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Research Article

Formulation of Naringin Solid Dispersion-Based Gel for Enhanced Solubility and Drug Release

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Abstract

Naringin, a natural bioflavonoid known for its therapeutic potential, faces problems in clinical use due to its low solubility. To address this, a topical gel was developed by using solid dispersions aimed at increasing both solubility and effectiveness. This was prepared using the kneading method and evaluated. Among the various formulations tested, F4 showed the highest drug release (98.6%), making it the most promising candidate. This optimized dispersion was then incorporated into a topical gel and evaluated. The final gel formulation (X5) exhibited a pH of 5.5, high drug content (98.6%), and a controlled release profile. Stability studies conducted over a period of 30 and 90 days, which demonstrated consistent physicochemical properties, with no observable changes in pH, drug content. These indicate that the developed solid dispersion gel has enhanced solubility and therapeutic use, offering an approach for topical drug delivery with the potential to improve patient adherence and clinical efficacy.

Keywords: *Naringin; Solubility; Kneading; Efficacy; Stability; In Vitro Studies*

Introduction

The demand for drug delivery systems that offer good patient convenience and therapeutic efficacy has grown in recent years. These systems not only improve treatment outcomes but also enhance patient compliance and ease of administration. Oral dosage forms continue to dominate due to their non-invasive nature and ease of use. However, they present limitations-particularly for drugs that exhibit low solubility in water. This leads to poor absorption in the gastrointestinal tract and reduced systemic availability [1,2]. This concern is relevant for the drugs that are classified as Biopharmaceutical Classification System (BCS) Class II, which have good permeability, but fail to dissolve adequately in gastrointestinal fluids [3,4]. Several strategies have been explored to overcome these challenges, including particle size reduction and the use of surfactants and polymeric carriers. Among these, solid dispersion has proven to be a more efficient technique [5-7]. It involves distributing a poorly water-soluble drug within a polymer matrix, leading to improved wettability and reduced particle size. The kneading method is a simple technique for preparing solid dispersions, which offers several benefits, including reduced solvent use and suitability for large-scale production [8].

Naringin is a flavonoid found in citrus fruits and is known for its beneficial effects. Despite these properties, its application is limited due to its poor water solubility (~0.1 mg/mL), low permeability, and instability [9,10]. Although some researchers have employed advanced delivery systems-like liposomes and nanocarriers-to address these issues, research on the topical delivery of naringin remains minimal [11,12].

Previous investigations have mostly focused on oral delivery systems. For example, Kumar., *et al*. (2021) utilized nanostructured lipid carriers to improve their antioxidant activity, and Bhattacharya., *et al*. (2020) developed a naringin-loaded nanoemulsion for oral use [13,14]. However, there is limited research on formulations using carriers like mannitol, which is combined with gelling agents such as Carbopol 940 for topical delivery. The current study focused on developing a topical gel formulation using naringin solid dispersions prepared by the kneading method, with mannitol serving as the carrier [15]. The optimized formulation was incorporated into a Carbopol-based gel, resulting in a stable and pharmaceutically accepted formulation.

Advantages

- Improved solubility through particle size reduction.
- Enhanced bioavailability.
- Controlled release capabilities.
- Increased wettability.
- Conversion to an amorphous state for improved therapeutic performance.

Materials

The study utilized a variety of pharmaceutical-grade materials. Naringin, the active pharmaceutical ingredient, and Mannitol, serving as the hydrophilic carrier, were obtained from Sigma Laboratories. Ethanol and Triethanolamine, used as solvents during formulation and gel preparation, were procured from HI Media Laboratories. Carbopol 940, employed as the primary gelling agent, along with Hydroxypropyl methylcellulose (HPMC), was also sourced from Sigma Laboratories. Additionally, Sodium dihydrogen phosphate (NaH_2PO_4) and Disodium hydrogen phosphate (Na_2HPO_4), required for buffer preparation in dissolution studies, were acquired from HI Media Laboratories and Sigma Laboratories, respectively.

Pre formulation studies of naringin

Determination of organoleptic properties

The properties of the pure drug-namely its physical state, colour, odour, and texture-were assessed through visual inspection to confirm its identity and initial quality.

Melting point determination

This is measured by using the capillary tube. A small sample was sealed in a capillary tube and heated. The temperature at which melting began was recorded. The test was repeated thrice, and the average value was reported [16].

