RESEARCH ARTICLE

Design and Evaluation of Tenofovir Alafenamide-Loaded Solid Lipid Nanoparticles Gel for Enhanced Transdermal Delivery

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Received: 29th Apr, 2025; Revised: 15th May, 2025; Accepted: 3rd Jun, 2025; Available Online: 25th Jun, 2025

ABSTRACT

This research essentially examines the design and evaluation of a gelling agent for transdermal delivery enhancement of Tenofovir Alafenamide (TAF)-loaded solid lipid nanoparticles (SLNs). Pre-formulation screening proved the drug is pure with a λ max 260 nm and a calibration curve ($R^2 = 0.9999$) for quantifying it. TAF-loaded SLNs showed a particle size distribution between 125.8 ± 2.0 nm to 274 ± 2.5 nm, with a PDI of 0.192 ± 0.04 to 0.214 ± 0.06 and zeta potential of -18.2 ± 4.1 mV to -26.6 ± 3.2 mV, denoting ideal characteristics for stability and drug delivery. Formulation optimization of SLN was carried out with 96.42% entrapment efficiency. The TAF-loaded SLN-gel is characterized by a homogeneous texture, adequate smoothness, and has pH values in the range of 6.02 to 6.15; during the *ex-vivo* permeation study, it was found that the cumulative TAF permeation over 24 h was 45.2 µg/cm². *In vitro* drug release data showed sustained release for 12 hours and a cumulative drug release at 71.4%. The gel showed good spreadability (7.2 cm) and extrudability (4.8-5.5 N) and minor variability over a period of 3 months. Acute dermal toxicity and skin irritation assessments were carried out and exhibited no significant side effects. The Primary Irritation Index (PII) of 0.44 classified it as a mild irritant. Therefore, it can be legitimately stated from the studies that the TAF-loaded SLN gel can be developed into a potential transdermal drug delivery system with sustained release characteristics, excellent entrapment efficiency, and good safety profiles.

Keywords: Tenofovir Alafenamide, Solid Lipid Nanoparticles, Transdermal Drug Delivery, SLN Gel, Sustained Release and Formulation Optimization.

How to cite this article: Ashish B Wadekar, Samir Atara, Dipak D Khumbhar. Design and Evaluation of Tenofovir Alafenamide-Loaded Solid Lipid Nanoparticles Gel for Enhanced Transdermal Delivery. International Journal of Drug Delivery Technology. 2025;15(2):519-30. doi: 10.25258/ijddt.15.2.20

Source of support: Nil

Conflict of interest: None

INTRODUCTION

The processes involved in developing advanced drug delivery systems have made a paradigm shift in the general pharmaceutical field; new methodologies for drug delivery are being coined in a contemporary sense to rectify the deficiencies of older means of drug administration.[1] TDDS offers a credible alternative in its own right, whereby first-pass metabolism can be circumvented, gastrointestinal irritation reduced, drug release controlled, and thus increase patient compliance.[2] Therefore transdermal drug delivery systems are ideal candidates for those drugs with poor oral bioavailability and ones requiring long-term maintenance of therapeutic concentration.[3]

SLNs represent a newer, versatile drug-delivery platform receiving wide acceptance in transdermal applications.[4] These lipid nanoparticles being biocompatible and biodegradable can encapsulate hydrophilic drugs as well as lipophilic drugs. Hence this system would also provide several advantages in terms of loading capacity of drugs and their stability, controlled-release mechanism, and enhanced permeation through skin due to a combination of nanosize and lipid composition. In brief, SLNs would protect the drug inside from degradation and thus enhance therapeutic efficacy.[5]

Tenofoviralafenamide (TAF) is an advanced prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor (NRTI) commonly used in HIV-1 infection and chronic hepatitis B treatment.[6] Compared to tenofovirdisoproxilfumarate (TDF), TAF is safer towards nephrotoxicity and lesser loss of bone mineral density[7]; on the downside, oral administration still poses challenges due to limited bioavailability because of first-pass hepatic metabolism, as well as the occurrence of potential systemic side effects at higher doses.[8] Consequently, these factors make it important to explore alternate routes for delivery to optimize therapeutic availability of TAF.

A transdermal route has promising alternative potential suitability for TAF. Transdermal delivery could enhance

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Table 1: Results of Calibration curve

Concentration (ug/ml)	Absorbance
2	0.1036
4	0.1672
6	0.2295
8	0.2979
10	0.3688

Table 2: Screening of lipid for formulation

Lipids	MP (^{0}C)	Solubility (mg/g)
Trimyristin (Dynasan 114)	54-58	70-90
Tripalmitin (Dynasan 116)	60-62	70-95
Tristearin (Dynasan 118)	65-67	95-115
Glycerylbehenate (Compritol 888 ATO)	52-55	40-60
Glycerylpalmitostearate (Precirol ATO 5)	43-54	20-40

Table 3: Screening of Surfactants for formulation

SN	Surfactant	Solubility (mg/5 ml)
1	Poloxamer (Pluronic P 85)	30
2	Polysorbate 20	38
3	Polysorbate 60	32
4	Polysorbate 80	39
5	Span 80	50

drugs' bioavailability while reducing potential systemic side effects by evade the gastric tract and hepatic metabolism.[9] The solid lipid inclusion nanoparticles (SLN) systems for TAF would therefore enhance skin permeation of TAF with sustained drug release profiles, thus improving therapeutic efficacy. The SLN lipid matrix also favorably interacts with the outmost cover of the skin, leading to increased drug penetration.[10]

In this study, SLN loaded with TAF were produced and formulated as a gel for transdermal use. The SLN formulation will enhance the solubility, stability, and permeability of TAF across the skin while extending the drug release from the incorporated agent. An optimized gel matrix was formulated to be easy to spread, have skin compatibility, and release the drug effectively. The characterization included various tests from the broadest to the narrowest aspects, mainly physicochemical properties to *in vitro* drug discharge kinetics and *in vitro* skin penetration.

The study investigates the orodispersible pattern of TAF and studies the possible breakthrough transdermal delivery device of TAF using novel TAF-loaded SLN-based gel. What could be the potential outcome is that this delivery system could significantly improve patient compliance and reduce the systemic toxicity with optimization of therapeutic efficacy when directed against HIV-1 and hepatitis B infections.

MATERIALS AND METHODS

Materials

The study materials included Tenofovir Alafenamide (TAF) obtained from Hetero Lab Ltd., India, and Dynasan-118 obtained from IOI Oleo Chemical, Germany, to serve as the lipid component. Carbopol 934, a gelling agent extensively used in the present study, was imported from Lubrizol India Pvt. Ltd. Span-80 suspended the emulsions and was sourced from Merck Life Sciences.

