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Development and Characterization of Rosuvastatin Calcium Niosome-Loaded Mucoadhesive Buccal Film

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ABSTRACT

Rosuvastatin Calcium is a potent HMG-CoA reductase inhibitor widely prescribed for hyperlipidemia. However, its clinical effectiveness is constrained by low aqueous solubility (BCS Class II) and limited absolute oral bioavailability (~20%) due to extensive hepatic first-pass extraction and acid degradation in the stomach. To address these limitations, this study engineered and evaluated a novel niosome-loaded mucoadhesive buccal film aimed at bypassing pre-systemic metabolism and providing controlled transmucosal drug release. Rosuvastatin-loaded niosomes (F1–F9) were synthesized by thin-film hydration using Span 60 and cholesterol. The optimized niosomal dispersion (F9) exhibited a mean vesicle size of 217.2 nm, polydispersity index of 0.196, zeta potential of -24.6 mV, entrapment efficiency of 96.92%, and an 8-hour cumulative release of 90.12%. Scanning electron microscopy (SEM) confirmed discrete, spherical vesicles. Formulation F9 was incorporated into a hydroxypropyl methylcellulose (HPMC E15) and Carbopol 934P polymeric matrix containing glycerol and PEG-400 as plasticizers via solvent casting to yield mucoadhesive buccal films (F1–F6). The optimized film (F6) displayed a surface pH of 6.71, thickness of 0.26 mm, weight of 58.3 mg, folding endurance exceeding 300 folds, swelling index of 230%, *in vitro* residence time of 3 h 27 min, and an *ex vivo* mucoadhesive strength of 0.602 N. The film achieved 90.29% cumulative drug release following zero-order kinetics (R2 = 0.9966) via non-Fickian/anomalous diffusion (n = 0.682). This hybrid carrier system demonstrates strong potential as an effective transmucosal delivery platform for statin therapy.

Introduction

Cardiovascular diseases remain the leading contributor to global mortality, with elevated low-density lipoprotein cholesterol (LDL-C) serving as a central modifiable risk factor [1]. Rosuvastatin Calcium, a synthetic HMG-CoA reductase inhibitor, effectively lowers circulating LDL-C levels and improves systemic lipid profiles [2]. However, as a Biopharmaceutics Classification System (BCS) Class II drug, its therapeutic efficacy is restricted by poor aqueous solubility, acid-catalyzed degradation in the stomach, and extensive pre-systemic hepatic extraction [3]. Consequently, conventional oral administration yields an absolute bioavailability of only ~20% [4].

Transmucosal buccal delivery provides direct access to the systemic circulation via the internal jugular vein, effectively bypassing hepatic first-pass clearance and gastrointestinal degradation [5]. Combining non-ionic surfactant-based vesicular carriers (niosomes) with mucoadhesive film matrices unites the solubilizing and permeation-enhancing properties of nanocarriers with the extended mucosal residence time and patient compliance offered by flexible films [6,7]. Niosomes encapsulate both hydrophobic and hydrophilic active pharmaceutical ingredients within non-ionic surfactant bilayers stabilized by cholesterol [8].

This investigation was undertaken to design, optimize, and characterize a Rosuvastatin Calcium niosome-loaded mucoadhesive buccal film capable of improving drug solubility, prolonging mucosal retention, and providing zero-order release kinetics across the buccal barrier.

Materials and Methods

Materials

Rosuvastatin Calcium was provided as a gift sample from Pharmafabrikon (Madurai, India). Sorbitan monostearate (Span 60) and cholesterol were obtained from HiMedia Laboratories (Mumbai, India). Hydroxypropyl methylcellulose (HPMC E15) was supplied by Colorcon Asia Pvt. Ltd., and Carbopol 934P was sourced from Loba Chemie (Mumbai, India). Polyethylene glycol 400 (PEG-400), glycerol, and all buffer reagents were of analytical grade.

Preformulation and Compatibility

Organoleptic properties, melting point (digital capillary apparatus), and equilibrium solubility across various aqueous/organic solvents were established. The partition

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coefficient was determined via the n-octanol/water shake-flask method. Drug-excipient compatibility was evaluated via Fourier Transform Infrared (FTIR) spectroscopy (PerkinElmer) across 4000 cm^{-1} to 400cm^{-1} [9].