Formulations

Formulation

Solid dispersions of Naringin were prepared using the kneading technique, a well-established method that promotes uniform dispersion of the drug within a hydrophilic polymer matrix and facilitates the conversion of the drug from a crystalline to a more soluble amorphous form [17,18]. Accurately weighed quantities of Naringin (100 mg) and mannitol, in pre-determined drug-to-carrier ratios, were thoroughly mixed using a mortar and pestle A small volume of an ethanol-water mixture (1:1 v/v) was slowly added to form a uniform paste. This mixture was then thoroughly kneaded to achieve consistent blending. The resulting mass was dried at 45°C in a hot air oven to eliminate any remaining solvent. After drying, it was ground into a fine powder and passed through a 24-mesh sieve to ensure uniform size. For improved uniformity, the powder was re-dried at the same temperature and further sieved through a 100-mesh sieve. The final solid dispersions were labelled as formulations F1 through F6, corresponding to different drug-to-polymer ratios. These were

stored in airtight containers until further evaluation. Furthermore, the preparation of multiple formulations allowed for the comparative assessment of how varying drug-to-carrier ratios influence these performance parameters [19,20].

Formulation code	Naringin (mg)	Mannitol (mg)	Ethanol (µl)	Water (ml)
F1	100	100	0.2	0.2
F2	100	200	0.3	0.3
F3	100	300	0.4	0.4
F4	100	400	0.5	0.5
F5	100	500	0.6	0.6
F6	100	600	0.7	0.7

Table 1: *Formulation variables of solid dispersions.*

Formulation of drug loaded Solid dispersion topical gel

Carbopol 940 was dispersed in distilled water and allowed to hydrate for 24 hours to ensure complete swelling. The swollen polymer was subsequently stirred at 1000 rpm with a magnetic stirrer to achieve a smooth and uniform dispersion [21,22]. After standing undisturbed for 15 minutes to eliminate air bubbles, the optimized solid dispersion of naringin (F4) was incorporated under continuous stirring to ensure uniform drug distribution. Gelation was induced by the gradual addition of triethanolamine, which neutralized the Carbopol and facilitated gel formation. Glycerine was added to improve moisture retention and texture [23,24], while methylparaben was included as a preservative to enhance stability and shelf life [25].

Formulation code	Naringin Solid dispersion F4 (mg)	Carbopol (gm)	Glycerine (ml)	Tri Ethanolamine (µl)	Methyl paraben (mg)	Water (ml)
X1	100	0.5	2	0.3	0.04	50
X2	100	1	2	0.3	0.04	50
X3	100	1.5	2	0.3	0.04	50
X4	100	2	2	0.3	0.04	50
X5	100	2.5	2	0.3	0.04	50

Table 2: *Formulation variables used in the preparation of the Solid dispersion gel.*

Evaluation studies of naringin solid dispersion

All the formulations (Fl- F6) were evaluated and characterized. They were evaluated for parameters such as FTIR, drug content, drug entrapment, and *in vitro* studies.

FTIR studies

This spectroscopy was used to examine the possible interactions between naringin and a carrier such as mannitol. The spectrum was recorded across a wavenumber of 400 to 4000 cm^{-1}, which helps in the identification of functional groups and assessing any molecular-level changes within the formulation [26,27].

Percentage of drug content

10 mg of the prepared formulation was weighed and dissolved in 10 mL of a previously prepared buffer solution. It was left to stand undisturbed for 24 hours to reach equilibrium. It was then stirred for 30 minutes to ensure complete solubilization. The resulting solution was filtered to remove any particulate matter. The filtrate was analysed using a UV-Visible spectrophotometer at 283 nm [28].

Drug entrapment efficiency

Drug entrapment efficiency was evaluated by dispersing 10 mg of the formulation in 10 mL of a saline-buffer solution. The dispersion was left aside for 24 hours and then stirred for an additional 30 minutes to ensure uniform mixing. Following filtration, the clear solution was analysed spectrophotometrically at 283 nm. Entrapment efficiency was calculated as the percentage of the initially used drug that remained encapsulated in the formulation.

In vitro studies

The release behaviour of naringin from the solid dispersion formulations (F1-F6) was studied using a USP Type II dissolution apparatus. Each sample was placed in 900 mL of dissolution medium, at a temperature of 37 ± 0.5°C, and stirred at 100 rpm [29]. At predetermined intervals, aliquots were withdrawn, filtered to remove any residual undissolved materials, and analysed at 283 nm using a UV spectrophotometer. This allowed for measurement of the cumulative drug release over time.