Pre-Formulation Study

The pre-formulation study of Tenofovir alafenamide consisted of pre-formulation analysis that was done to characterize its properties. Scanning from 200 to 400 nm revealed the finest wavelength to be 258 nm**.** Tenofovir alafenamide (10 mg) was suspended in methanol to produce a 1000 µg/ml the stock solution, which was subsequently diluted to a level of 10 µg/ml to form the working standard solution. In order to achieve amounts of 20, 30, 40, then 50 µg/ml, additional dilutions were produced. Tenofovir alafenamide's melting point was ascertained by use of a digitally auto melting point device and the capillary approach. By drying 1g of the medication sample and utilizing the following formula to determine a percentage of moisture loss, the moisture content was determined in accordance with AOAC guidelines (2000). by drying 1g of the drug sample and calculating the percentage of moisture loss. Differential Scanning Calorimeter (DSC) analysis was conducted by sealing a 2-10 mg sample in a DSC pan and measuring the heat flow during heating, identifying thermal transitions such as melting and crystallization through the thermogram, which provided insights into the sample's thermal properties.[11]

Table 4: Result of impact of formulation variables on the properties of TAF loaded SLNs

Batch Code	Factors (X)			Responses (*Y*)		
	1	2	3	1	2	3
	Amt. of lipid (mg)	B: Power (Watt)	C: Sonication time (Min)	Z-Avg (nm) ± SD	PDI ± SD	ZP (mV) ± SD
A1	400	25	03	227.2 ± 3.2	0.198 ± 0.06	-20.2 ± 4.5
A2	400	70	10	229.7 ± 1.5	0.214 ±0.06	-24.1 ± 3.2
A3	50	70	03	250.8 ± 2.0	0.204 ± 0.04	-18.2 ± 4.1
A4	400	25	10	218.4 ± 1.5	0.194 ± 0.12	-21.8 ± 3.2
A5	56	25	10	247.2 ± 1.5	0.213 ± 0.02	-19.4 ±4.5
A6	50	70	10	274 ± 2.5	0.215 ± 0.05	-24.8 ± 7.1
A7	400	70	03	125.8 ± 2.0	0.192 ± 0.04	-26.6 ± 3.2
A8	50	25	03	248.4 ± 1.5	0.211 ± 0.08	-19.7 ± 4.1

Table 5: Summary of TAF-SLN Gel Evaluation

Parameter	Results/Values
Visual Appearance & pH	Clear, smooth, homogeneous; pH: 6.02-6.15
Ex-Vivo Permeation	Cumulative TAF (24 hrs): 45.2 µg/cm²
Viscosity	25°C (10 s^{-1}): 150 cP; 37°C (10 s^{-1}): 180 cP
Spreadability	Spread (60s): 7.2 cm; Index: 190
Extrudability	Force: 4.8 - 5.5 N
Permeability	Flux (0.5 hr): 50.6 µg/cm²/hr; Kp: 0.002 cm/hr
Texture Analysis	Hardness: 12.5 g; Elasticity: 75%

Screening of Solid Lipids, Surfactants, and Compatibility Studies of Tenofovir Alafenamide

Lipid screening for Tenofovir Alafenamide was conducted to assess solubility in various lipids. The drug, 10 mg, was added to 200 mg of melted lipid while stirring continually, and more lipid was added gradually until a clear solution was formed. Surfactant studies took an additional dimension in solubility screening of Tenofovir Alafenamide in Tween-80, Span-20, and Poloxamer 188 (Pluronic F 68). About 10 mg of the drug was suspended in 10 ml of surfactant while stirring until a clear solution was formed incrementally after adding the surfactants. Compatibility studies included IR Spectroscopy analysis, where physical mixtures of Tenofovir and Dynasan 118 were analyzed to detect interactions by comparing key absorption bands, and Thermo Gravimetric Analysis (TGA) to assess thermal stability. TGA was done on individual samples of Tenofovir Alafenamide and Dynasan 118, and degradation temperatures were compared to ensure that they would not interfere with each other in any formulation involving melted solid lipids.[12]

