Nanomicelle-Based Sublingual Film for Repaglinide Delivery: Formulation, Optimization, and *In Vitro* Evaluation

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Abstract

Background: Repaglinide is an antidiabetic agent classified as a meglitinide. It exhibits poor solubility and high permeability, categorizing it as a Class II drug according to the Biopharmaceutics Classification System (BCS). Its poor water solubility contributes to its limited oral bioavailability.

Methods: In this study, the dissolution rate of repaglinide was improved through the nanomicelles (NMs) formation and converting these NMs into a sublingual film (SLF) for its rapid disintegration, and ease of administration. The thin film hydration method was employed for the preparation of repaglinide micellar dispersions using Soluplus® and poloxamer 338. Furthermore, repaglinide NM-loaded SLF were developed via the solvent casting technique. The Box-Behnken design was used to study the effect of different formulation parameters on film disintegration time and percentage elongation (E%).

Results: The optimized formulation exhibited a desirability value of 0.73, with a disintegration time of 23 seconds and a percentage elongation of 17%. Drug release was significantly enhanced, achieving 100% release within 10 minutes, whereas the conventional film demonstrated only 31% release over the same period.

Conclusion: The developed NM-loaded SLF represents a promising approach for enhancing the release of repaglinide, potentially improving its oral delivery and therapeutic performance.

Keywords: Repaglinide, Box-Behnken design, Polyvinyl alcohol, Film casting method, Disintegration time

Introduction

Sublingual oral films (SLFs) are solid dosage forms that dissolve or disintegrate within seconds of being placed in the mouth, eliminating the necessity for water or chewing. Polymers, plasticizers, surfactants, flavorings, colorants, and sweeteners constitute oral films. Hydrophilic polymers are employed in the formulation of SLFs, which rapidly disintegrate in the oral cavity, thereby enabling the medication to enter the systemic circulation.[1]

There are numerous benefits to SLFs, such as ease of administration in pediatric, geriatric, and psychiatric patients who may have difficulty swallowing conventional tablets. The medication has the potential to initiate action promptly due to its rapid dissolution and bypasses first-pass metabolism and enables rapid drug absorption. Therefore, these films provide enhanced bioavailability, particularly for hydrophobic and poorly soluble medications.[2]

In order to be manufactured as an SLF, pharmaceuticals must meet a variety of requirements, including a pleasant flavor, a low dose that is suitable for incorporation into the film matrix, and sufficient water solubility.[3] To enhance solubility and prevent grainy texture and sedimentation during production, drugs can be formulated as nanomicelles (NMs) prior to incorporation into the film matrix.[4]

Repaglinide is a medication used to manage diabetes, classified under the meglitinide category of pharmaceuticals. It rapidly stimulates insulin secretion from pancreatic β-cells in a glucose-dependent manner. The inhibition of ATP-sensitive potassium channels facilitates increased calcium influx, thereby promoting insulin release.[5] Despite its therapeutic efficacy, repaglinide is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by poor oral bioavailability (approximately 56%), primarily due to low water solubility and extensive first-pass metabolism.[6] Accordingly, formulating repaglinide into NMs and incorporating them into an SLF represents a rational strategy to overcome these challenges.

In this study, the dissolution rate of repaglinide was improved by formulating it into NMs, which were then incorporated into an SLF that rapidly disintegrates, thereby enhancing both dissolution and ease of administration.

Materials

Repaglinide was obtained from Huainan Lianke Biological Medicine Co., Ltd., China. Soluplus® was obtained from BASF SE, Ludwigshafen, Germany. Poloxamer 338 was obtained from Eastman Chemical Company, USA. Potassium dihydrogen phosphate (KH_2PO_4) and disodium hydrogen phosphate (Na_2HPO_4) were sourced from Panreac, Barcelona, Spain. High-performance liquid chromatography (HPLC)-grade methanol was obtained from Chem-Lab, Belgium. Polyvinyl alcohol (PVA) was obtained from HIMEDIA, India. Mannitol was obtained from Thomas Bakers, India. Polyethylene glycol 400 (PEG 400) was obtained from Loba Chemie Pvt. Ltd., India, whereas croscarmellose sodium was acquired from Shanghai-Ruizheng, China.

Preparation of repaglinide nanomicelle (REP-NM)

The micellar dispersion of repaglinide was prepared using the thin film hydration method.[7] In this process, 35 mg of Soluplus® and 19 mg of Poloxamer 338, were dissolved in 5 mL methanol in a round-bottom flask. Separately, repaglinide (0.5 mg) was dissolved in another 5 mL methanol in a beaker. Both solutions were agitated for 30 minutes at 40°C. Subsequently, the drug solution was gradually added to the polymer solution under continuous stirring. The mixture was then connected to a rotary evaporator, at 150 rpm and 60 °C under a vacuum pressure of 7.4 kPa for 30 minutes until a thin film was formed.[8] The films were allowed to dry overnight to ensure complete desiccation. The dried film was then added to 12 mL of deionized water and moistened. Micelles were produced by stirring at a rate of 50 rpm at 50 °C, for 2 hours using a magnetic stirring.[9]

In Vitro Characterization of REP-NM

Particle Size and Polydispersity Index (PDI) Analysis

The particle size and polydispersity index (PDI) of the NMs were evaluated for all prepared formulations using the Zetasizer (Malvern Instruments Ltd., United Kingdom). This measured the intensity of scattered light over time at 25 °C and a scattering angle of 90°.

Encapsulation Efficiency (EE%)

Encapsulation efficiency was determined using an Amicon® Ultra-4 centrifugal filter with a molecular weight cutoff (MWCO) of 10 kDa. REP-NM were centrifuged at 4000 rpm for 30 min. The absorbance of the filtrate was measured using a UV–visible spectrophotometer at the maximum wavelength (λmax) of 242 nm to determine the concentration of repaglinide. Drug concentration was calculated using an established calibration curve. Samples were subsequently diluted with methanol prior to analysis. Each experiment was performed in triplicate.

The encapsulation efficiency (EE%) of each formulation was calculated using the following equation:

$$\boldsymbol{EE}\% = \frac{(\text{Amount of REP entrapped} \times 100)}{\text{Actual REP content}}$$

Zeta Potential Determination

The zeta potential of the selected formulation was evaluated to determine the type and magnitude of its surface charge using the same analyzer (Malvern Zetasizer, Spectris Company, United Kingdom) at 25 °C.