Preparation of Niosomal Dispersions

Niosomes were prepared using thin-film hydration shown in figure 1 [10]. Varied molar ratios of Span 60 and cholesterol (Formulations F1–F9) along with a fixed dose of Rosuvastatin Calcium (10 mg) were dissolved in a 1:1 (v/v) mixture of chloroform and ethanol. Organic solvents were evaporated under reduced pressure using a rotary evaporator (Büchi, Switzerland) at 60°C to form a thin lipid film on the flask wall. The dry film was hydrated with 10 mL of phosphate buffer (pH 6.8) at 60°C for 1 h. Vesicle dimensions were homogenized using probe sonication for 3 min.

Table 1: Composition of Rosuvastatin Calcium Niosomal Mucoadhesive Buccal Films

Code	HPMC (mg)	Carbopol (mg)	PEG (% w/w)	Glycerol (% w/w)	TEA (drops)	Niosomal Dispersion (mL)	Purified Water (q.s. to, mL)
F1	200	20	20	10	3	5	10
F2	200	30	20	10	4	5	10
F3	250	20	25	10	3	5	10
F4	250	30	25	10	4	5	10
F5	300	20	30	10	3	5	10
F6	300	30	30	10	4	5	10

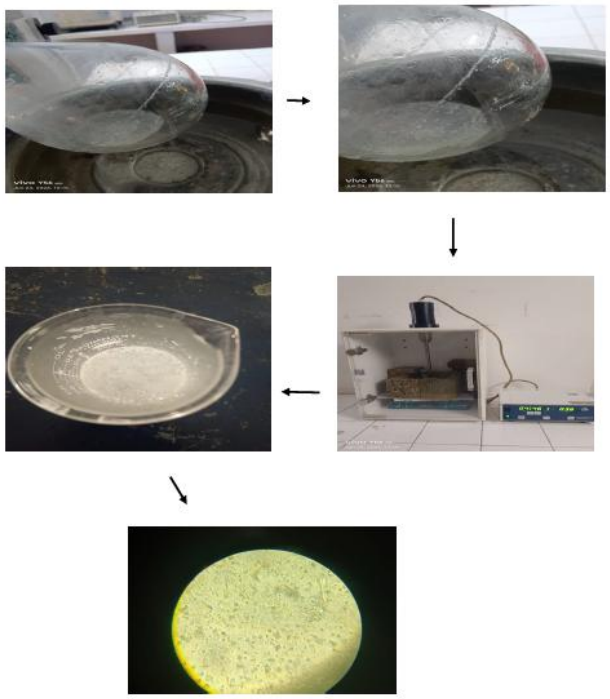

Figure 1: Preparation of Rosuvastatin Calcium Niosomes by Thin Film Hydration Method

Preparation of Niosome-Loaded Buccal Films

Films were fabricated using solvent casting shown in Table 1 [11]. Polymeric blends of HPMC E15 and Carbopol 934P were dissolved in purified water containing glycerol (2% v/v) and PEG-400 (1% v/v) as plasticizers. The optimized niosomal dispersion (F9) was incorporated into the polymeric gel under gentle mechanical stirring. The mixture was degassed under vacuum, cast into leveled glass Petri dishes, and dried at room temperature for 24 h. The dried films were sectioned into 2 x 2cm^2 patches shown in figure 2 (Formulations F1–F6).

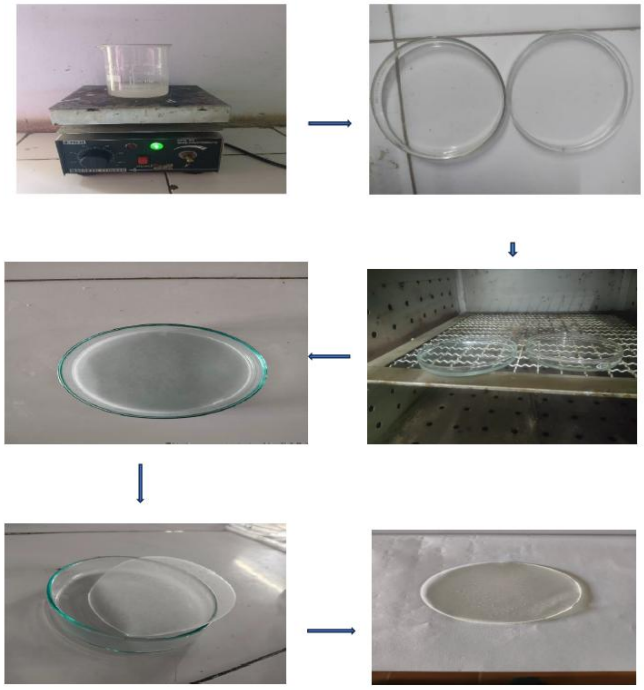

Figure 2 : Preparation of Rosuvastatin Calcium Niosomal Mucoadhesive Buccal Film by Solvent Casting Method