Production of TAF-SLNs and Effect of Variables in Formulation

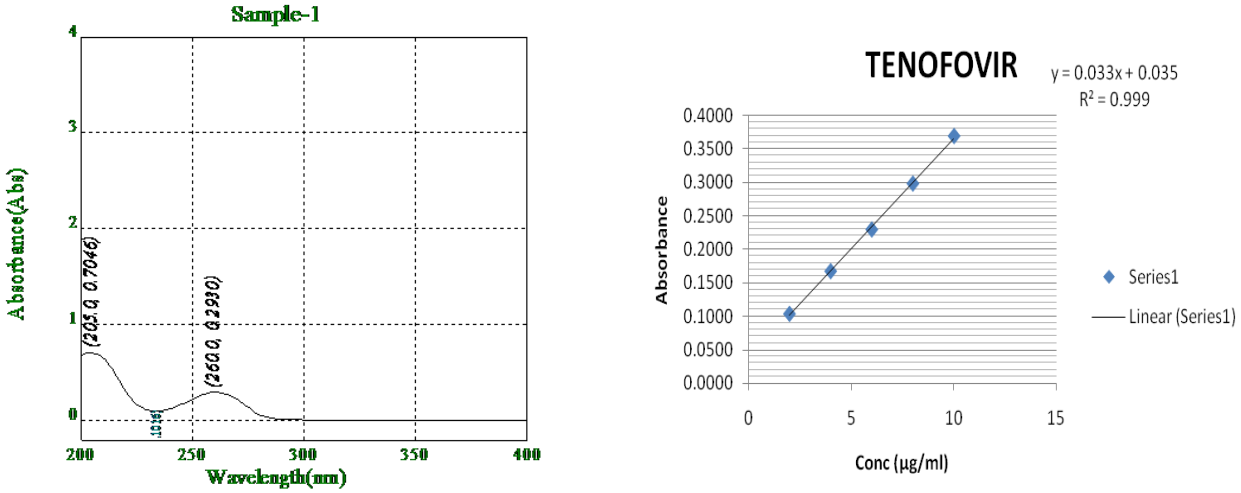


Figure 1: (a) UV Spectra (b) Calibration curve of Tenofovir alafenamide

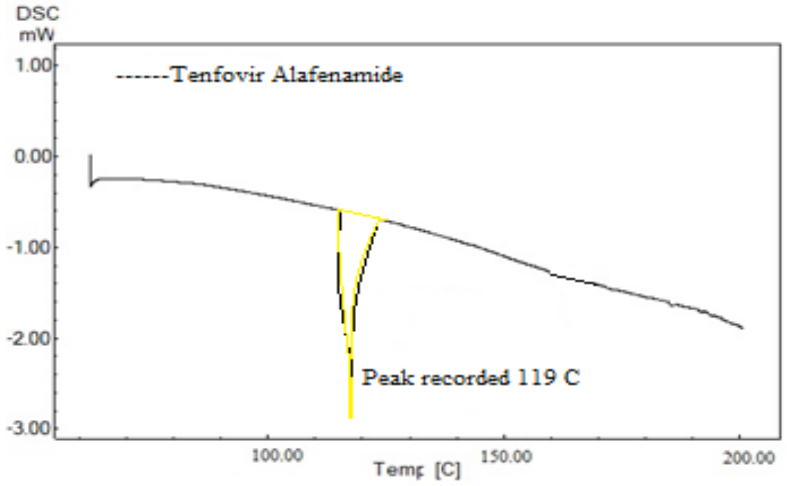


Figure 2: DSC thermo gram of Tenofovir Alafenamide API

Table 6: Results of Stability Studies

		Month			
Storage time		0	1	2	3
Particle Size (nm)	A7	45.25±12	45.63±11	44.74±09	44.72±11
Zeta potential (mV)	A7	-27.51±0.8	-28.55±0.2	-26.88±0.4	-27.81±0.5
Polydispersity index (PDI)	A7				
Entrapment efficiency (%)	A7	88.41±0.4	86.56±0.6	85.21±0.4	87.56±0.07

Table 7: Acute Dermal Toxicity Evaluation (OECD 402)

Parameter	Observation Period	Results
Mortality/Morbidity	Day 1 - Day 14	Nil
Body Weight (g)	Day 1	220.7
	Day 7	240
	Day 14	256
Signs of Toxicity	First 24 hours	No clinical signs observed
Signs of Toxicity	Day 1 - Day 14	No clinical signs observed

Melt emulsification-probe sonication was used to create TAF-loaded solid nanoparticles of lipid (SLNs).[13] Tenofovir Alafenamide (TAF) was added after Dynasan-118 and Span 80, which had been carefully weighed, were melted at 80°C to a transparent, oily phase. In the meantime, another aqueous polymer dispersion was prepared using deionized water from distillation (DDW) at the same temperature (80°C), into which Pemulen was mixed for 1 min utilizing an ultra-turrax (T25 Basic, IkaWerke, Germany). After adding three milliliters of this dispersion to the oily phase, the probe was sonicated for three minutes at 70 W using an IKASONIC U 200 S (Germany). After that, the resulting main emulsion was mixed with the remaining polymeric dispersion and homogenized for three minutes at 6,500 rpm using an ultra-turrax. After cooling the heated mixture to normal temperature, the lipid was able to recrystallize and create nanoparticles. A Plackett-Burman design was used to examine the impact of formulation factors on TAF-loaded SLNs, taking into account three nondependent factors: lipid concentration (X1), sonication power (X2), along with sonication time (X3). Particle size (Y1), polydispersity index (PDI) (Y2), and zeta potential (Y3) were among the responses that were analyzed. Design Expert, version 13.0.0.5, was used to do multiple regression analysis on the data. The remaining excipients, Pemulen (50 mg), The range-80 (1.2 ml), and TAF (25 mg), were kept at the same concentration in every batch.[14]

Characterization of TAF-SLNs

Characterization of TAF-loaded SLNs is part of a number of analyses to assess their physical properties. Particle sizes were examined Zetasizer Nano ZS with dispersal of nanoparticles in double-distilled water (DDW) at 25°C. Zeta potentials were

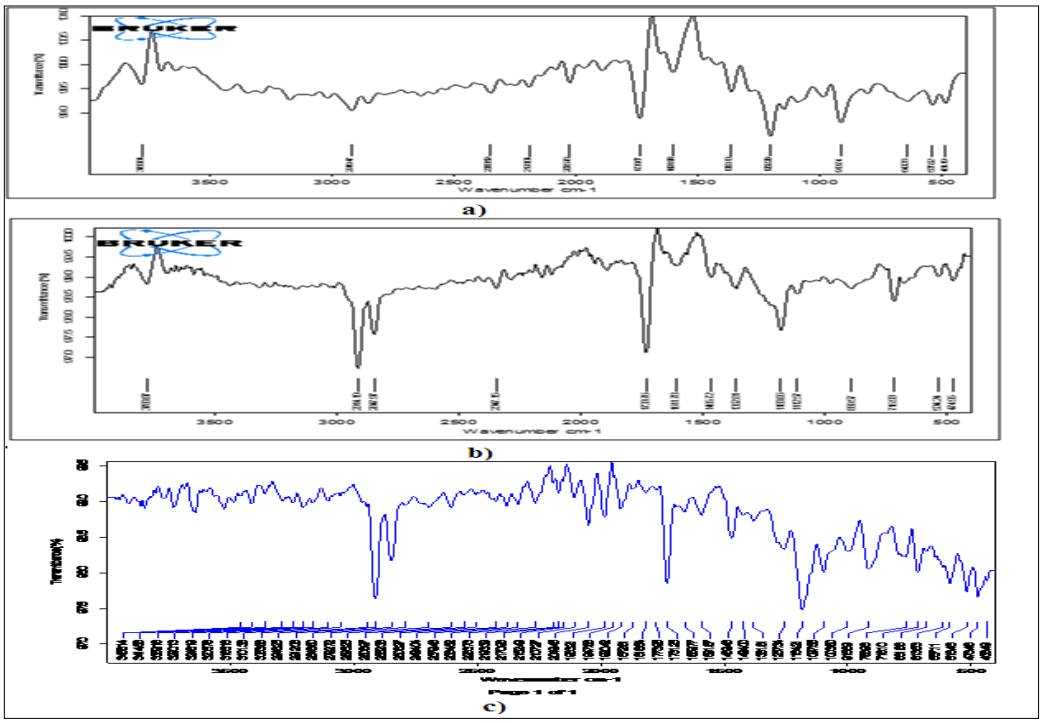
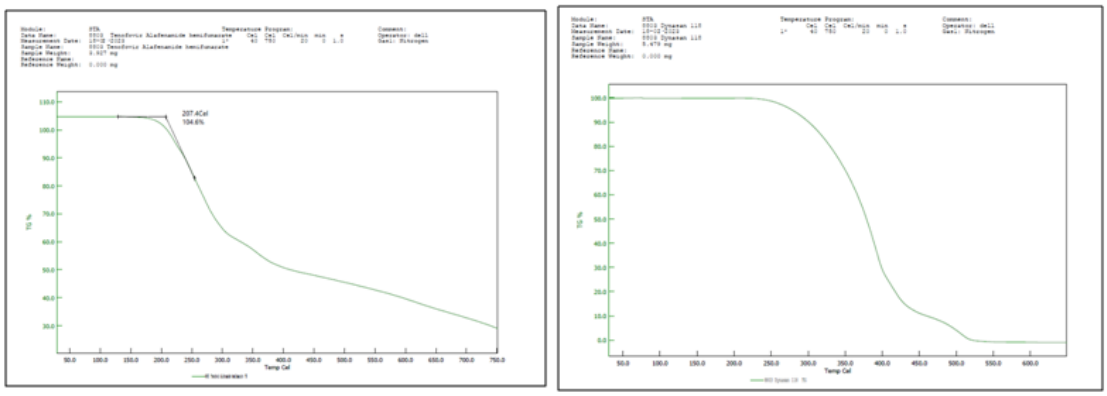