Drug Loading (DL%)

DL% was experimentally evaluated using the indirect ultrafiltration method. 3 mL of the NM dispersion were transferred into Amicon Ultra-4 centrifugal filter tubes (MWCO 10 kDa) and centrifuged at 4000 rpm for 20 min at 25 °C. The filtrate containing the free drug was collected and analyzed using a UV–visible spectrophotometer at 242 nm. The amount of encapsulated drug was calculated by subtracting the amount of free drug from the total amount initially added.[10]

$$\text{DL}\% = \frac{\text{weight of REP} - \text{NM}}{Total\ weight\ of\ NM\ (REP + polymer)} \times 100$$

Determination of Surface Morphology

The surface morphology of the lyophilized optimized REP-NM formulation was examined using a field emission scanning electron microscope (FESEM). The sample was mounted onto the FESEM specimen holder using double-sided carbon tape. Surface characteristics were evaluated by observing the samples under different magnification levels.[11]

Preparation of REP-NM-loaded SLF

REP-NM-loaded SLFs were developed using a computer-based experimental design based on the Box-Behnken design (BBD). They were prepared by the solvent casting method using PVA as the film-forming polymer at various concentrations. PVA was dissolved in 15 mL of hot distilled water at 70°C under continuous stirring for 60 minutes to obtain a homogeneous solution. After cooling, a plasticizer (PEG 400) was added at varying concentrations, under continuous stirring for 30 minutes. Mannitol (4%) was incorporated as a sweetening agent, and croscarmellose was added as a superdisintegrant to the polymeric solution.[12]

The REP-NM aqueous dispersion was incorporated into the polymer solution with continuous stirring for an additional hour. The solution was sonicated for 1 minute, followed by a resting period to eliminate entrapped air bubbles. The final solution was left to dry overnight at room temperature in a petri dish. Then, the film was peeled off and stored in aluminum foil for further assessment. A film containing pure REP was also produced to evaluate the effect of NMs on the drug characteristics and release behavior.[13]

Optimization of parameters based on the Box-Behnken design (BBD)

BBD is a statistical approach employed to optimize processes and experimental designs. It is particularly useful in response surface methodology for evaluating the relationships among multiple variables. It was performed using Design-Expert® software (version 13). The three independent variables studied were X1 (PVA concentration in the range of 28.5% to 42.8%), X2 (PEG concentration between 10% and 30%), and X3 (croscarmellose concentration between 0% and 4%). The dependent variables were Y1 (disintegration time) and Y2 (percentage elongation, %E), as presented in Table 1. Analysis of variance

(ANOVA) was conducted to determine the statistical significance of the model at a significance level of $\alpha = 0.05$ ($p < 0.05$).

Fifteen formulations of REP-NM-based SLF were developed utilizing Design-Expert® software, each consisting of a distinct combination of the three listed variables. The formulas are presented in Table 1.

Table 1. Formulas of REP-NM based SLF proposed by BBD

Formula	PVA%	PEG 400%	Croscarmellose%
1	42.8	10	2
2	42.8	20	4
3	35.7	10	4
4	28.5	10	2
5	35.7	30	0
6	28.5	20	4
7	42.8	20	0
8	35.7	20	2
9	42.8	30	2
10	35.7	20	2
11	28.5	30	2
12	35.7	30	4
13	35.7	10	0
14	35.7	20	2
15	28.5	20	0

Evaluation of REP-NM based SLF

In vitro disintegration test (DT)

The disintegration test involved placing a 2×2 cm^2 film in a glass Petri dish containing 10 mL of water. Stirring was performed at 10-second intervals. The time required for complete disintegration of the film was recorded. The determination of DT was performed in triplicate for all formulations.

Mechanical properties measurement

Applying tension to the film sample causes stretching, also known as strain. Strain is defined as the deformation of a film divided by its initial length. The percentage elongation was calculated by measuring the increase in length of the film and using the following formula:[14]

$$\%Elongation = \frac{Final\ length\ -\ Initial\ length}{Initial\ length} \times 100$$

Evaluation of formulation

The optimized formulation was subsequently subjected to further evaluation as described in the following sections.

Visual appearance

The film's visual characteristics, including homogeneity, surface texture, and degree of transparency were evaluated by visual inspection.

Weight variation test

Weight variation was assessed by individually weighing 3 evenly cut film pieces (2 × 2 cm) using a digital balance and calculating the average weight.

Thickness

Three films were randomly selected, and their thickness was measured at 5 different points using an electronic vernier.

Drug content

A film segment containing 0.5 mg of REP was added to a 100 mL beaker containing phosphate buffer (pH 6.8) and stirred using a magnetic stirrer for 30 minutes. After filtration and dilution, the absorbance of the resultant solution was measured with a UV spectrophotometer (Shimadzu UVmini-1240) to determine the drug concentration.

Surface pH

In this experiment, the film was in contact with 5 mL of distilled water at room temperature, and the pH was measured with a pH meter. This procedure was performed three times, and the average value was calculated.

Folding endurance measurement

The folding endurance of the film was evaluated by repeatedly folding a single film at the same point until it either fractured or reached a maximum of 300 manual folds, considered sufficient to signify acceptable mechanical properties. The number of folds a patch can withstand at a particular site without failing indicates its folding endurance. This evaluation was performed on three randomly selected films.

In-vitro dissolution study

Selected formulations were assessed in comparison to a pure drug film. The films were placed at the bottom of a dissolution vessel containing 200 mL of sodium phosphate buffer (pH 6.8) with 1% w/v sodium dodecyl sulfate as the dissolution media. The system was maintained at 37°C and stirred at 100 rpm using the USP dissolution apparatus type II (paddle type). Three-milliliter samples were withdrawn at predetermined time intervals (2, 4, 6, 8, 10, and 15 minutes) and replaced with an equal volume of fresh dissolution medium. Samples were filtered through a 0.22 µm filter and analyzed at 284 nm using a UV spectrophotometer (Shimadzu UVmini-1240). All measurements were performed in triplicate.

Results and Discussion

In Vitro Characterization of REP-NM

Particle Size and Polydispersity Index (PDI) Analysis

The particle size and polydispersity index (PDI) of the REP NMs were analyzed using a Malvern Zetasizer. The analysis showed a mean particle size of 61.25 nm and a PDI of 0.085, indicating a narrow particle size distribution. The entrapment efficiency (EE%) of the formulation was 87%.

