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Research

Preparation and characterisation of atorvastatin calcium loaded nanogel as topical gel-based formulation

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Abstract

Atorvastatin calcium suffers from poor bioavailability due to its low water solubility and extensive first-pass metabolism. To overcome these limitations, Atorvastatin calcium nanogels were developed to enhance solubility, promote controlled drug release, and improve wound-healing efficacy through localized delivery. Nanocrystals were prepared using a 2^3 factorial design via the solvent–antisolvent precipitation method, optimizing factors such as stabilizer (Pluronic F-127), solvent–antisolvent ratio, and stirring time. The optimized nanosuspension (F8) was incorporated into an aloe vera–carbopol gel to form a nanogel, which was evaluated for physicochemical and rheological properties, pH, moisture content, spreadability, stability, and permeability in an ex vivo model. The formulated nanogel exhibited clear appearance, smooth texture, and a pH of 6.5, ensuring skin compatibility without irritation. It demonstrated high viscosity (8500 cp), ensuring good adherence at the application site. Compared to the pure drug and conventional gel, the nanogel showed significantly higher saturation solubility and enhanced drug permeation, releasing 400 ± 18 µg/cm² over 24 hours versus 50 ± 8 µg/cm² for the control. Stability studies confirmed no notable changes after 90 days of storage. Overall, the Atorvastatin calcium nanogel exhibited sustained drug release, improved therapeutic performance, and superior patient compliance due to its non-greasy, transparent, and easily applicable nature.

Keywords: Atorvastatin Calcium, Nanocrystals, Solvent Antisolvent Precipitation Method and Nanogel.

INTRODUCTION

Nanogels are emerging as an advanced and efficient drug delivery system that combine the advantages of nanosized particles and hydrogels. They possess unique characteristics such as high water content, biocompatibility, and the ability to encapsulate both hydrophilic and hydrophobic drugs. These properties make nanogels particularly useful for topical applications, where they can provide controlled and sustained drug release, improved skin permeation, and targeted delivery at the site of action. The small particle size of nanogels allows them to penetrate deeper skin layers, thereby enhancing therapeutic efficacy while minimizing systemic side effects. Additionally, their soft, transparent, and non-greasy nature improves patient compliance and comfort, making them an ideal choice for dermatological and wound-healing formulations[1,2].

Atorvastatin calcium[3], a lipid-lowering agent, has recently gained attention for its wound-healing and anti-inflammatory properties. However, its poor aqueous solubility and extensive first-pass metabolism limit its oral bioavailability and therapeutic efficiency. To overcome these challenges, formulating Atorvastatin calcium as a topical nanogel offers a promising approach. The nanogel system enhances solubility, provides localized and sustained drug release, and promotes better absorption through the skin, leading to improved bioavailability and faster wound healing. Therefore, developing an Atorvastatin calcium-loaded nanogel as a topical gel-based formulation addresses the need for an effective, stable, and patient-friendly drug delivery system that enhances therapeutic outcomes and minimizes systemic exposure.

METHODOLOGY

Atorvastatin Calcium as a gift sample from Yarrow Chem Products, Mumbai; Pluronic F-127 procured from Sigma-Aldrich, Bangalore; Carbopol & Methyl paraben procured from S.D. Fine Chem. Ltd; Aloe vera procured from Local Market, Vijayawada.

Drug–Excipient Compatibility Studies

Selecting suitable excipients with the active pharmaceutical ingredient (API) is crucial for a stable and effective formulation. Though pharmacologically inactive, excipients enhance stability, bioavailability, and patient compliance. Drug–excipient compatibility was assessed using a Fourier Transform Infrared (FTIR) spectrophotometer with the KBr pellet method (Bruker). Spectra of Atorvastatin calcium and Pluronic F-127 confirmed their compatibility.

Formulation of Nanocrystals

2^3 Factorial Design

To optimize the formulation of Atorvastatin calcium nanocrystals, a 2^3 factorial design was employed, varying three key formulation variables—stabilizer concentration, solvent-to-antisolvent ratio, and stirring time. These factors were systematically studied at two levels (high and low) to evaluate their individual and interactive effects on the final product characteristics. Statistical analysis was performed to determine the significance of these parameters and their interactions on nanocrystal formation and stability.

Table 1: Statistical design to select key formulation variables

S. No	Type	3 Factors	2 Levels	
			Low level (-1)	High Level (+1)
1	Formulation parameter	Stabilizer	5%	10%
		Solvent: Antisolvent ratio	1: 5	1: 10
2	Critical process parameter	Stirring Time	15 min	30 min

For ease of comparison and interpretation, the eight formulations developed during the optimization phase were categorized into four groups. Group I (F1) included formulations where all variables were maintained at low levels. Group II (F2, F3, and F5) consisted of formulations with any one of the three variables at a high level. Group III (F4, F6, and F7) included formulations with two variables at high levels, while Group IV (F8) represented the formulation in which all three variables were optimized at the highest level.