Figure 3: FTIR spectra of Tenofovir API, D118, and their physical mixture



a) b)

Figure 4: TGA analysis of Tenofovir Alafenamide and Dynasan 118

measured for the SLNs in the same equipment, whereupon surface charge was assessed. The amount of TAF within the supernatant was measured using UV-Vis spectrophotometry at 258 nm after high-speed centrifugation was used to determine the optimized batch's percent efficiency of entrapment (%EE) (A7). Selected functional groups of the pure substance, Dynasan-118, Pemulen, lyophilized SLNs, plus drug-lipid melt were subjected to FT-IR investigations. Using Differential Scanning Calorimetry (DSC), the thermal characteristics of drug, pemulen, drug-lipid that had already melted, and lyophilized SLNs was evaluated.

Phosphotungstic acid and uranyl acetate stains were used in the transmission electron microscopy (TEM) morphological analysis of the improved batch (A7). Atomic force microscopy (AFM) mode of tapping was used to evaluate the samples' surface topography in order to ensure the best scanning parameters with a 512 × 512 pixel resolution. A regulated temperature of 25±1°C was used for all experiments.[15]

Preparation of SLN Gel Transdermal Gel Containing Tenofovir

Alafenamide loaded solid lipid nanoparticles were prepared by using Carbopol 934 as a gelling agent. Slowly distilled water was mixed with 1% w/w Carbopol 934 and stirred for the next ten minutes at 1500 rpm. Finally, a dispersion of freshly prepared TAF-SLNs was added into the prepared gel mix, stirred for another ten minutes, and then the pH was attuned to 5.5 by addition a few drops of triethanolamine. The prepared gels were allowed to stand overnight to allow the entrapped air to escape.[16]

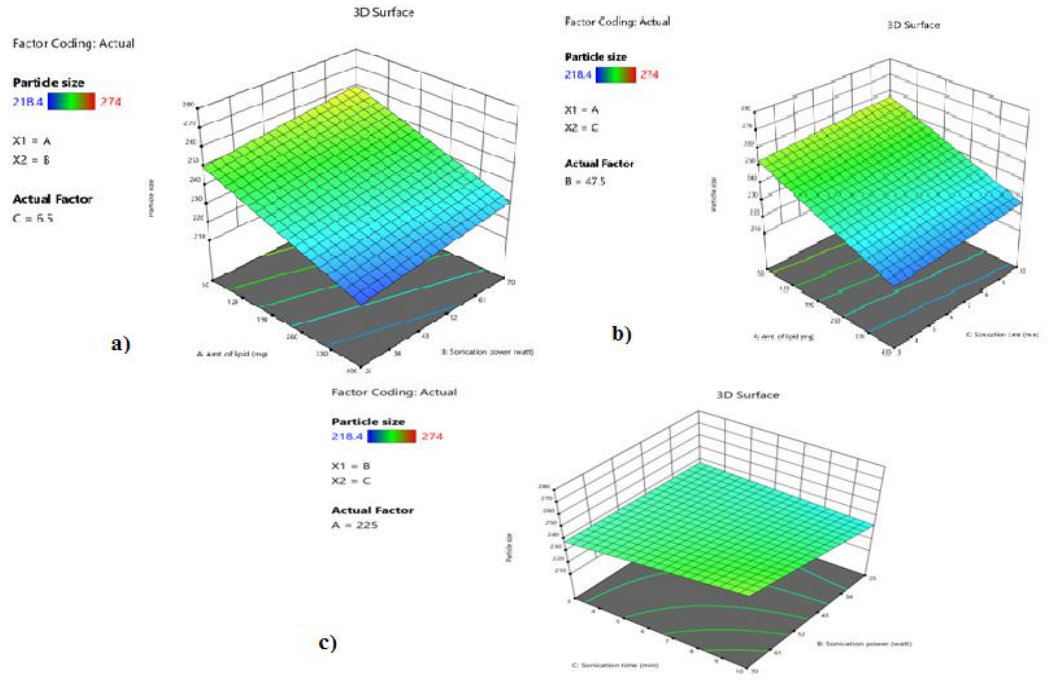


Figure 5a: 3D Surface Plots Depicting the Impact of Formulation Variables on Particle Size