Measurement of the Zeta Potential

The zeta potential of the optimized REP-NM formulation was -3.133 ± 0.36 mV (Figure 1). The stability of NMs can be enhanced through steric stabilization, where polymer or surfactant layers create a physical barrier that prevents particle aggregation via steric hindrance. Soluplus® micelles exhibited an inherently negatively charged surface. The negative surface charge of the nanomicelles suggests that the outer shell of Soluplus®

possesses a higher negative charge density than the encapsulated drug molecules. Additionally, the presence of polar functional groups in the Soluplus® structure facilitates interactions with surrounding water molecules, resulting in the formation of a hydration layer. This hydration shell contributes to the observed negative zeta potential of the nanomicelle system.[15]

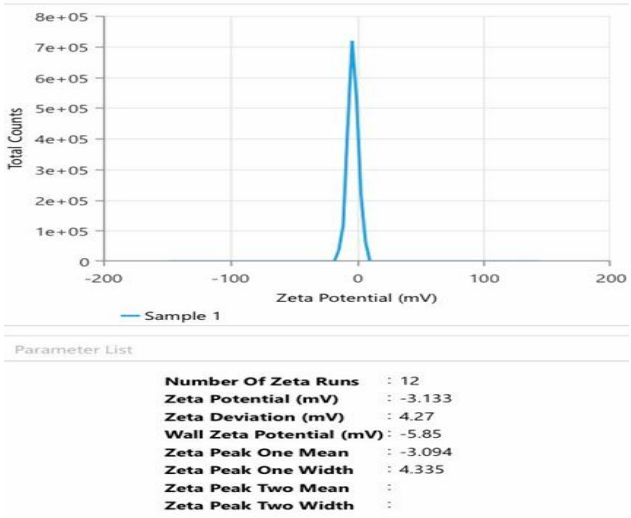


Figure 1: Zeta potential of the REP-NM

Drug Loading (DL)

DL% is influenced by the characteristics and concentration of the polymers, as well as the properties and lengths of the core-forming and shell-forming blocks within the micelles. The DL of the selected formulation averaged 14.5 ± 0.09%.

Determination of Surface Morphology

Based on the obtained data, the NMs exhibited an approximately spherical morphology within the nanoscale range. Field emission scanning electron microscopy (FESEM) was used to evaluate the surface morphology of the optimized formulation. The images obtained at different magnifications revealed the micelles of the selected formulation. As observed in the micrographs in Figure 2, the micelles exhibited small and uniform particle sizes with smooth and homogeneous surfaces.

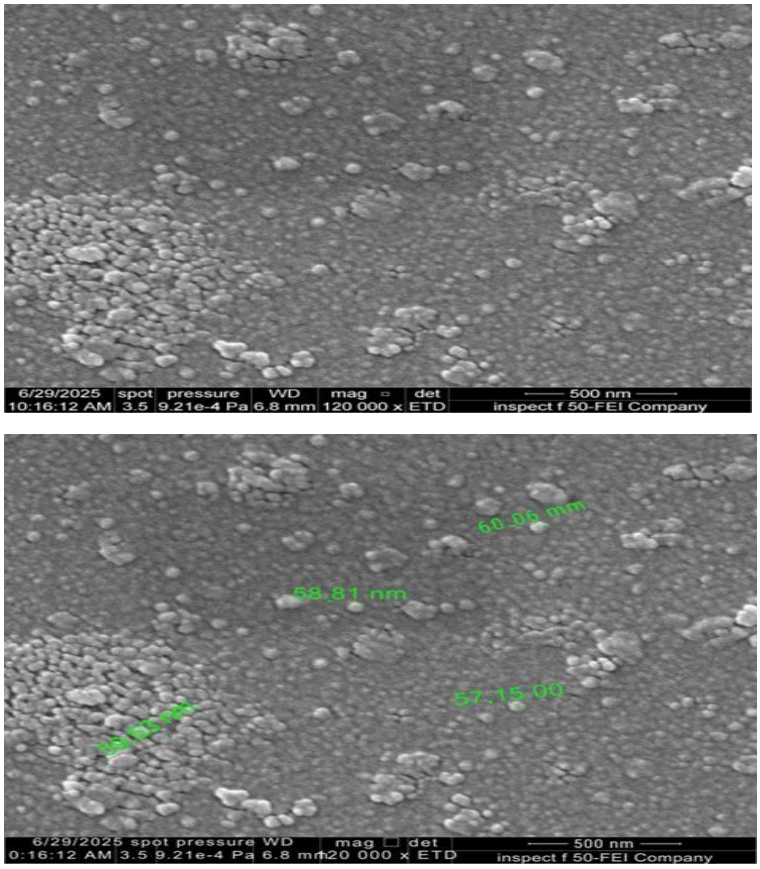


Figure 2: Field Emission Scanning Electron Microscopy (FESEM) of REP-NM

Preparation and characterization of REP-NM-based SLF

The film casting method was successfully employed for preparation of SLF, offering advantages such as safety, rapidity and reproducibility. The results of the 15 formulations with different levels of disintegration time (DT) and percentage elongation (%E) are presented in Table 2.

Table 2. Responses of REP -NM-based SLF using BBD. Experiments were done in triplicate, with results represented as mean ± SD

Formula	**DT (sec)**	**%E**
F1	41.1±1.6	24.7±0.2
F2	31.3±0.1	21.0±0.13
F3	21.0±0.11	14.1±0.5

F4	28.1±0.08	11.0±3.7
F5	27.0±0.11	8.5±0.9
F6	25.0±0.8	8.1±1.7
F7	45±1.4	20.7±0.12
F8	23.0 ±0.3	12.0±1.5
F9	37.0±0.14	17.0±2.1
F10	21.3±0.15	12.42±0.7
F11	30.1±1.23	6.08±0.11
F12	20.0±1.12	8.11±2.18
F13	31.0±0.3	15.3±0.15
F14	20.1±1.0	10.4±1.3
F15	34.1±0.9	7.75±2.13

Analysis of Box-Behnken Design

Multiple models, including linear, 2-factor interaction (2FI), quadratic, and cubic models, were evaluated for their suitability for the dependent variables (DT and %E) using Design-Expert® software. The model exhibiting the highest adjusted R^2 and adequate precision was selected. As presented in Table 3, the predicted R^2 values for all responses demonstrated reasonable agreement with the adjusted R^2 values.