Table 2: Formulation of nanocrystals

Formulation	Stirring time (min)	Stabilizer concentration	Solvent: Antisolvent ratio
F1	15	5%	1:5
F2	30	5%	1:5
F3	15	10%	1:5
F4	30	10%	1:5
F5	15	5%	1:10
F6	30	5%	1:10
F7	15	10%	1:10
F8	30	10%	1:10

Solvent Antisolvent Precipitation Method

In this approach, the solvent mixture incorporates the antisolvent mixture at a predetermined rate. Solvent mixture is prepared by dissolving the drug (10mg) in acetone (2 ml). This mixture is added at a predetermined rate (0.2ml/min or 0.6 ml/min) to the antisolvent mixture containing Pluronic F-127 (stabilizer) and water under continuous stirring (Remi) at a predetermined time (15 min or 30 min) and speed (2000rpm). The formed nanosuspension is freezedried to obtain nanocrystals of Atorvastatin Calcium.

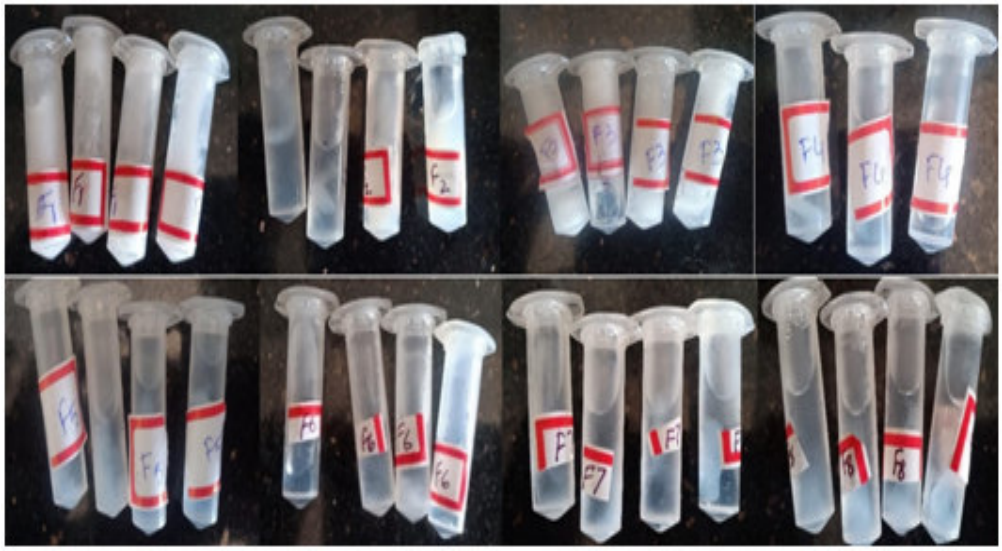


Fig 1: Prepared formulations

EVALUATION OF NANOCRYSTALS

Particle Size and Size Distribution Analysis[4]

The particle size of the prepared nanocrystals was measured using Dynamic Light Scattering (DLS), also known as Photon Correlation Spectroscopy (PCS), with a Zetasizer® 3000 (Malvern Instruments, Sura Labs, Hyderabad). Each sample was diluted with sterile water and analyzed for 180 seconds at scattering angles of 25° and 90°. The average particle diameter was determined from cumulative analysis performed in triplicate, and the size distribution was characterized using the polydispersity index (PDI). The reported values represent the mean of three independent measurements, ensuring accuracy and reproducibility

$$\text{PolydispersityIndex} = \frac{\text{Squares of measured diameter}}{\text{Squares of average of measured diameter}}$$

Morphological Studies[5]

Nanocrystals' morphology was analyzed with a scanning electron microscope (SEM). (Tecnai 20 G2 S TWIN atSura labs, Hyderabad).The orientation of molecules and the arrangement of components within nanocrystals are two structural factors that can influence their behavior and stability. SEM, or scanning electron microscopy, was used for this purpose.

Zeta potential determination[6]

Nanocrystals were characterized with Zeta potential (ζ) using a Zeta Sizer. Samples were diluted (with ultra-pure water) and placed in the capillary measurement cell, where the cell location was automatically changed, and the measurements were taken using an aqueous dip cell.

Drug Content

The drug content was calculated using a centrifugation technique. To isolate the free drug in the supernatant, the nanocrystal suspension was centrifuged at 20,000 rpm for 45 minutes at 4°C. After proper dilution, the Atorvastatin Calcium concentration in the supernatant was measured using UV - Visspectrophotometry at 242 nm.