Evaluation of gel formulation

pH and viscosity

The pH of the gel formulation was measured using a digital pH meter. Viscosity was evaluated using a Brookfield viscometer operated at 100 rpm, which provided insights into the gel's ease of application [30].

Drug content analysis

To assess the drug distribution within the gel, a pre-weighed amount of the gel formulation was dissolved in ethanol. The solution was then subjected to spectrophotometric analysis at 283 nm to determine the concentration of naringin, ensuring consistency and uniformity in drug content across the formulation.

Spreadability evaluation

This is estimated by placing a known quantity of the gel between two glass plates. A standardized weight was then applied for a fixed duration. Afterward, the diameter of the resulting spread circle was measured. This parameter is essential in evaluating how evenly the gel can be applied to the skin [31].

Stability study

The gel formulation was subjected to short-term accelerated stability testing under specific storage conditions. Samples were evaluated at 30-day and 90 days intervals for changes in appearance, drug content, and other physicochemical parameters to assess formulation stability and predict shelf life [32].

Results and Discussion

Organoleptic property: The observed organoleptic property of the drug is given below.

S. No	Description	Naringin drug
1	State	Solid
2	Color	Pale yellow
3	Odor	Odorless

Table 3: *Organoleptic properties of naringin.*

Melting point

The experimentally determined melting point of naringin was 171°C, which aligns with the reported literature value. This consistency supports the compound's identity and suggests a high level of purity.

Solubility of naringin

Naringin, a class II drug, is low soluble and highly permeable. The experimental results are mentioned in the following table.

Solvent	Solubility	Observation
Water	Soluble	Poorly soluble
Methanol	Soluble	Soluble (50 mg/ml)
Ethanol	Soluble	soluble (50 mg/ml)

Table 4: *Solubility studies of naringin.*

Characterization and evaluation studies of naringin solid dispersion

FTIR studies of naringin

The infrared (IR) spectral analysis of the compound displayed characteristic absorption bands corresponding to specific functional groups, confirming the structural identity of naringin. A broad absorption peak observed at 3283.4 cm^{-1} indicated the presence of hydroxyl (-OH) groups. Absorption bands at 2903.0 cm^{-1} and 1403.64 cm^{-1} were attributed to the C-H stretching of methyl (CH_3) and bending vibrations of methylene (CH_2) groups, respectively. The presence of aromatic moieties was evidenced by absorption peaks at 1627.5 cm^{-1}, corresponding to aromatic C=C stretching, and at 822.0 cm^{-1}, indicating aromatic ring vibrations. Additionally, the ether (C-O-C) functional group was confirmed by a strong absorption band at 1040.1 cm^{-1}. These spectral features are consistent with the known chemical structure of naringin, supporting its identity and the integrity of the compound.

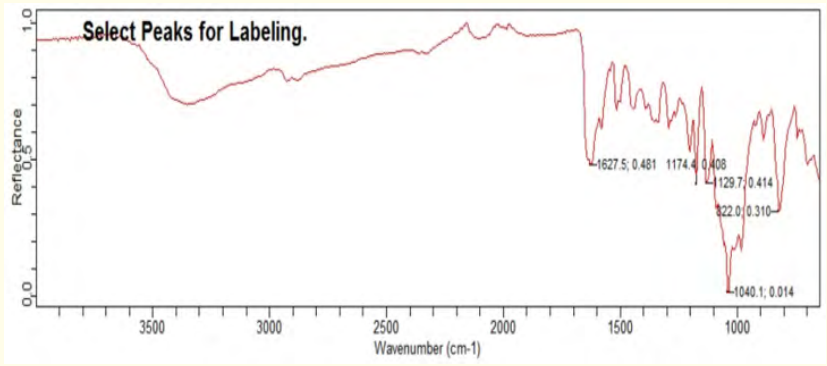

Figure 1: *FTIR spectrum of pure sample of naringin.*

Functional groups	Wave numbers (cm^{-1}) obtained
O-H	3283.4
CH_3	2903.0
Aromatic C=C stretching	1627.5
C-H group of CH_2	1403.64
C-O-C stretching vibration	1040.1
Aromatic ring	822.0