Characterization of Niosomes and Films

Vesicle Size, Zeta Potential, and Morphology: Particle size, polydispersity index (PDI), and zeta potential were evaluated using dynamic light scattering (Malvern Zetasizer Nano ZS). Morphological evaluation was performed via Scanning Electron Microscopy (SEM).

Entrapment Efficiency (%EE): Unentrapped drug was separated by centrifugation at 10,000 rpm for 30 min. Supernatant drug concentration was quantified by UV-Visible spectrophotometry at 242 nm:

%EE = {Total Drug} - {Free Drug}\{Total Drug} x 100

Film Evaluation: Thickness (digital micrometer), weight variation, surface pH, folding endurance, swelling index, drug content uniformity, *in vitro* residence time, and ex vivo mucoadhesive strength (using modified physical balance with excised goat buccal mucosa) were measured [12].

In Vitro Drug Release and Release Kinetics: Dissolution studies were performed in phosphate buffer (pH 6.8) at 37 ± 0.5°C using a USP dissolution apparatus II (paddle method) fitted with Franz diffusion cells. Samples were analyzed at specified time intervals. Mathematical kinetics models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas) were fitted to the cumulative drug release data:

Zero Order: $Qt = Q0 + K0\,t$

First Order: $\log Qt = \log Q0 - (K1\,t / 2.303)$

Higuchi Model: $Qt = KH\,t^{½}$

Korsmeyer–Peppas Model: $Mt / M\infty = Kp\,t^{n}$

Hixson–Crowell Model: $W0^{1/3} - Wt^{1/3} = Ks\,t$

where Mt/Mα is the fractional drug release, k is the kinetic constant, and n is the release exponent describing the release mechanism [13].

Results and Discussion

Preformulation and Compatibility

Rosuvastatin Calcium was verified as an amorphous white powder with a melting point of 158 -159 °C and an n-octanol/water partition coefficient (log P) of -0.642. FTIR spectrum analysis of pure drug and physical mixtures confirmed chemical compatibility without key characteristic functional group degradation.

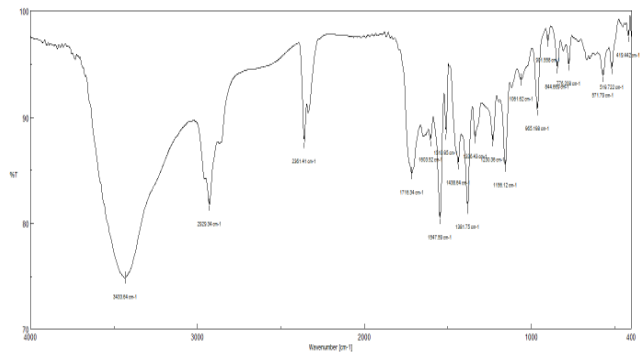

Figure 3: (FTIR Spectroscopy): FTIR spectra of (A) pure Rosuvastatin Calcium

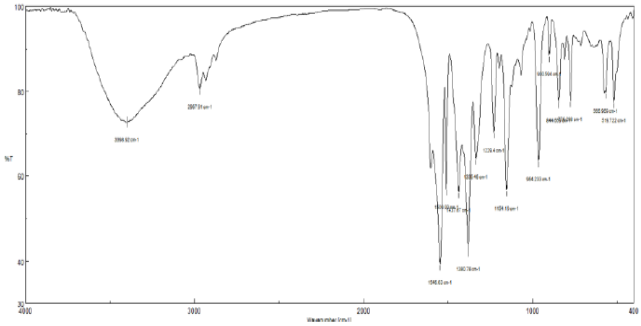

Figure 4: (FTIR Spectroscopy): FTIR spectra of Optimized Formulation

FTIR analysis confirmed the compatibility of Rosuvastatin Calcium with Span 60, cholesterol, HPMC, and Carbopol 934P. The absence of significant spectral changes suggests that there was no chemical interaction between the drug and excipients during formulation. Therefore, the selected excipients are suitable for the development of the niosome-loaded mucoadhesive buccal film.