***In vitro* Dissolution studies**[7]

The USP dissolving equipment II was used to conduct the dissolution tests. (Labindia Pvt., Ltd., India). In a pH 6.8 buffer of 900 cc at 37+ 0.5C. 50 RPM per minute was selected for the paddle speed. Both the pure medication and the nanocrystals (each representing 10 mg of Atorvastatin Calcium) were introduced into the dissolution device. At regular intervals, 10 ml samples were taken out of the sink and replaced with fresh medium to keep everything running smoothly. Filtrates from all of the retrieved samples were analyzed quantitatively using a UV-Visible double-beam spectrophotometer set to 242 nm.

Design of Experiments

The preparation of Atorvastatin calcium nanosuspension was optimized using a full 2^3 factorial design to study the influence of three independent variables stirring duration (A), stabilizer concentration (B), and solvent–antisolvent ratio (C) on dependent variables such as mean particle size, entrapment efficiency, and drug release. Preliminary investigations indicated that these formulation parameters significantly affected the critical quality attributes of the nanosuspension. Further optimization was carried out using response surface methodology (RSM) based on the Box–Behnken design, which required sixteen experimental runs. The wide variation observed among formulations confirmed the sensitivity of the dependent variables to the selected factors.

Statistical analysis[8]

It was performed using SigmaXL Design-Expert® software (V9.1), applying ANOVA and multiple linear regression to generate polynomial equations representing the relationships between variables. The model showed statistical significance ($p < 0.05$), with an F-value of 21.03 for particle size (Y1), indicating a strong influence of formulation parameters. Among the variables, stirring duration had the most pronounced effect on particle size, followed by the solvent–antisolvent ratio and stabilizer concentration. Three-dimensional response surface and perturbation plots demonstrated that an increase in stirring time led to a corresponding increase in particle size, highlighting the interactive effects of process parameters on nanosuspension characteristics.

PREPARATION OF ALOEVERA CARBOPOL GEL

Preparation of aloe vera extract

Thick succulent aloe vera leaves are taken and kept in an inverted position to keep the yellow liquid out and it is removed. Then the thick and white pulp is separated with the help of a spoon and kept in a bowl. The pulp is neutralized with 0.1 N NaOH and repeatedly washed with hot water. The mucilage is subjected to centrifugation to remove any suspended leafy particles etc and is removed. The extract is stored in a container and kept in refrigerator for further use.

Preparation of aloe-carbopol gel

After adding the thick aloe extract (50 ml) and the gelling agent (1% w/w carbopol 974) over 24 hours, the consistency was perfect. We next filter the extract through muslin to eliminate any remaining sediment. The gel was then combined with the preservative methyl paraben (0.2% w/w) until a homogeneous, viscoussolution was created. Triethanolamine (TEA) was added to the gel while it was being stirred, and the pH was adjusted to a range from 5.5 to 6.0. Once the gel has formed, it is placed in a container and stored in the fridge

Formulation of atorvastatin-based Nanogel

A candidate formula F6 (10 mg ATC) was chosen due to its small particle size, high entrapment efficiency, and high percentage of drug release, as determined by the characterisation methods described above and the results of the major impacts of the adopted factorial design. Formulating the chosen F6 nanosuspension formulation into Nanogel (NG) involved adding 1% (w/w) Carbopol 934 while magnetically stirring at 800 rpm. To ensure that Carbopol was evenly distributed, the stirring process was maintained. A triethanola-mine solution was used to neutralize the dispersions. Nanogel formulation containing 10 mg ATC dispersion was prepared for comparison.

Evaluation of nano gel

The **transparency**, **smoothness**, and **relative density** of the formulated gel were assessed visually and by touch, while relative density was determined using a specific gravity bottle. The **pH** was measured using a calibrated pH meter to ensure skin compatibility. **Moisture content** was determined by drying the gel and comparing weight loss before and after desiccation to calculate the percentage of moisture lost.

The **rheological behavior** of both unloaded and drug-loaded nanogels was studied using an MCR-52 dynamic rheometer (Anton Paar, Germany) at 25°C with a parallel plate setup to determine viscosity and flow characteristics. **Spreadability** was evaluated by measuring the increase in diameter of 250 mg of gel compressed between glass plates under a 500 g weight for five minutes. **Drug content uniformity** was assessed by dissolving gel samples (equivalent to 5 mg drug) in methanol, centrifuging, and analyzing the filtrate spectrophotometrically.

For **ex-vivo permeation studies**, rat skin mounted on a Franz diffusion cell was used, with the receptor compartment containing phosphate buffer (pH 7.4). Samples were collected periodically for 48 hours and analyzed spectrophotometrically. **Stability studies** were conducted on the optimized formulation stored at 40 ± 2°C and 75 ± 5% RH for three months, with data analyzed statistically using one-way ANOVA to confirm formulation stability.