Table 3. Statistical summary of response surface models for DT and %E.

Responses	R^2	R^2 Adjusted	R^2 Predicted	Adequate precision	Significant factors
DT	0.98	0.96	0.86	20.9	PVA %, Croscarmellose %
%E	0.99	0.98	0.95	29.5	PVA % , PEG 400 %

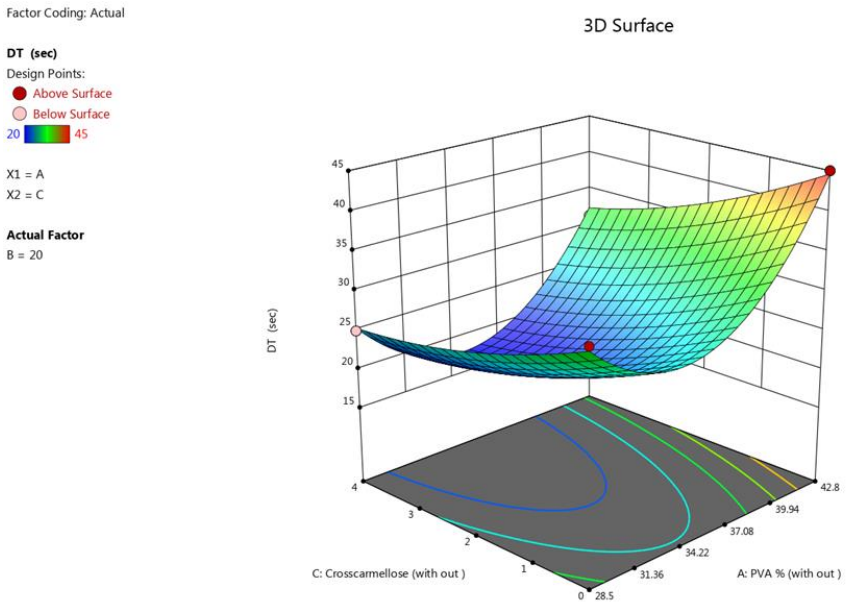
Effects of formulation variables on disintegration time

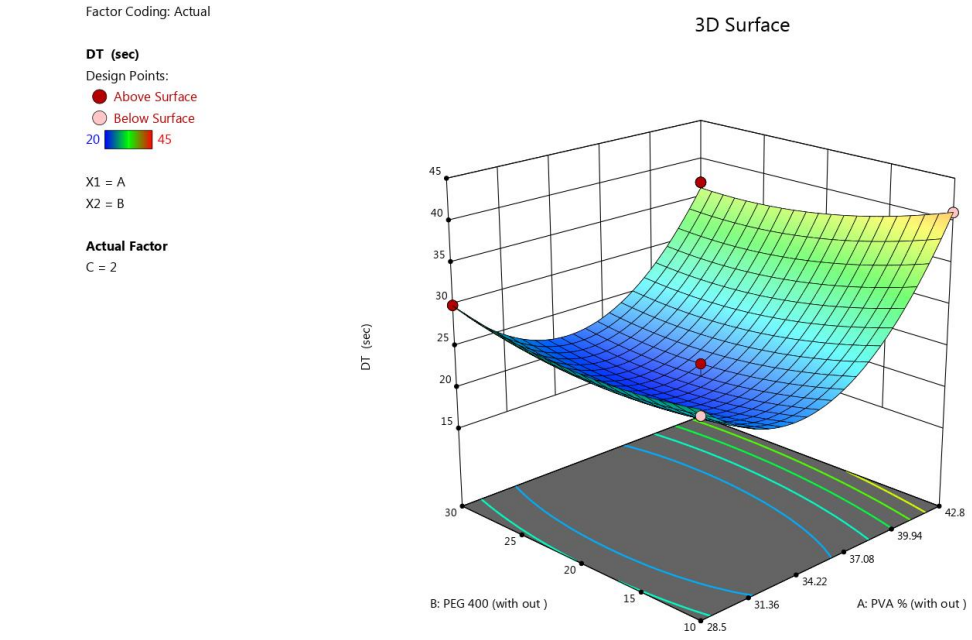
REP-NM-based SLF exhibited a mean disintegration time ranging from 20 ± 1.1 to 45 ± 1.4 seconds, as presented in Table 2. Analysis of Variance (ANOVA) demonstrated that PVA% (X1) and Croscarmellose % (X3) significantly affected DT ($p < 0.05$), whereas

PEG 400% (X2) showed no significant effect ($p > 0.05$). The effects of the independent variables on DT are illustrated in the 3D response surface plots (Figure 3).

The concentration of PVA (X1) had a significant positive effect on disintegration time ($P = 0.0003$), indicating that increasing PVA concentration prolonged DT. Films with higher polymer content formed a thicker gel layer upon contact with the medium, leading to an extended disintegration time. Similar findings were reported for metoprolol tartrate films.[16]

In contrast, increasing croscarmellose concentration (X3) significantly decreased disintegration time ($P = 0.0002$). Croscarmellose sodium is a cross-linked polymer of sodium carboxymethyl. Its porous particle structure facilitates rapid liquid absorption through capillary action and promotes disintegration via a wicking mechanism.[17]