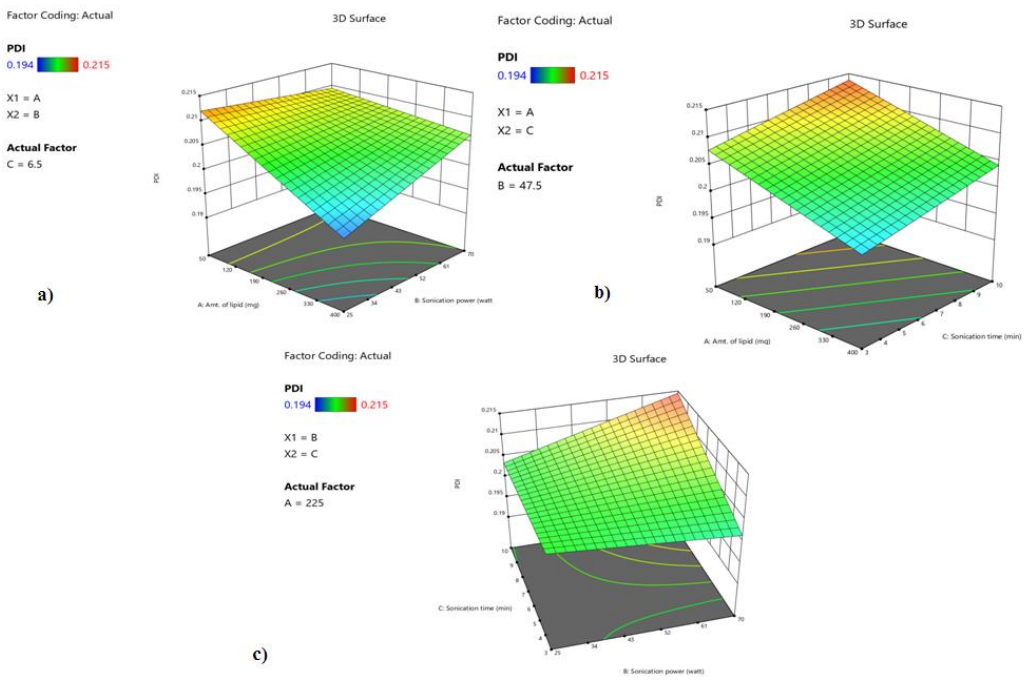


Figure 5b: 3D surface plot for effect of formulation variables on polydispersity index (PDI)

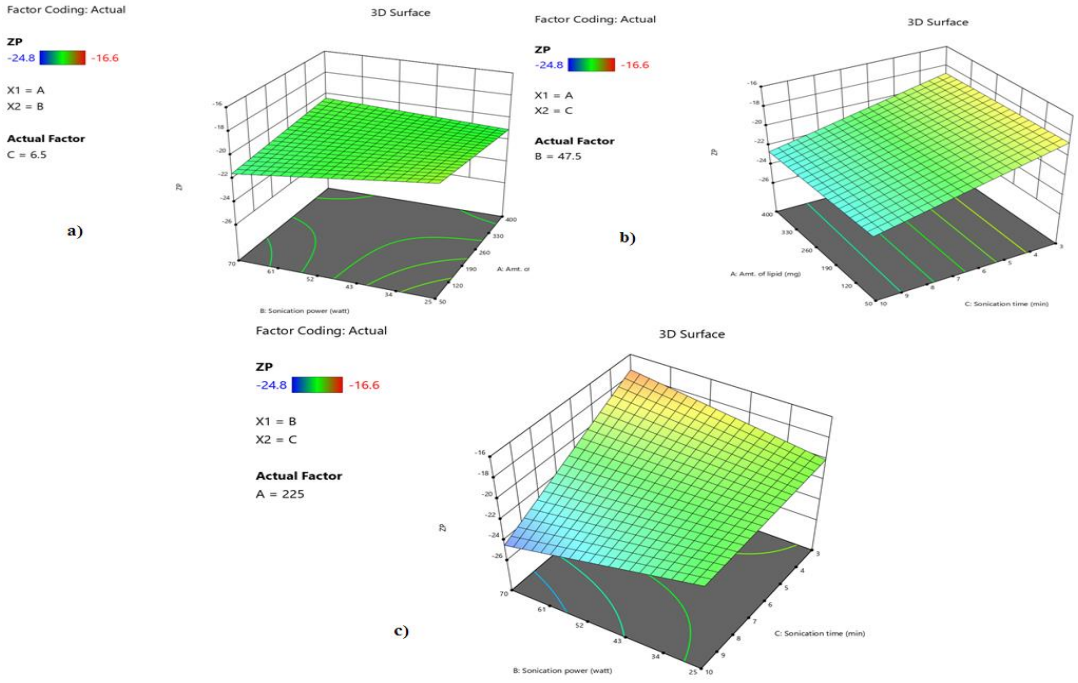


Figure 5c: 3D surface plot for effect of formulation variables on zeta potential

Evaluation of TAF-SLN Gel Formulations

Evaluation of gel formulations of TAF-loaded solid lipid nanoparticles (SLNs) involves several tests to determine their physical, chemical, and drug delivery properties. The physical appearance and pH of the gel were noted, with the determination of pH by a pH meter showing all gels within the range of 6.02 - 6.15. The *ex vitro* permeation examination was done by means of a specially designed diffusion cell where the gel was applied to the donor compartment, and the permeation of TGF was analyzed using HPLC. Viscosity and spreadability of the gels were evaluated to assess their flow characteristics and surface-spreading capabilities. The extrudability of the gel was determined by measuring the force required to extrude the gel, and texture analysis was

performed for the assessment of hardness, adhesiveness, cohesiveness, and elasticity from a mechanical point of view. Stability studies were undertaken to monitor the gel's physical, chemical, and microbiological stability over time, whereas *in vitro* drug release experiments in Franz diffusion cells were used develop release profile of TAF from the gel. In the diffusion study, the dialysis membrane was coated with optimized TAF-loaded SLN gel, while at predetermined intervals, samples of the receptor fluid were analyzed by UV spectrophotometry.[17]

Animal studies on dermal irritation and acute topical toxicity

Study dermal irritation and acute dermal toxicity of TAF solid lipid nano-particle gel formulation at RANS-GENICA SERVICES PVT. LTD., India, following OECD 402 and OECD 404 guidelines. The study involved Sprague Dawley (SD) rats and New Zealand White (NZW) rabbits for evaluating the safety profile of the gel. For acute dermal toxicity, SD rats were given dose of 2000 mg/kg of the TAF SLN gel. Fur was shaved before the application of the gel on the dorsal surface. The mortality, morbidity, clinical signs, and body weight changes were observed up to a 14-day period. For dermal irritation experience, NZW rabbits received 0.5 gm of TAF SLN gel, applied on 6 cm² skin area for a 4-hour exposure. After the patch was removed, the animals were checked for erythema, swelling, and irritation at 1, 24, 48, and 72 hours. The Draize test criteria were then used to grade the results.. The primary irritation index (PII) was calculated so that classification could be made for the