RESULTS AND DISCUSSIONS

Drug–Excipient Compatibility Studies

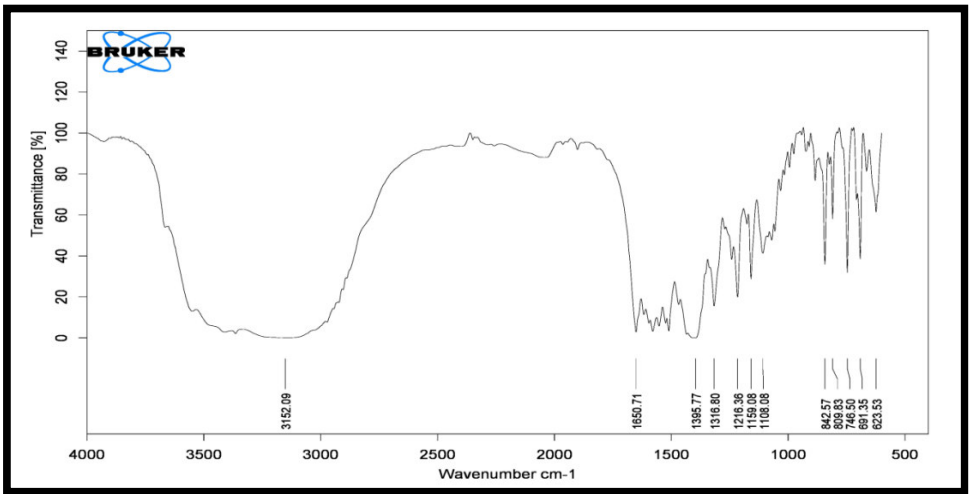


Fig 2: FT-IR spectra for the pure Atorvastatin calcium

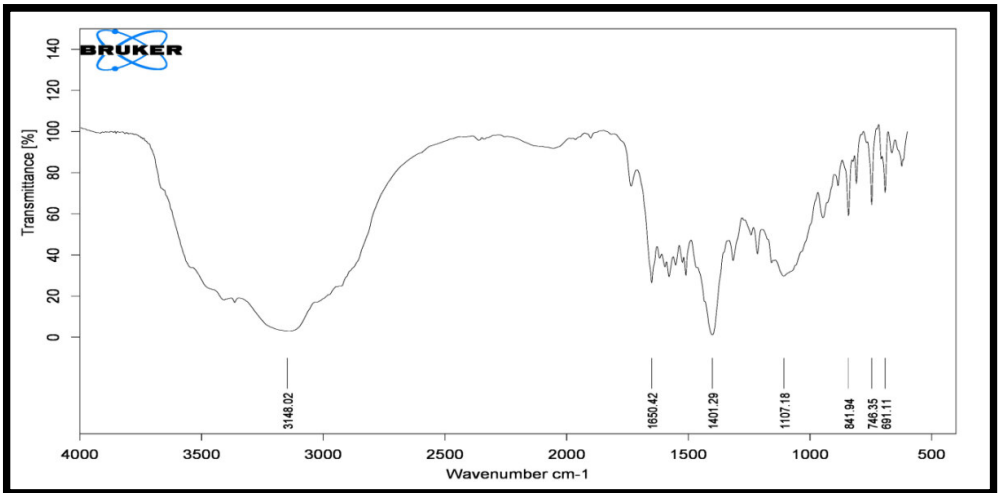


Fig 3: FT-IR spectra for Atorvastatin calcium and Pluronic F-127

Table 3: Characteristic peaks observed in FTIR spectrum

Type of peak	Characteristic value	Pure	Formulation
C-F- stretching	691.35	Yes	Yes
-OH bending	1159.08 cm^{-1}	Yes	Yes
C-N – Stretching	1316.80cm^{-1}	Yes	Yes
-C=O stretching	1650.71 cm^{-1}	Yes	Yes
C=C – bending	1650.71 cm^{-1}	Yes	Yes
N-H – stretching	3152.09 cm^{-1}	Yes	Yes

Drug-excipient interactions in nanocrystal formulations were investigated with the use of interaction studies. Figures displayed the FTIR spectra of Atorvastatin calcium in its pure form and in combination with various excipients used in its manufacture. The formulation and the excipients did not have any sort of chemical reaction, as evidenced by the presence of a broad peak in the same area as the peak detected in the spectrum of pure Atorvastatin calcium