Table 5: *FTIR Characteristic peaks of naringin.*

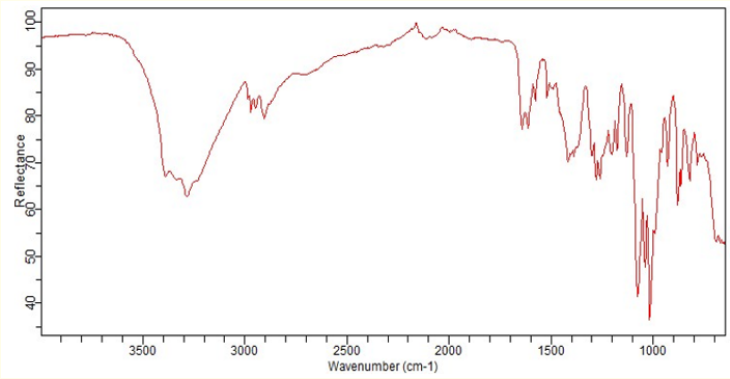

Figure 2: *FTIR spectra of optimized F4.*

Functional groups	Wave numbers (cm^{-1}) obtained
O-H	3283.4
CH_3	2903.0
Aromatic C=C stretching	1644.3
C-H group of CH_2	1415.64
C-O-C stretching vibration	1073.7
Aromatic ring	877.9

Table 6: *FTIR characteristic peaks of optimized formulation.*

Percentage of drug content

All formulations were evaluated for drug content, with results ranging from 84.57% to 98.10%. These values indicate efficient drug loading, as the majority of the formulations demonstrated high drug incorporation within the solid dispersion matrix.

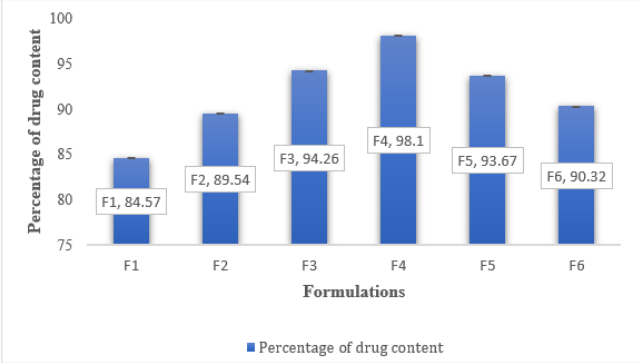

Figure 3: *Percentage of drug content for naringin formulations.*

Drug entrapment efficiency (in percentage)

The solid dispersions exhibited drug entrapment efficiencies between 81.12% and 97.15%, reflecting successful incorporation of the drug into the polymeric matrix with only minor losses observed during preparation.

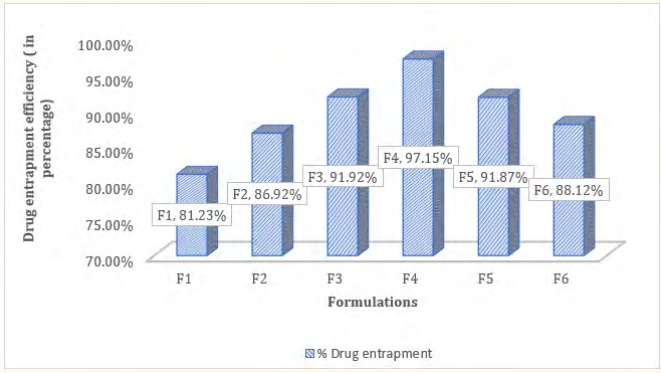

Figure 4: *Drug entrapment efficiency of all formulation.*

In vitro studies

These studies were carried out for formulations F1 to F6 to evaluate their drug release profiles. The results demonstrated drug release ranging from 71.63% to 98.65%. Among these, formulation F4 exhibited the highest release (98.65%) along with favourable physicochemical properties, making it the most promising candidate for further development. Detailed data is illustrated in the figure 5.