Niosome Characterization

Surfactant-to-sterol ratios significantly influenced vesicle growth and encapsulation efficiency. Formulation F9 displayed the optimum combination of submicron vesicle size, narrow PDI, high negative charge density, and maximal drug loading (Table 1).

Table 2: Characterization parameters of Rosuvastatin Calcium-loaded niosomal formulations (F1–F9).

Formulation Code	Span 60 : Cholesterol (Molar Ratio)	Mean Vesicle Size (nm)	Polydispersity Index (PDI)	Zeta Potential (mV)	Entrapment Efficiency (%EE)
F1	1 : 1	342.5 ±4.2	0.321 ±0.02	-14.2 ±0.8	74.12 ±1.2
F2	1 : 2	388.1 ±5.1	0.354 ±0.01	-12.8 ±1.1	68.45 ±1.5
F3	2 : 1	298.4 ±3.6	0.284 ±0.03	-18.5 ±0.9	82.30 ±1.1
F4	2 : 2	312.0 ±4.0	0.298 ±0.02	-17.1 ±0.7	79.80 ±1.4
F5	3 : 1	265.8 ±3.1	0.241 ±0.01	-20.4 ±1.0	88.64 ±0.9
F6	3 : 2	280.2 ±3.8	0.260 ±0.02	-19.8 ±0.8	85.10 ±1.3
F7	4 : 1	240.1 ±2.9	0.215 ±0.01	-22.1 ±0.6	92.45 ±0.8
F8	4 : 2	255.4 ±3.3	0.230 ±0.02	-21.0 ±0.9	89.90 ±1.0
F9	5 : 1	217.2 ±2.4	0.196 ±0.01	-24.6 ±0.5	96.92 ±0.6

Data expressed as Mean ± SD (n = 3).

