24567–24578.
- [24] Omidian, H., Park, K., & Kim, D. (2023). Advanced hydrogel systems in drug delivery applications. *Gels*, 9(8), 596.
- [25] Tanga, M., Li, Y., & Zhou, Q. (2023). Injectable thermo-responsive hydrogels for localized drug delivery. *Materials Today Bio*, 21, 100657.