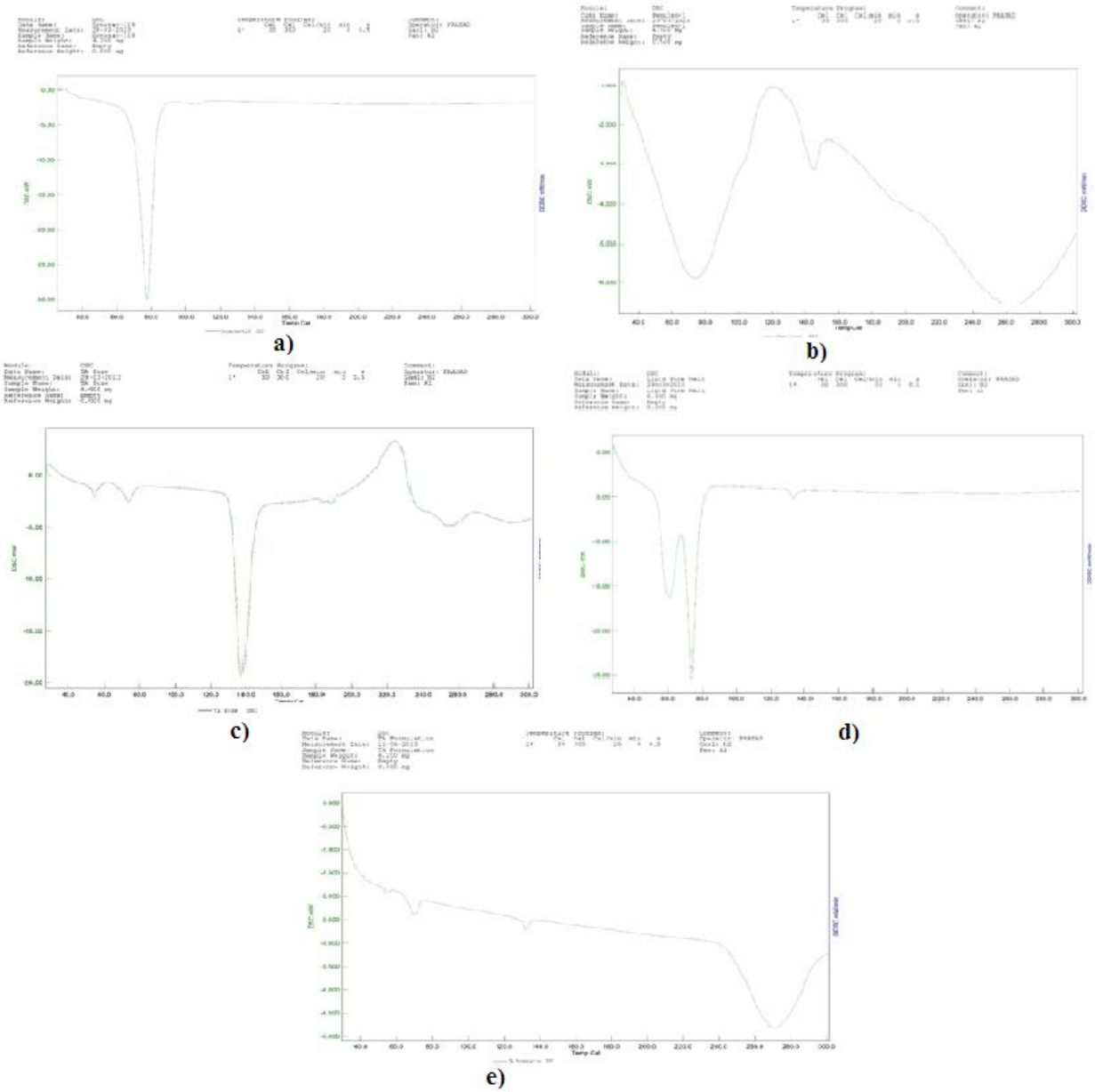


Figure 6: DSC thermograms of a) Dynasan-118, b) Pemulen, c) TAF, d) drug-lipid melt, and e) the final formulation

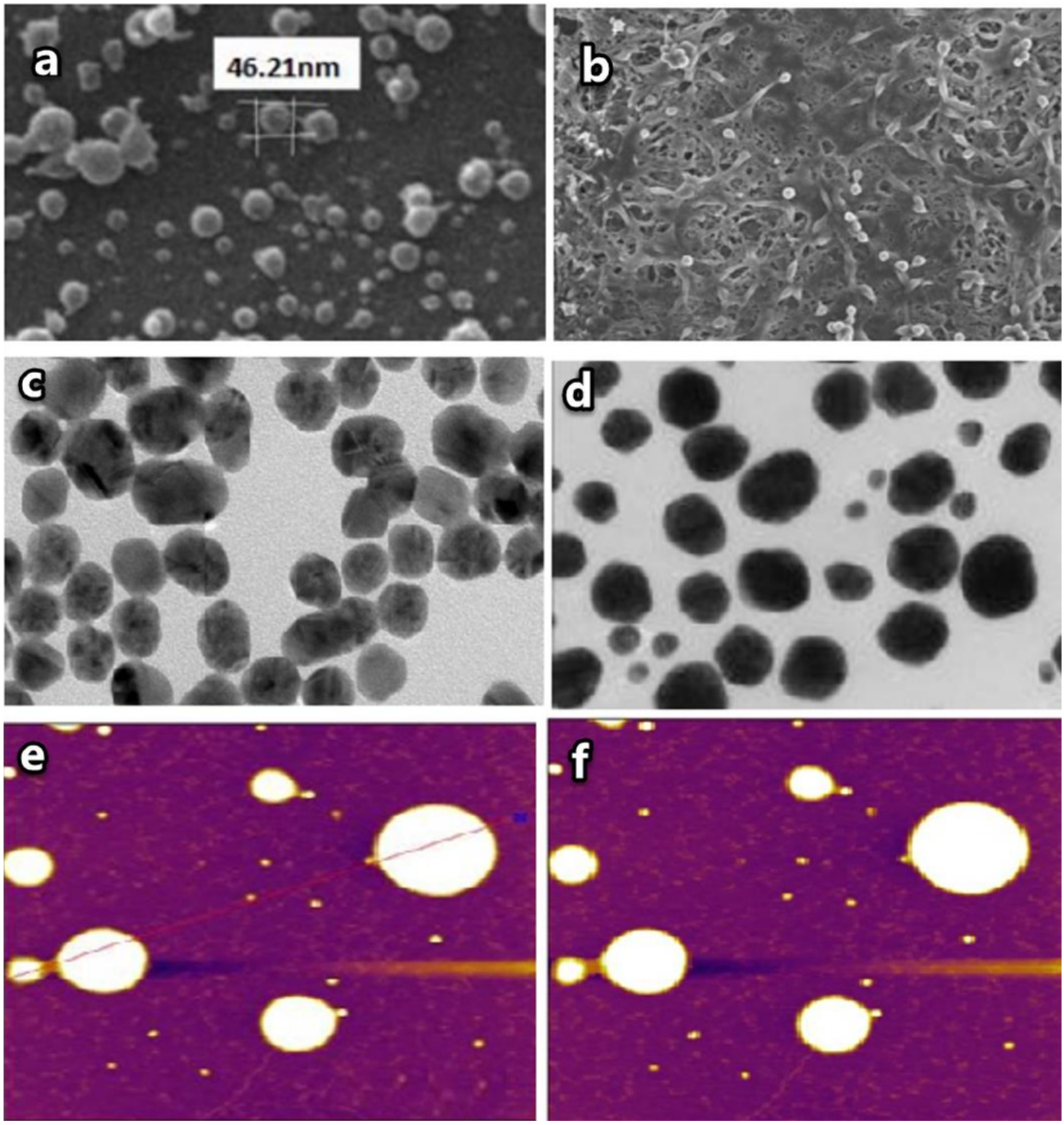


Figure 7: (a) TEM, (b) SEM, and (c) AFM images of optimized batch (A7)

irritancy level. Distilled water was used as vehicle for the application and all procedures were run in accordance with OECD recommendations.[18]