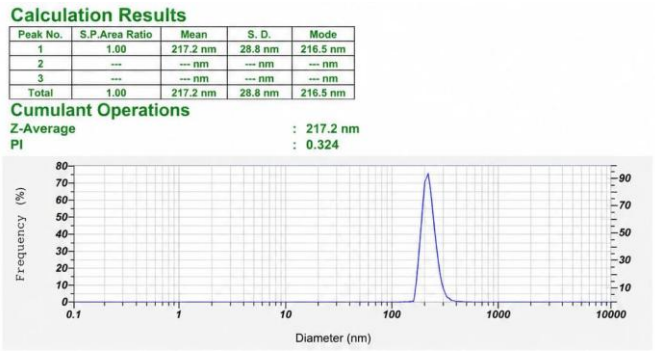

Figure 5: Particle size result of Rosuvastatin niosomes F9

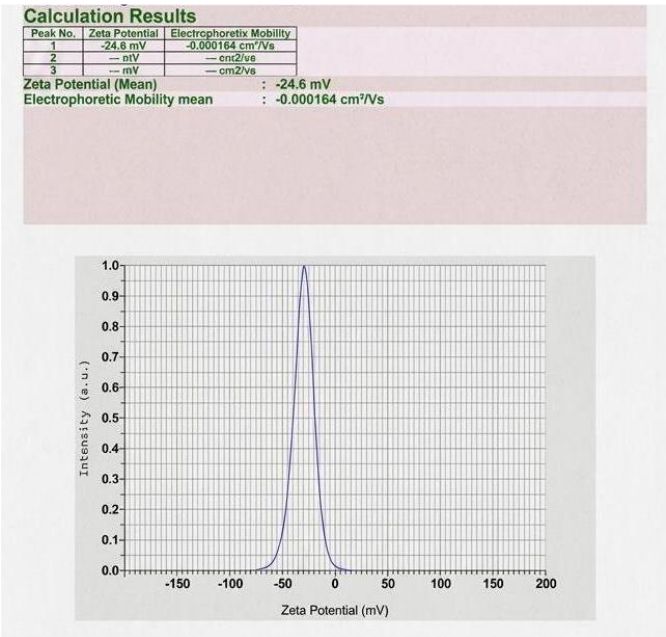

Figure No 6: Zeta potential result of Rosuvastatin niosomes F9

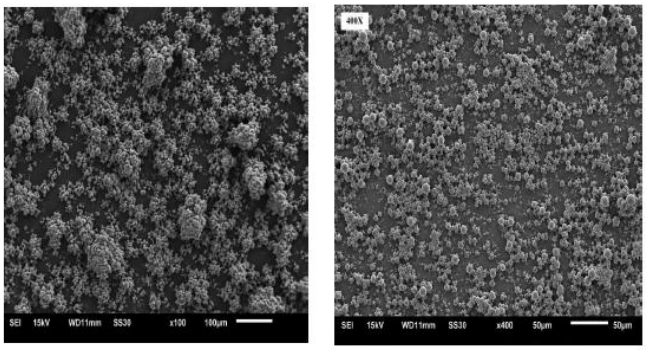

Figure No 7: Scanning Electron Microscopy (SEM) micrograph of optimized niosome formulation F9 displaying smooth, spherical, non-aggregated vesicular structures

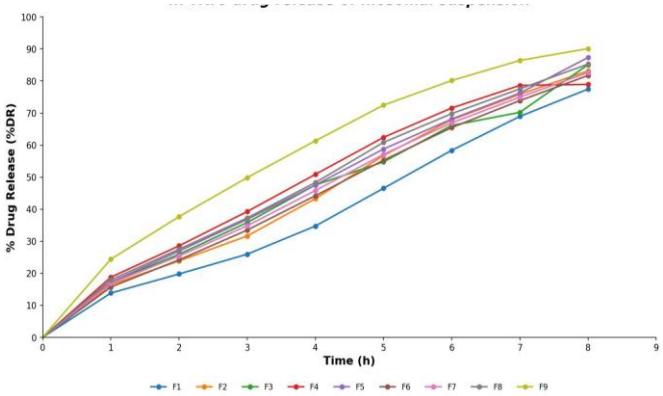

Figure 8: Comparative in vitro release curves of Rosuvastatin Calcium from niosomal formulations F1–F9 in phosphate buffer (pH 6.8) over an 8-hour period.

Mucoadhesive Buccal Film Evaluation

Formulation F6, consisting of HPMC E15 and Carbopol 934P in a 2:1 polymer ratio, displayed optimal mechanical strength, bioadhesion, and swelling capabilities (Table 3).

The surface pH of F6 (6.71 ±0.05) is close to physiological buccal pH, indicating low risk of mucosal irritation. High swelling (230%) and mucoadhesive force (0.602 N) were driven by carboxylic acid groups on Carbopol 934P forming interpolymer complexes and hydrogen bonds with mucin glycoproteins.

Table 3: Physicochemical and mechanical evaluation of niosome-loaded buccal films (F1–F6).

Film Code	Polymer Blend Ratio (HPMC E15 : Carbopol 934P)	Thickness (mm)	Weight (mg)	Surface pH	Folding Endurance	Swelling Index (%)	Mucoadhesive Force (N)	In Vitro Residence Time
F1	1 : 0	0.18 ±0.01	42.1 ±1.1	6.82 ±0.03	185 ±6	120 ±5	0.285 ±0.02	1 h 45 min
F2	1 : 0.5	0.20 ±0.01	46.5 ±1.4	6.78 ±0.04	220 ±8	155 ±7	0.392 ±0.03	2 h 10 min
F3	1 : 1	0.22 ±0.02	50.2 ±1.2	6.69 ±0.02	250 ±10	180 ±6	0.468 ±0.02	2 h 40 min
F4	2 : 0	0.21 ±0.01	48.8 ±1.5	6.85 ±0.05	240 ±7	140 ±4	0.340 ±0.01	2 h 05 min
F5	2 : 0.5	0.24 ±0.01	53.6 ±1.0	6.75 ±0.03	285 ±9	195 ±8	0.512 ±0.03	3 h 00 min
F6	2 : 1	0.26 ±0.01	58.3 ±1.3	6.71 ±0.05	>300	230 ±9	0.602 ±0.02	3 h 27 min

Data expressed as Mean ± SD (n = 3).

In Vitro Drug Release and Mathematical Modeling

Film F6 sustained drug release over 8 h, achieving a cumulative release of 90.29 ±1.8%. Mathematical fitting demonstrated near-perfect linearity for zero-order release kinetics (R^2 = 0.9966). The Korsmeyer-Peppas exponent (n = 0.682) indicated non-Fickian (anomalous) transport, where drug release is governed simultaneously by polymer hydration, matrix relaxation, and vesicular diffusion through the gel layer.