CHARACTERISATION OF PREPARED NCs

Size Analysis

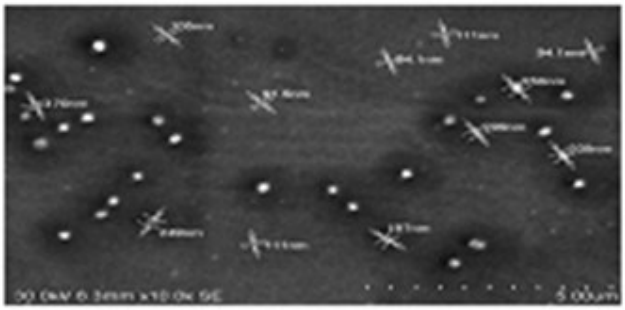
Formulation F8 showed small particle size of 128 nm, whereas, F1showed maximum particle size of 316 nm. The results indicate that the particle size decreased with increasing stabilizer (Pluronic F-127) concentration from 5-10 % and the particle size got smaller with the number of solvent antisolvent ratio from 1:5-1:10. The particle size of NCs was also decreased with increasing stirring time from 15-30 min. When the percentage varied in Pluronic F-127 (5-10 %) increased, reduces the interfacial tension, which resulted in significantly increased shear stress during solvent / antisolvent interface mixing and the resultant formation of smaller droplets. Thus, the mean diameter of NCs decreased with the presence and increase of Pluronic F127.

Table 4: Mean particle size of NCs (F1 – F8)

Formu-lation	Mean particle Size (nm)	Polydispersity	%Drug Content	% Yield
F1	316 ± 1.32	0.51 ± 0.14	59 ± 1.22	55.3 ± 1.33
F2	297 ± 5.24	0.43 ± 0.12	57 ± 1.53	61.5 ± 1.53
F3	211 ± 1.36	0.50 ± 0.08	78 ± 1.36	65.9 ± 1.42
F4	190 ± 2.36	0.52 ± 0.17	72 ± 2.06	76.3 ± 1.89
F5	217 ± 1.21	0.44 ± 0.11	55 ± 1.74	63.7 ± 1.46
F6	194 ± 2.16	0.51 ± 0.12	50 ± 1.26	72.1 ± 1.55
F7	148 ± 3.45	0.50 ± 0.04	70 ± 1.69	86.2 ± 1.74
F8	128 ± 2.53	0.43 ± 0.12	69 ± 1.43	88.9 ± 1.65

Scanning Electron Microscopy (SEM)

The optimizes formulation F8 was analyzed by scanning electron microscopy to determine their surface shape and no collapse can be seen on the surface of any of the eight different NC formulations.



F-8

Fig 4: Scanning electron micrographs of NCs of F8

Surface Charge (Zeta Potential)

The F8 formulation was found to have a zeta potential of -38.2, indicating good stability. Aggregation is avoided because particles with like electric charges are repelled by one another.

Drug Content

The nanoparticles obtained from the F3 formulation had the highest drug content (78 1.36), while the nanoparticles obtained from the F6 formulation had the lowest drug content. (50 ± 1.26).There was an increase in drug contentPluronic F-127 concentration from 5-10%. It wasdecreased with an increased solvent antisolvent ratio from 1:5 –1:10 and decreased significantly with increasing stirring time.

Saturation Solubility

It was determined whether or not the NCs and the pure medication were saturatedly soluble. In phosphate buffered solution (PBS) at pH 6.8, the saturation solubility of NCs was determined to range between 88.9 and 55.3 g/ml, and that of the pure medication to be 50.0 g/ml. The improved nanosuspension formulation demonstrated significantly higher solubility at saturation compared to the pure medication. Reducing particle size to the nanometer range has been reported to greatly boost solubility; more accurately, quick dissolution kinetics is anticipated to be significantly increased**.**

In vitro Dissolution profile

The pure drug showed a slow and incomplete release profile, with only 44.7 ± 0.67% of the drug dissolved after 60 minutes. This limited dissolution is a common challenge for poorly water-soluble drugs and can lead to low bioavailability and suboptimal therapeutic efficacy. In stark contrast, all nanocrystal formulations (F1-F8) displayed a markedly faster and more extensive drug release. The enhancement is evident from the earliest time point. At 10 minutes, the pure drug had released only 15.56%, whereas formulation F8 had already released 54.23% an improvement of approximately 3.5-fold. This rapid initial release is a key characteristic of nanocrystal technology, as the reduction in particle size leads to a dramatic increase in the surface area available for dissolution, thereby accelerating the process according to the Noyes-Whitney equation.

The superiority of formulation F8 is consistent throughout the entire dissolution period. By 20 minutes, F8 had released over 63%, a value the pure drug failed to reach even after 60 minutes. The dissolution rate of F8 continued to outpace all other formulations, culminating in a near-complete release of 98.53 ± 0.43% at the 60-minute endpoint. This represents a more than two-fold increase in the total cumulative drug dissolved compared to the pure drug.

When compared to the other leading formulations, such as F4 and F7, F8 consistently showed the highest or among the highest values at every interval, ultimately achieving the highest cumulative release. The low standard deviation associated with F8's results also indicates excellent batch-to-batch reproducibility and formulation stability.