RESULTS AND DISCUSSION

Pre-Formulation Study

The UV spectra of Tenofovir Alafenamide were used to determine the λ max at 260 nm, optimizing sensitivity for quantification. A linear calibration curve (Figure 1) was constructed with absorbance values increasing from 0.1036 at 2 µg/ml to 0.3688 at 10 µg/ml,given in table 1 confirming the method's reliability within this concentration range. The regression equation (y = 29.857x - 7.481) and a correlation coefficient of 0.9999 indicate a strong linear relationship, supporting the accuracy and sensitivity of the spectrophotometric method. The melting point of Tenofovir Alafenamide was found at 119°C, aligning with the standard range of 118–120°C, confirming its purity and suitability for use. The moisture content was found to be 1.17±0.19%, with water activity of 0.124±0.01, indicating the drug's

hygroscopic nature. Differential Scanning Calorimetry (DSC) analysis (Figure 2) revealed a individual endothermic fusion peak at 119°C, correlating with the observed one and further confirming the drug's thermal properties. These findings establish the physical characteristics and reliability of Tenofovir Alafenamide for subsequent pharmaceutical applications.[19]

Screening of Solid Lipids, Surfactants, and Compatibility Studies

In the screening of solid lipids based on drug solubility, Tristearin (Dynasan 118) demonstrated the highest drug solubilizing capacity at 10510 mg drug/gram of lipid, followed by Tripalmitin (Dynasan 116) and Trimyristin (Dynasan 114) as detailed in table 2. This highlights Tristearin as the preferred choice for further research due to its superior solubility and GRAS designation. In surfactant screening, Span 80, a sorbitan ester with hydrophobic nature, showed the highest drug solubility (50 mg per 5 ml), making it ideal for further formulation studies as given in table 3. Compatibility studies, including FTIR analysis, revealed no significant changes in functional group absorption peaks in Tenofovir API, Dynasan 118, and their physical mixture as observed in figure 3, indicating no adverse interactions between the drug and lipid. The TGA analysis of Tenofovir Alafenamide and Dynasan 118 showed that Tenofovir begins to degrade at 207.4°C, while Dynasan 118 starts to degrade at 294.6°C can be seen in figure 4, demonstrating that both materials remain stable at the melting point of the solid lipids, ensuring their suitability for drug delivery systems. These findings collectively suggest that both the solid lipid and surfactant are compatible with the drug and have favorable thermal properties for pharmaceutical formulations.

TAF-loaded Solid Lipid Nanoparticles (SLNS)

The formulation variables, including lipid concentration, sonication power, and sonication time, were investigated using a Plackett-Burman factorial design to optimize the formulation process. The results given in table 4 and figure 5a, 5b and 5c indicated that variations in these factors significantly influenced nanoparticle characteristics, such as Z-Average size, Polydispersity Index (PDI), and Zeta Potential (ZP). Increasing lipid concentration generally increased particle size, while higher sonication power and longer sonication time led to smaller particles and more consistent PDIs. The study emphasizes the importance of controlling formulation variables to achieve optimal nanoparticle properties for stability and therapeutic efficacy, demonstrating the value of systematic experimental designs in pharmaceutical nanoparticle formulation.

Characterization of SLNs

Particle size, the polydispersity index (PDI), as well as zeta potential (ZP) were all analyzed in order to characterize TAF-loaded Solid Lipid Nanoparticles (SLNs). An F-value about 10.60 and a p-value about 0.0408 showed that the amount of lipid had a statistically significant impact on particle size, with the formulations' particle sizes falling between 125.8 ± 2.0 and 274 ± 2.5 nm. The PDI varied from -0.192 ± 0.04 to 0.214 ± 0.06, with significant effects from lipid amount and interactions between sonication power and time. The zeta potential ranged from -18.2 ± 4.1 to -26.6 ± 3.2 mV, with sonication time showing a significant impact on ZP. Particle

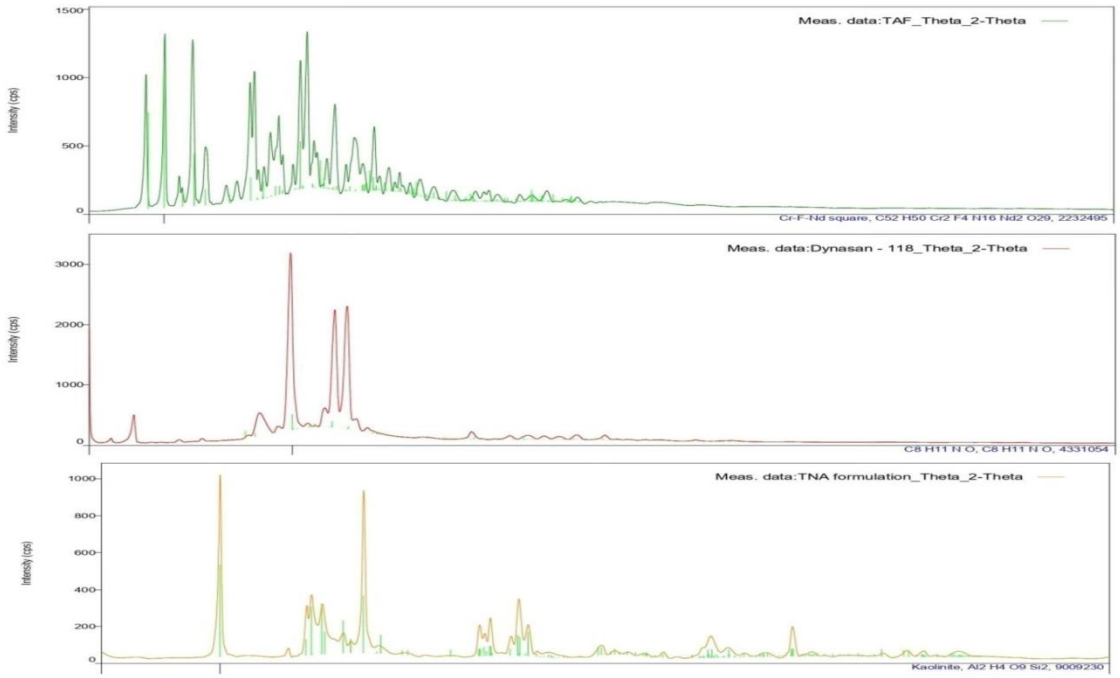


Figure 8: XRD patterns of (a) TAF (b)Dynasan-118 and (C) SLNs. Formulation

Table 8: Skin Irritation Test (OECD 404)