Summary and Conclusion

The present study was successfully undertaken to develop and characterize a Rosuvastatin Calcium-loaded niosomal mucoadhesive buccal film as an alternative drug delivery system for overcoming the limitations associated with conventional oral administration. The study was designed based on the biopharmaceutical limitations of Rosuvastatin Calcium, particularly its poor aqueous solubility and limited oral bioavailability, with the

objective of developing a formulation capable of providing efficient drug release and prolonged residence at the buccal mucosal surface. The selected approach combined the advantages of niosomal drug delivery with those of a mucoadhesive buccal film.

Preformulation studies confirmed the suitability of Rosuvastatin Calcium for formulation development. The drug was obtained as a white to off-white crystalline powder with acceptable organoleptic characteristics, and the melting point was found to be 158.6 ± 0.45°C, supporting the identity and purity of the drug. Solubility studies demonstrated limited aqueous solubility, whereas satisfactory solubility was observed in the selected formulation and analytical media. The partition coefficient study produced a log P value of −0.642, supporting the hydrophilic character of the drug and the need for an appropriate carrier system for buccal delivery. FTIR studies demonstrated retention of the characteristic drug peaks without significant disappearance or formation of new peaks, confirming compatibility of Rosuvastatin Calcium with the selected excipients.Rosuvastatin Calcium-loaded niosomes were successfully prepared by the thin-film hydration method using Span 60 and cholesterol. Nine formulations (F1–F9) were prepared by varying the concentrations of surfactant and cholesterol. Among the formulations, F9 was selected as the optimized niosomal formulation based on its overall physicochemical characteristics. F9 produced a uniform milky-white dispersion without visible aggregation or sedimentation and exhibited a mean vesicle size of 217.2 nm, confirming nanoscale vesicle formation. The formulation showed a low PDI of 0.196 ± 0.01, indicating a relatively narrow and homogeneous particle-size distribution. The zeta potential was found to be −24.6 mV, indicating acceptable colloidal stability. Importantly, F9 exhibited the highest entrapment efficiency of 96.92%, demonstrating efficient incorporation of Rosuvastatin Calcium within the niosomal vesicles. SEM analysis further confirmed predominantly spherical, smooth and discrete vesicles without prominent aggregation or structural deformation. The optimized niosomal formulation demonstrated a progressive drug-release profile, with F9 showing 90.12% cumulative drug release at 8 hours. The sustained release behaviour was attributed to the vesicular bilayer structure formed by Span 60 and cholesterol, which provided controlled diffusion of the entrapped drug. The optimized niosomal dispersion was subsequently incorporated into a mucoadhesive buccal film using HPMC as the film-forming polymer and Carbopol as the mucoadhesive polymer, with PEG and glycerol serving as plasticizers. The solvent-casting technique successfully produced a smooth and translucent film suitable for buccal application.

Among the prepared buccal-film formulations, F6 demonstrated favourable overall characteristics. The optimized F6 film exhibited a smooth and translucent appearance, surface pH of 6.71, thickness of 0.26 mm, weight of 58.3 mg, and folding endurance of more than 300 folds, indicating acceptable physical integrity and flexibility. It showed 97% drug content, 90.29% in vitro drug release, a residence time of 3 h 27 min, and a swelling index of 230%. These findings indicate adequate drug loading, hydration, flexibility, prolonged mucosal residence and controlled drug release.

The ex-vivo mucoadhesive study further demonstrated that F6 possessed satisfactory adhesion to buccal mucosa, with mucoadhesive strength values ranging from 0.579 to 0.638 N and a mean value of approximately 0.602 N. The release-kinetic study showed that the drug-release data of F6 fitted best to the Zero-order model (R^2 = 0.9966), indicating relatively controlled drug release, while the Korsmeyer–Peppas analysis indicated a non-Fickian/anomalous diffusion mechanism, suggesting the combined contribution of drug diffusion, polymer swelling and polymer relaxation.Overall, the study demonstrated the successful development of a Rosuvastatin Calcium niosome-loaded mucoadhesive buccal film with satisfactory physicochemical characteristics, high drug entrapment, controlled drug release, adequate flexibility, swelling, and mucoadhesive performance. The combined niosomal and buccal-film approach provides a promising platform for improving the delivery of Rosuvastatin Calcium and potentially reducing the limitations associated with conventional oral administration. Thus, the developed formulation may serve as a promising candidate for further ex-vivo, pharmacokinetic, stability, scale-up and in-vivo investigations to establish its therapeutic performance and potential clinical applicability.

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