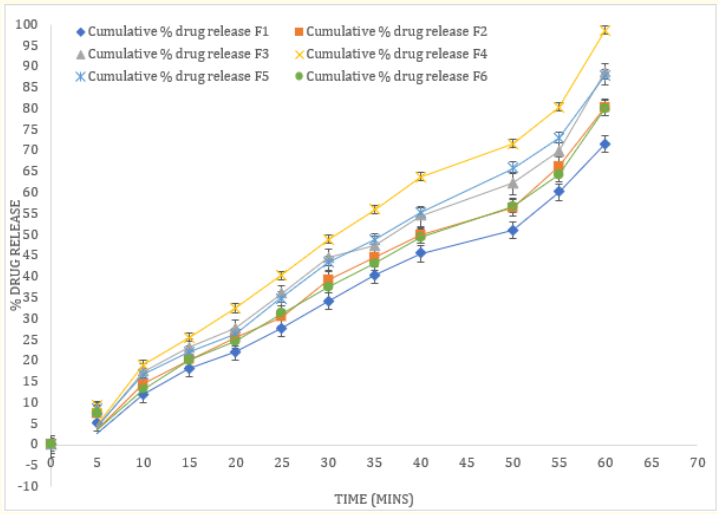

Figure 5: *Cumulative percentage of drug release of F1 to F6.*

Kinetics of drug release

To gain insight into the release profile of the developed formulation was evaluated using kinetic models. As shown in figure 6, the data were fitted into various models, allowing for analysis of the release pattern. The correlation coefficient (R^2) for each model was calculated to determine the best fit, with the model showing the highest R^2 value considered most appropriate for describing the release kinetics. The dissolution data were further examined using kinetic plots, including zero-order models, to assess the reliability and predictability of drug release from the system.

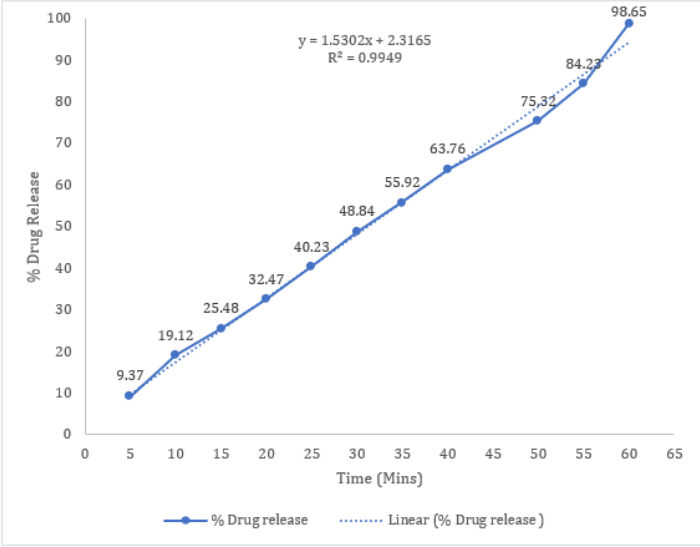

Figure 6: *Zero-order kinetics plot.*

Among the various kinetic models applied to analyse the drug release profile of the optimized Naringin formulation, the zero order demonstrated the highest correlation coefficient (R^2 = 0.9949), indicating the best fit. This suggests that the release mechanism follows an anomalous diffusion pathway.

Statistical evaluation

To assess the drug release performance of F1 through F6, statistical analysis was conducted using Welch's unpaired t-test, specifically comparing the percentage of drug released at the 60-minute interval. Among all the tested, F4 exhibited the highest drug release of 98.65 ± 0.01%, which was notably greater than the release observed from F1 (71.63 ± 0.05%), F2 (80.26 ± 0.04%), F3 (88.72 ± 0.05%), F5 (87.89 ± 0.03%), and F6 (79.86 ± 0.03%). The p-values obtained from pairwise comparisons between F4 and each of the other formulations were all below 0.0001, confirming statistically significant differences at a 95% confidence level. These results clearly demonstrate that formulation F4 has a significantly enhanced drug release profile, justifying its selection as the optimal candidate for further formulation development.

Characterization and evaluation studies of naringin solid dispersion gel

Physical parameters

The gels that were developed appeared clear, smooth, and uniform, with no visible clumps or particles. Their pH values ranged between 4.5 and 5.5, which is considered suitable for topical application and helps reduce the likelihood of skin irritation. Viscosity, a factor that influences both the ease of application and drug release, was recorded between 2,300 and 3,560 cps. These variations were mainly due to differences in the concentrations of Carbopol 940 and Mannitol used in the formulations. An increase in Mannitol content resulted in thicker gels. The drug content was consistently high across all samples, ranging from 93% to 98.6%, indicating reliable mixing and uniform distribution of the active ingredient.