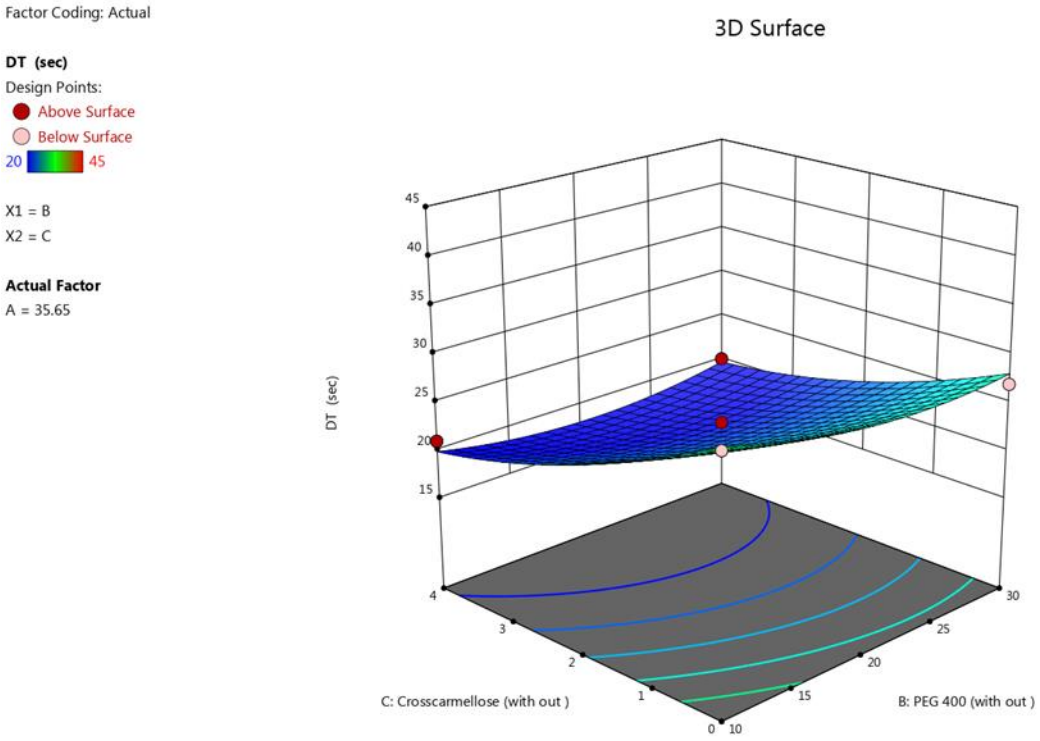


Figure 3: Three-dimensional response surface plots showing the effect of independent variables on DT.

Effects of formulation variables on% E

The percentage elongation of REP-NM-based SLF ranged from 6.1 to 24.7%. ANOVA results indicated that PVA% (X1) and PEG 400% (X2) significantly influenced %E ($p < 0.05$), whereas croscarmellose concentration had no significant effect ($P > 0.05$). The effects of the independent variables on %E are depicted in the 3D response surface plots, as shown in Figure 4.

A direct relationship was observed between %E and the concentration of PVA and PEG 400. The correlation between E% and PVA concentration ($p < 0.0001$) showed a notable increase in elongation with higher polymer levels, attributed to enhanced elasticity of the polymer matrix. Similar observations were reported by Trivedi et al.[18]

Regarding PEG 400%, the 3D response surface plot demonstrated a significant positive effect on %E ($p < 0.0001$). Increasing plasticizer concentration increased film flexibility and reduced stiffness, resulting in higher percentage elongation. This observation may be attributed to increased molecular mobility and the hydrogen bond formation between the polymer and plasticizer, enhancing flexibility and resistance to rupture.

Factor Coding: Actual

%E (with out)

Design Points:

Above Surface

Below Surface

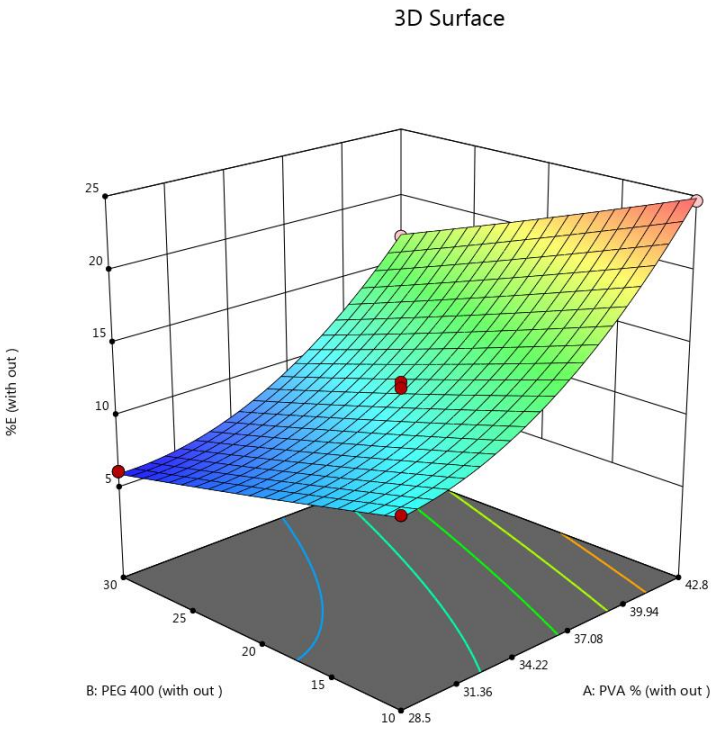
6.08 24.7

X1 = A

X2 = B

Actual Factor

C = 2



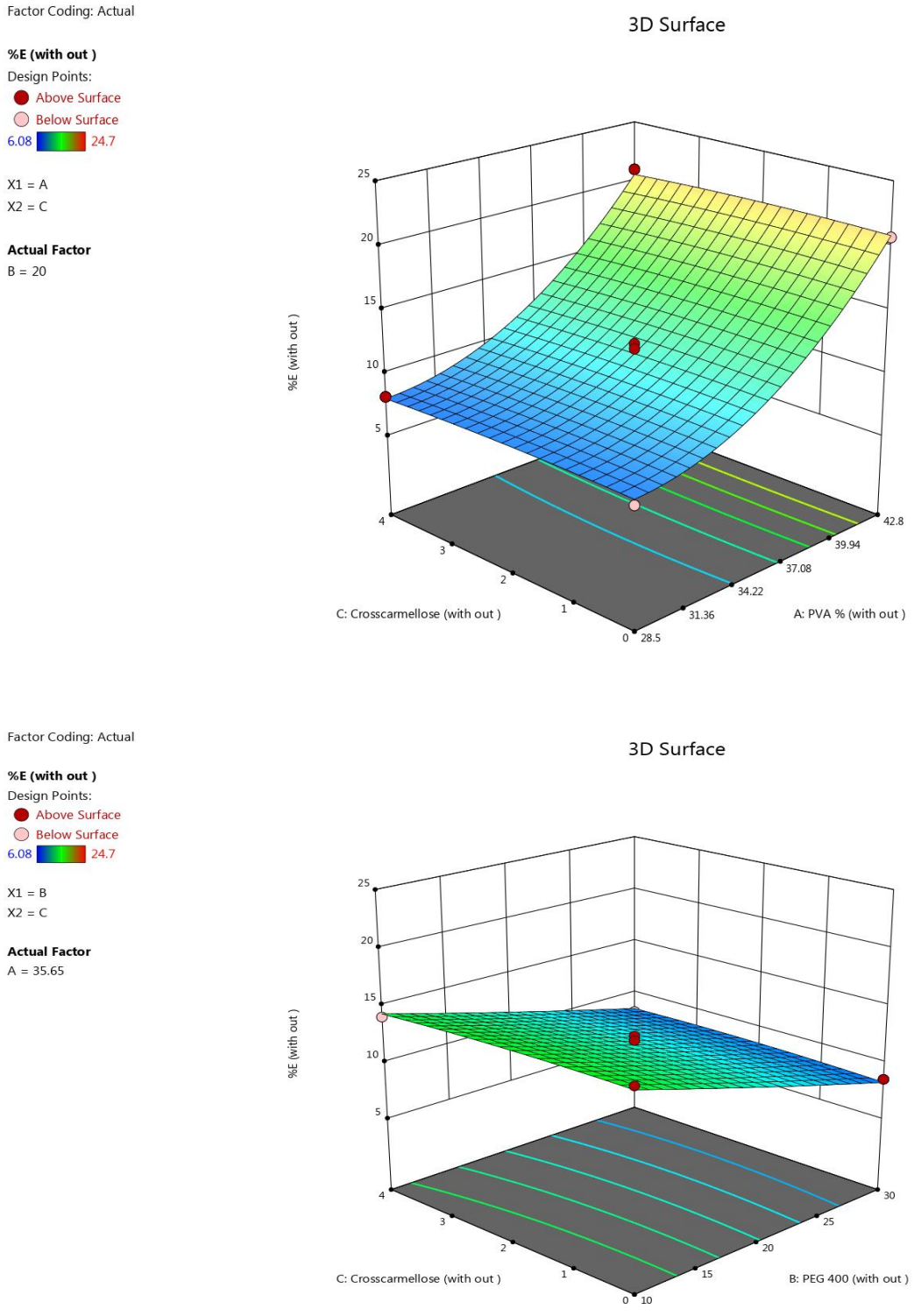


Figure 4. Three-dimensional response surface plots showing the effect of independent variables on %E

Diagnostic plots of DT and %E responses

The residual diagnostics, comprising the residuals vs. predicted plot and the normal plot of residuals, confirmed the adequacy of the model assumptions. The randomly scattered points within the red border lines in the residuals vs. predicted plot in Figure 5, confirm homoscedasticity. However, the linear distribution of points in the normal plot of residuals in Figure 6 indicates a normal distribution of residuals.[19]

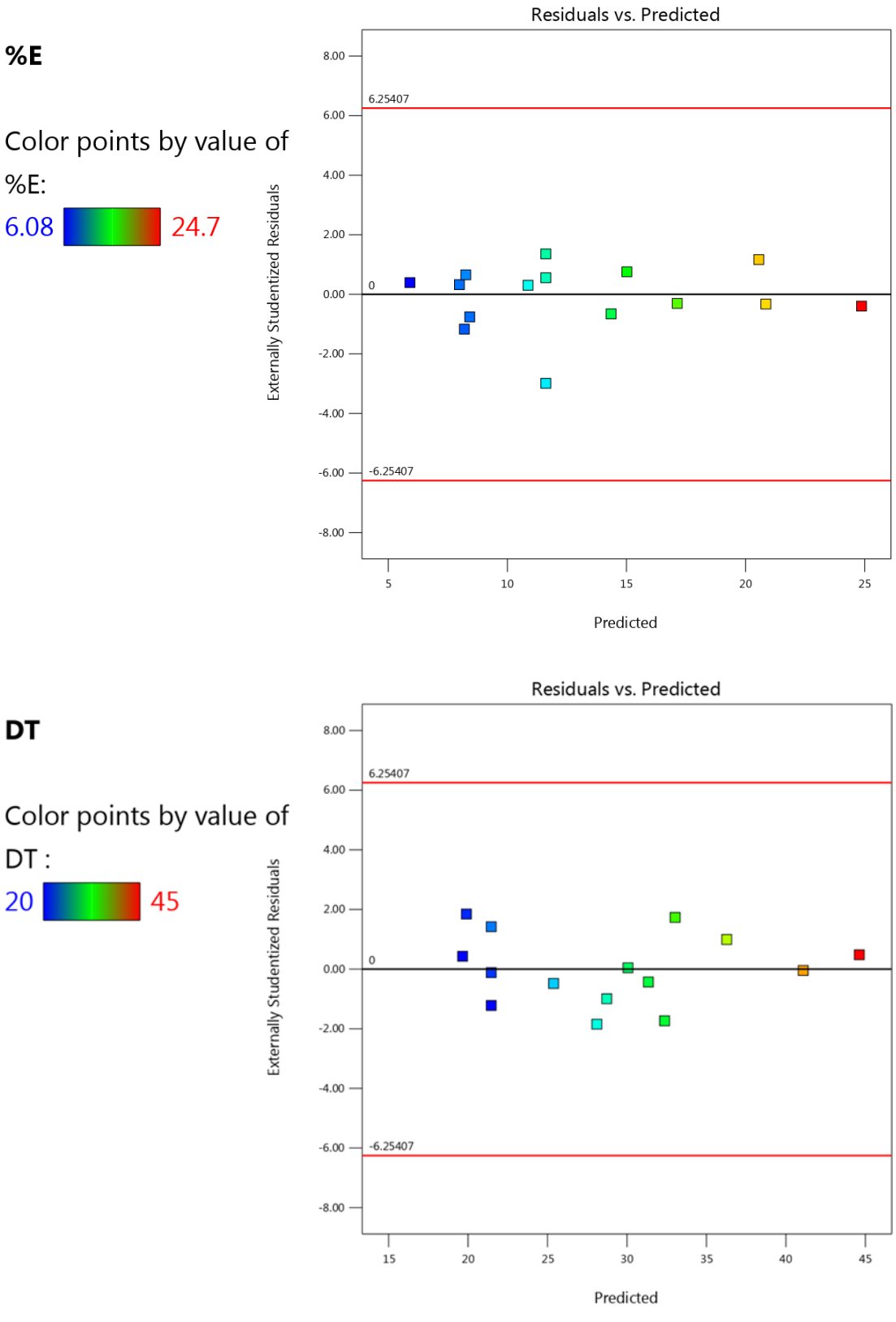
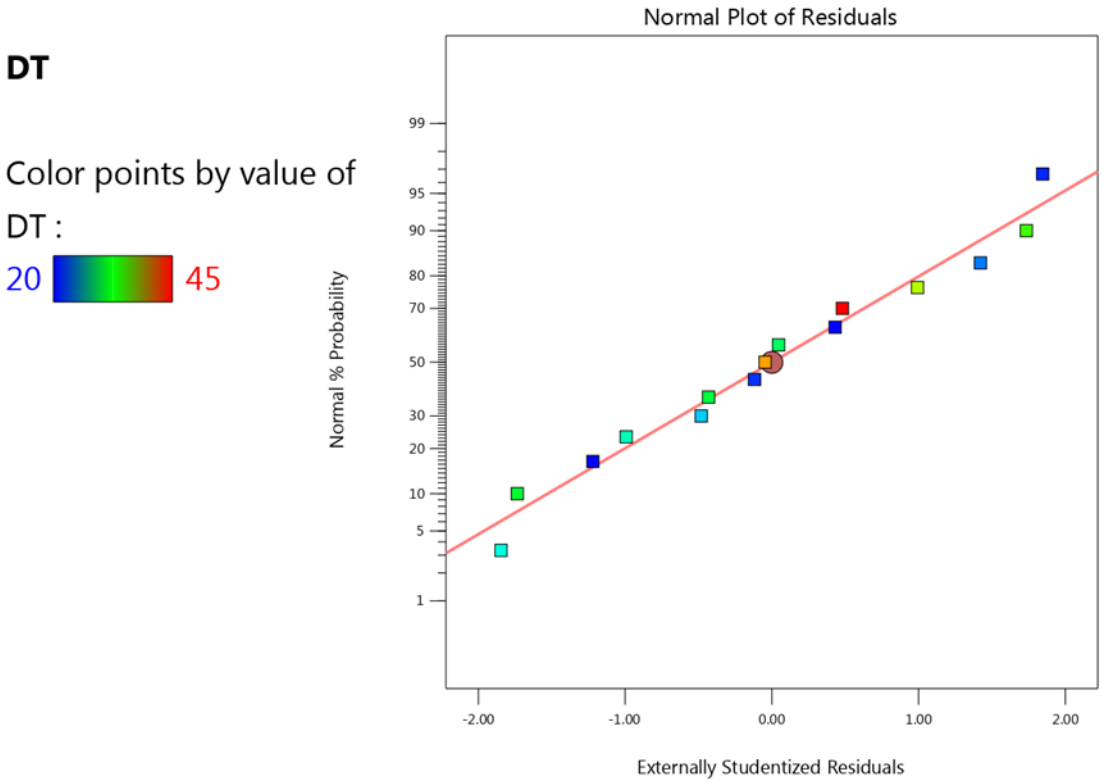