The data unequivocally demonstrates that the nanocrystal formulation strategy successfully overcame the dissolution limitations of the pure drug. Formulation F8, in particular, emerged as the optimal formulation, providing the most rapid and complete drug release profile. This enhanced dissolution performance suggests that F8 has the strong potential to improve the oral bioavailability and in-vivo absorption of the drug, making it the most promising candidate for further development and pharmacokinetic studies.

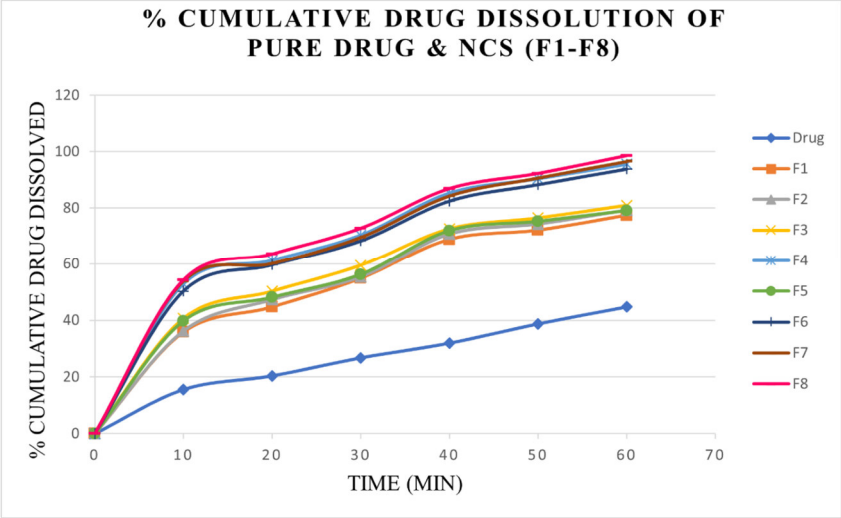


Fig 5: % Cumulative drug dissolution of pure drug and NCs (F1 – F8)

Statistical Data Analysis

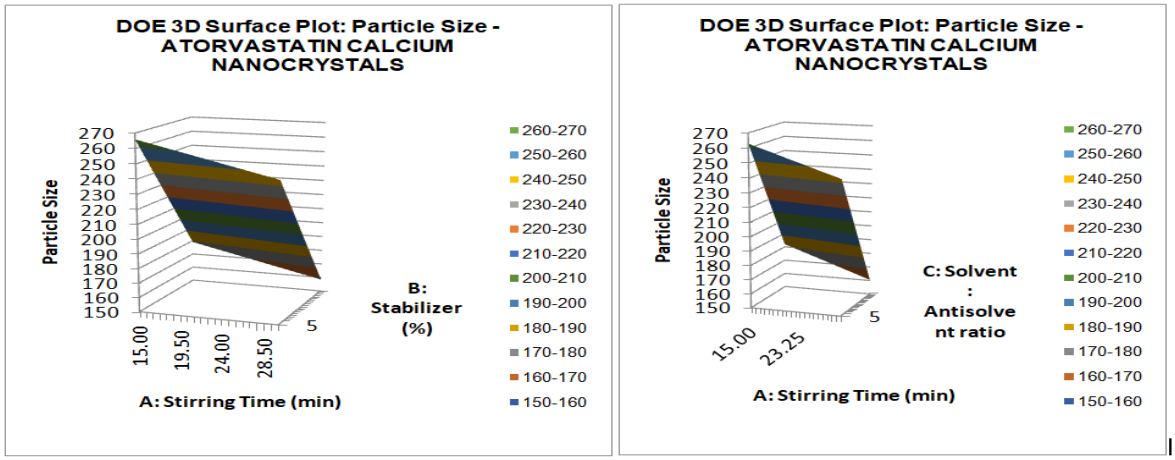
Table 5: Composition of full factorial design batches (n=2)

Formulation Batches	A	B	C	Y1 (Particle Size, nm)	
	Stirring Time (min)	Stabilizer (%)	Solvent: Antisolvent Ratio	Observed	Predicted
F1	-1	-1	-1	316	316.125
F2	+1	-1	-1	297	295.875
F3	-1	+1	-1	211	209.875
F4	+1	+1	-1	190	190.125
F5	-1	-1	+1	217	215.875
F6	+1	-1	+1	194	194.125
F7	-1	+1	+1	148	148.125
F8	+1	+1	+1	128	126.875

Table 6: Analysis of Variance for Model

Source	DF	SS	MS	F	P
Model	7	60048	8578.3	17157	**0.0000**
Error	8	4	0.500000		
Pure Error	8	4	0.500000		
Total (Model + Error)	15	60052	4003.5		

Particle Size Y1 = (212.125) + (-10.375) * A: Stirring Time (min) + (-43.375) * B: Stabilizer (%) + (-40.875) * C: Solvent : Antisolvent ratio + (0.125) * AB + (-0.375) * AC + (9.625) * BC + (0.625) * ABC