S. No		Formulations	Viscosity (Cps)	Morphology	Content of drug (%)	pH
i.	1	X1	2300	Homogenous	93.0±0.5	5.5 ± 0.1
ii.	2	X2	2700	Homogenous	93.5±0.3	5.5 ± 0.1
iii.	3	X3	3000	Homogenous	95.4±0.4	5.5 ± 0.1
iv.	4	X4	3400	Homogenous	95.5±0.6	5.5 ± 0.2
v.	5	X5	3560	Homogenous	98.6±0.2	5.5 ± 0.1

***Table 7**: Evaluation parameters of naringin solid dispersion loaded gel.*

Stability study

Formulation F4 was subjected to stability testing by ICH guidelines to evaluate its shelf life and overall durability. At regular intervals, drug content was measured to monitor any changes over time. The results indicated that the formulation maintained its stability throughout the study period, with no significant degradation or variation observed (Table 8 and figure 7).

Stability	Temperatures					
	25 ± 2°C			40 ± 2°C		
Days	pH	Drug content	Homogeneity	pH	Drug content	Homogeneity
Initial	5.5 ± 0.1	98.6	Smooth and transparent	5.5 ± 0.1	98.6	Smooth and transparent
10 days	5.5 ± 0.2	98.3	Smooth and transparent	5.5 ± 0.2	98.3	Smooth and transparent
20 days	5.4 ± 0.1	98.1	Smooth and transparent	5.3 ± 0.2	98.15	Smooth and transparent
30 days	5.3 ± 0.2	98.0	Smooth and transparent	5.2 ± 0.3	98.0	Smooth and transparent
90 days	5.1 ± 0.1	98.0	Smooth and transparent	5.0 ± 0.1	96.5	Smooth and transparent

***Table 8:** Stability studies of naringin solid dispersion loaded gel.*

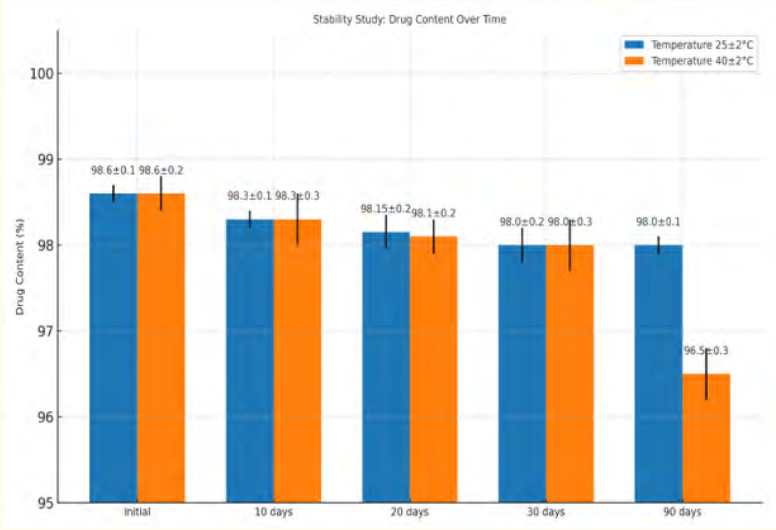

Figure 7: *Stability graph of naringin solid dispersion gel.*

Conclusion

The present study successfully developed and evaluated a topical gel formulation of naringin using solid dispersion technology via the kneading method. Among the six formulations prepared with varying drug-to-carrier ratios, formulation F4 demonstrated superior performance, achieving a maximum drug release of 98.65% at 60 minutes. The marked enhancement in solubility and dissolution rate is primarily attributed to the reduction in particle size, increased wettability, and partial transformation of the drug, as evidenced by FTIR analysis. Among the formulations studied, mannitol emerged as an efficient hydrophilic carrier, contributing significantly to the improved performance of the system. The optimized solid dispersion (F4) was successfully incorporated into a Carbopol-based gel. The resulting formulations exhibited desirable physicochemical characteristics, including suitable pH, homogeneity, viscosity, and high drug content (up to 98.6%). The gel formulation also showed excellent stability under accelerated storage conditions over 90 days, with no significant changes in appearance, pH, or drug content.

Overall, this study demonstrates that solid dispersion-based gel formulations offer a promising strategy to enhance the topical delivery of poorly water-soluble compounds like naringin. The use of a simple and scalable preparation method, combined with effective polymer carriers, supports the potential of this formulation for further preclinical and clinical development in topical therapeutic applications.

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