Figure 5. Residual vs. predicted plots of DT and % E responses.



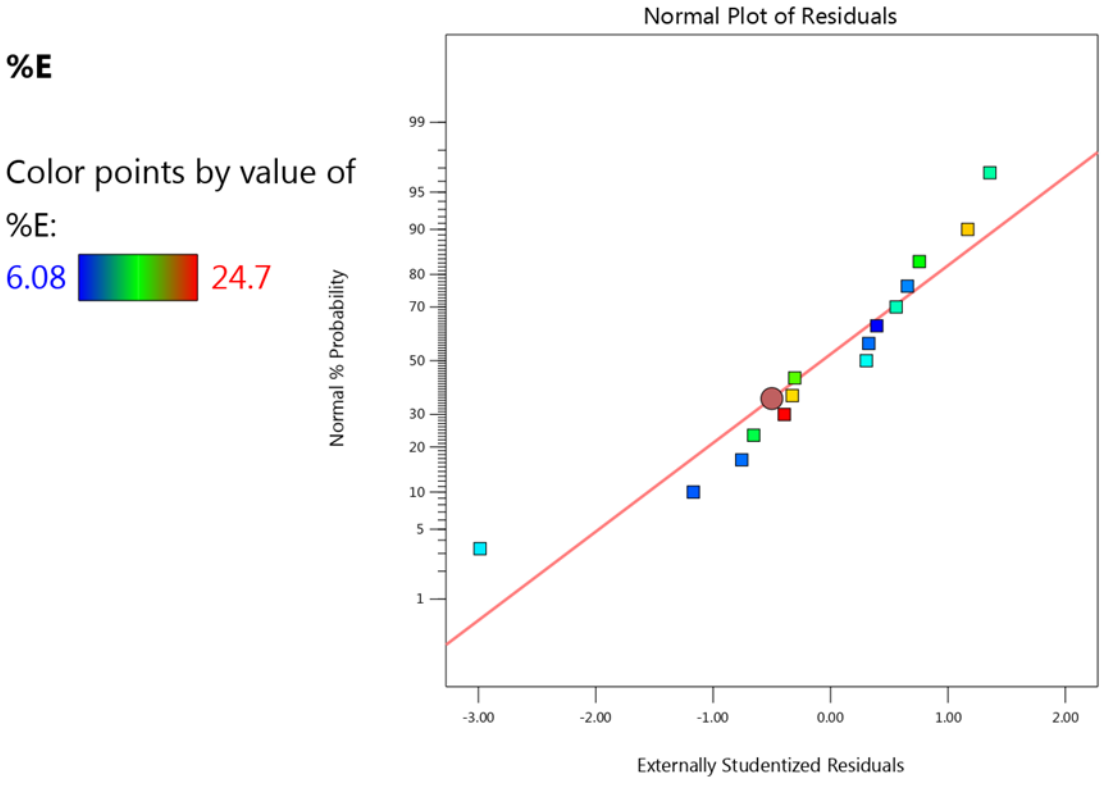


Figure 6. Normal plot of residuals for DT and %E responses.

Optimization of REP- NM -based SLF

The optimization process was performed using the desirability function approach to identify the optimal formulation of REP-NM-based SLF. The desirability value was found to be 0.73, indicating an acceptable compromise between the evaluated responses. At this optimum point, the predicted and actual values for DT were 25.1 s and 23.4 s, respectively, while the predicted and actual values for %E were 18.6% and 17.0%, respectively. The close agreement between predicted and actual responses confirms the validity and reliability of the optimization model.