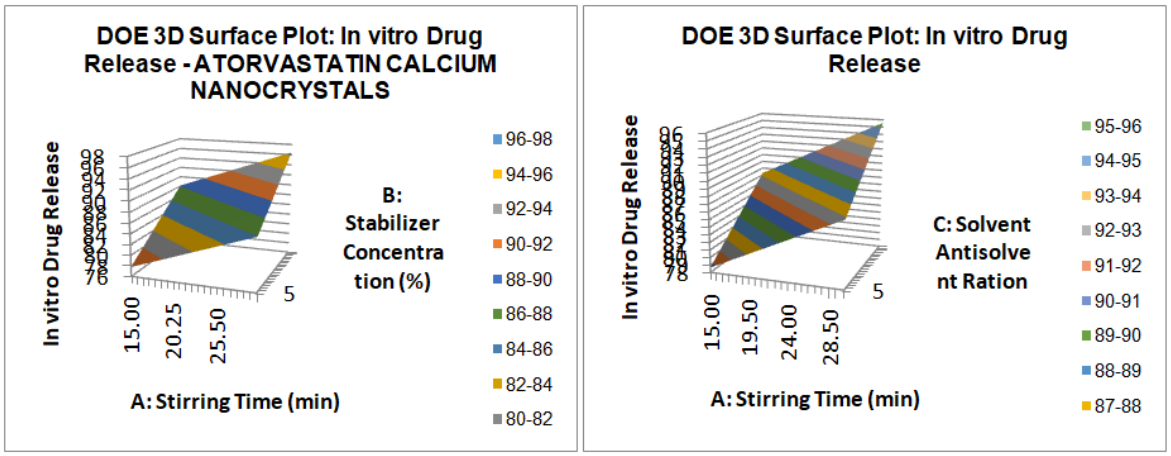


(A), Concentration of Stabilizer (B) and Solvent Antisolvent Ration (C) on Particle size (Y1, nm) of ATC loaded NCs.

Fig 6: 3D Surface plots showing the influence of the Stirring Time

In the case size of particle (Y1), the coefficients of main effects (A, B, and C) and interaction effects AB and ABC are statistically significant (P<0.05), whereas the coefficients of BC and AC are not (P> 0.05). The coefficients associated with the independent parameters A, B, C, and the interaction coefficient AC had a negative effect on the response variable(Y1), implying that the size of particledecreased as the concentration of these parameters increased, whereas the coefficients associated with the terms AB, BC, and ABC had a positive effect. There are both negative and positive interactions found. The pareto chart was used to assess the influence of main variables and interactions on particle size decreases in the order of B, C, A, and BC.

To demonstrate the connection between three variables: two independent and one dependent variable, the contour and 3D Scatter plots were utilized. The particle size values for A verses B and A verses C combinations are presented in these graphs. The A and B standards are represented on the X and Y axes, respectively, while the Z value (Y1) is represented by contour lines and bands. The contour lines' close spacing suggests that particle size differs rapidly. To find the best combinations of two independent variables, the contour and 3D Scatter plots were utilized.



(A), Concentration of Stabilizer (B)and Solvent Antisolvent Ration (C) on In vitro release (Y3, %)of ATC loaded NCs.

Fig 7: 3D Surfece plotsillustrating the impact of the Stirring Time

For in-vitro drug release (Y3), the main effect coefficients for stirring duration (A), stabilizer concentration (B), and solvent–antisolvent ratio (C) were positive (4.119, 5.200, and 4.353, respectively), indicating that higher levels of these variables increased drug release. The three-factor interaction (ABC) showed a negative coefficient (–3.150), suggesting a minimal combined effect. The derived model for drug content (Y2) was statistically significant (F = 383.71, p = 0.000), confirming that A, B, C, and their three-factor interaction (ABC) significantly influenced drug release ($p < 0.05$), while two-factor interactions (AB, AC, BC) were not significant ($p > 0.05$).

Pareto analysis revealed that stabilizer concentration (B) had the greatest influence on drug release, followed by solvent–antisolvent ratio (C) and stirring time (A). Contour and 3D response surface plots further illustrated the combined effects of these variables. At a constant C, increasing A and B led to higher drug release from 76% to 78% at low A and up to 98% at high A levels. Overall, the optimized nanocrystal formulations exhibited desirable in-vitro drug release profiles, balancing key factors such as particle size and drug content for effective performance.

EVALUATION TESTS FOR NPS LOADED NANOGEL

The Atorvastatin calcium (ATC) loaded aloe-carbopol gel (AG) and nanoparticle-loaded gel (ANG) were clear, viscous, and transparent with no visible particles, indicating good homogeneity and smoothness. The relative density of the nanogel was found to be 1.2 g/cc, making it lightweight and easy to handle. The pH of the formulation was 6.5, which is nearly neutral and skin-friendly, ensuring no irritation upon application. The moisture content of the nanogel was 98.6%, confirming good hydration and gel consistency. Rheological evaluation revealed a viscosity of 8500 cp, indicating suitable thickness and slightly plastic flow behavior, which allows the gel to remain at the site of application without spreading uncontrollably.

The spreadability test showed a diameter difference of 5.2 cm, suggesting excellent spreading properties and improved patient compliance. Drug content uniformity analysis revealed a consistent distribution of the drug, with values of 98.5 ± 1.2%, confirming homogeneity within the formulation. Ex-vivo permeation studies using rat skin mounted on a Franz diffusion cell demonstrated effective drug permeation from the nanogel. The donor compartment contained the gel, while phosphate buffer (pH 7.4) in the receptor compartment was stirred at 100 rpm, with periodic sampling and replacement to maintain sink conditions. These results confirm that the optimized nanogel possesses desirable physicochemical and permeation characteristics suitable for topical drug delivery.

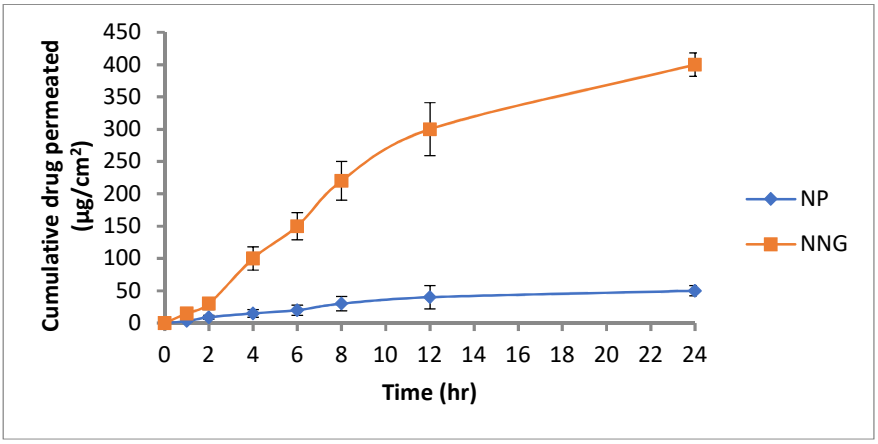


Fig 8: Ex-vivo permeation studies of ANG

The exvivo drug permeation studies showed that the AG showed a release of 50±8 µg/cm^2 at the end of 24 hours whereas the ANG showed a release of 400±18 µg/cm^2. The permeation rate is increased nearly 8 folds when compared with that of AG.

Stability studies

The final formulation underwent stability testing according to ICH criteria; the results are tabulated below. Once the final formulation's pH, % drug content, and % drug penetrated were measured, the results showed no significant changes after 90 days of storage.

Table 7: Stability testing of ANG

Time of sample	pH	Drug content	% Drug permeated at 24 hours
Initial (0 month)	6.5 ± 0.3	98.5 ± 1.2	98.67 ± 2.49
1st month	6.1 ± 0.1	97.6 ± 1.9	94.51 ± 3.29
2nd month	6.8 ± 1.2	98.4 ± 1.3	96.46 ± 3.63
3rd month	6.5 ± 0.5	98.4 ± 1.6	95.82 ± 3.92

CONCLUSION

Based on the analytical report, Atorvastatin Calcium (ATC) was characterized as an amorphous, poorly soluble powder. A robust analytical method was established with a λ max of 242nm, and the standard curve in phosphate buffer (pH 6.8) demonstrated linearity with an R^2 of 0.9925, confirming its validity for analysis. FTIR studies confirmed the drug's identity and indicated no undesirable chemical interactions with the formulation excipients, ensuring the integrity of the final product. Nanocrystals of ATC were successfully prepared using a Solvent Antisolvent precipitation technique, optimized via a 2^3-factorial design. Among the eight batches (F1-F8), formulation F8 was identified as the optimal candidate due to its small particle size, high drug content, and superior performance. The nanocrystals significantly enhanced the drug's saturation solubility and dissolution rate, with F8 releasing 98.53% of the drug within 60 minutes—a substantial increase over the 44.7% released by the pure drug. This nanosuspension (F8) was subsequently incorporated into an aloe-carbopol base to form a nanogel (ANG). The resulting ANG was transparent, spreadable, and had a suitable pH. It demonstrated a remarkable 8-fold increase in ex vivo drug permeation over 24 hours compared to a conventional gel, along with excellent stability over 90 days. This study concludes that the developed ATC Nanogel effectively enhances solubility, enables sustained release, and significantly improves topical delivery, offering a promising solution to the limitations of conventional dosage forms.

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