Statistical validation and adequacy of BBD models

Statistical analysis of the BBD models for DT and %E indicated satisfactory model fitting. The lack-of-fit test for both responses yielded non-significant p-values ($p>0.05$), with F-values of 0.97 and 0.26, for DT and %E, respectively, suggesting that the models adequately fit the experimental data.

Evaluation of selected REP-NM-based SLF

The folding endurance exceeded 300 folds, indicating superior mechanical properties. The physicochemical characteristics of REP-NM-based SLF are presented in Table 4.

The results indicated that the PVA-based film exhibited a uniform and transparent appearance with a smooth surface texture. The average weights of the SLFs were consistent, meeting the requirements of the weight variation test with minimal standard deviation. Film thickness was within the acceptable range of 50–1000 μm.

The study confirmed that NMs were uniformly dispersed within the film matrix and that the preparation method was effective and reproducible, resulting in homogeneous films with high drug content and low standard deviation values. The surface pH of the films was 6.5 ± 0.08, which is compatible with the pH of the oral mucosa and did not cause irritation, making the films suitable for sublingual administration.

Table 4. Physicochemical characteristics of selected REP-NM-based SLF

Visual appearance	**Weight Variation**	**Film thickness (mm)**	**drug content%**	**surface pH**	**Folding endurance**
Flexible transparent, clear, smooth surface ,	128 ± 3.7 mg	0.123 ± 0.015 mm	98.3%± 0.051	6.5 ± 0.08	> 300

In-vitro dissolution study of REP-NM-based SLF

The comparison of release profiles between the pure REP film and the REP-NM-based SLF formulation demonstrated that incorporating REP as NMs (Figure 7) significantly enhanced drug release compared with the pure drug. The complete release of the PVA-based film within 10 minutes may be attributed to the high concentration of the hydrophilic polymer PVA, which promotes rapid swelling and facilitates drug diffusion from the film matrix.[20]

In contrast, the conventional film exhibited only 31% release after 10 minutes, which may be attributed to the limited solubility of REP in phosphate buffer (pH 6.8) containing 1% sodium dodecyl sulfate (SDS).

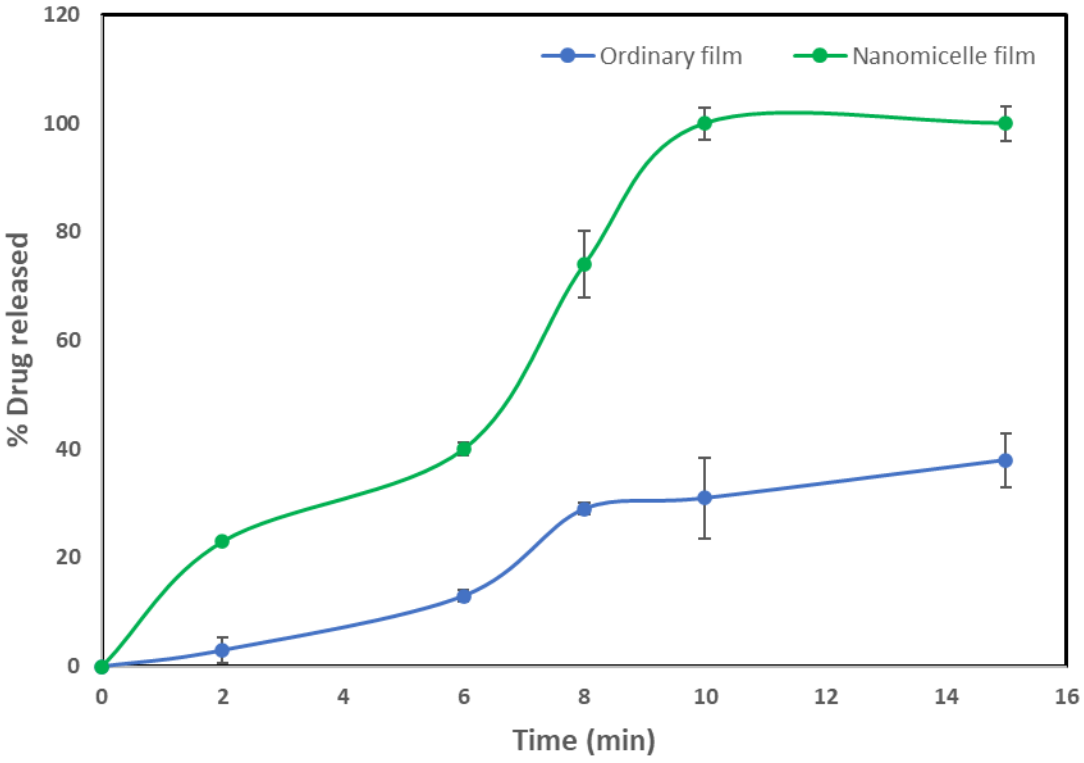


Figure 7. In vitro dissolution profiles of the pure REP oral film and REP-NM film in phosphate buffer (pH 6.8)

Conclusion

The study successfully developed a REP-NM-loaded SLF using PVA as the film-forming polymer, PEG 400 as the plasticizer, mannitol as the sweetening agent, and croscarmellose as the superdisintegrant. The disintegration time of the oral film increased with increasing PVA concentration; however, it decreased with increasing croscarmellose concentration. The percentage elongation of the SLF increased with increasing concentrations of PVA and PEG 400 and was not significantly affected by variations in croscarmellose percentages. Drug release was significantly enhanced when repaglinide was formulated as NMs compared with its pure form. Compatibility studies confirmed the absence of chemical interactions among the film components.

Authors' Contribution

Conceptualization: Lubna Abdalkarim Sabri

Methodology: Zainab Ahmed Sadeq, Lubna Abdalkarim Sabri

Investigation: Lubna Abdalkarim Sabri

Writing - Original Draft: Zainab Ahmed Sadeq

Writing - Review & Editing**: Lubna Abdalkarim Sabri**

Competing Interests

The authors have no relevant financial or nonfinancial interests to disclose.

Data Availability Statement

The data used for the preparation of the current manuscript is available from the corresponding author upon reasonable request.

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