Parameter	Observation Period (Hr.)	Results
Defatting of Skin	-	No defatting of skin
Systemic Adverse Effects	-	No clinical signs of toxicity
Erythema Score	1	0.33
	24	0.66
	48	0
	72	0
Oedema Score	1	0.66
	24	0.66
	48	0
	72	0
Primary Irritation Index (PII)	-	0.44
Nature of Irritation	-	Mild irritant

size, PDI, and ZP 3D surface plots helped optimize nanoparticle blends for desired properties in pharmaceutical applications by clearly illustrating the impact of formulation variables such lipid amount, sonication strength, and sonication time. The optimized SLN formulation (A7) demonstrated a high entrapment efficiency of 96.42.

Differential scanning calorimetry (DSC) analysis revealed distinct thermal behaviors for various components. The DSC thermogram showing the drug-lipid melt did not display a typical TAF melting endotherm, suggesting molecular dispersion of the substance inside the lipid carrier matrix, whereas pure TAF had a melting endothermic maximum at 119°C. As seen in figure 6, the SLN formulation (A7) displayed a peak that was smaller at 123°C, indicating a decrease in crystallinity. Visual confirmation of the nanoparticles' spherical shape and consistent size distribution was obtained by Transmission Electron Microscopy (TEM) (Figure 7a) and Scanning Electron Microscopy (SEM) (Figure 7b), with average sizes of 45 nm and 46.21 nm, respectively, supporting their suitability for drug delivery applications. Atomic Force Microscopy (AFM) analysis given in figure 7c further validated the nanoparticles' uniformity and topography, with high-resolution images revealing surface details at the nanoscale. Finally, X-Ray Diffraction (XRD) analysis (Figure 8) showed that TAF was crystalline in its pure form but became amorphous in the SLN formulation, with a reduction in the lipid crystallinity observed in the SLN's diffraction patterns.[20]

Evaluation of SLN Gel

The transdermal gel containing Tenofovir Alafenamide (TAF) loaded solid lipid nanoparticles (SLNs) was prepared using Carbopol 934 as a gelling agent. The gel exhibited good visual appearance, smoothness, spreadability, and a pH of 6.02–6.15. *Ex-vivo* permeation studies demonstrated a sustained release profile, with 45.2 µg/cm² of TAF permeating through the skin after 24 hoursShear-thinning behavior was demonstrated by viscosity tests, which showed that viscosity decreased with increasing shear rate and temperature. The gel showed excellent spreadability, extrudability, and consistent texture, with desirable characteristics for easy application. Stability studies over 3 months at 4°C showed minimal changes in particle size, zeta potential, and entrapment efficiency, indicating good stability. *In-vitro* drug release studies as shown in figure 9 demonstrated a sustained release of TAF, with 71.4% cumulative drug release over 12 hours. Table 5 Summarizes results of TAF-SLN Gel Evaluation. These findings suggest that the TAF-loaded SLN gel formulation is stable, has favorable drug release kinetics, and could be an effective

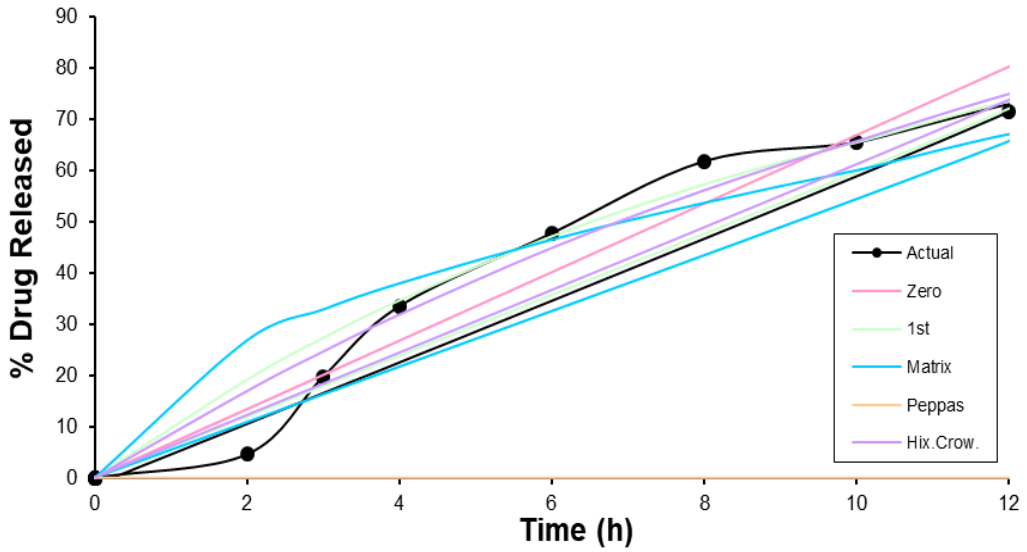


Figure 9: *In-Vitro* drug release Study of SLN gel formulation

transdermal drug delivery system, potentially improving patient compliance and therapeutic efficacy in clinical applications.[21] Table 6 shows results of Stability Studies.

Dermal Irritation and Acute Dermal Toxicity Study

The acute dermal toxicity and skin irritation studies (OECD 402 and OECD 404) evaluated the safety and irritancy of a Novel Tenofovir Alafenamide (TAF) formulation loaded into Solid Lipid Nanoparticles (SLN) gel. The acute toxicity study at a dose of 2000 mg/kg applied topically showed no mortality, morbidity, or clinical signs of toxicity, with stable body weights and no adverse effects observed over a 14-day period. The skin irritation test with a 0.5 g dose showed no defatting of the skin or systemic adverse effects, and minimal erythema and edema were observed, resolving within 72 hours. The Primary Irritation Index (PII) was 0.44, classifying the formulation as a mild irritant.Table 7 gives results of Acute Dermal Toxicity Evaluation (OECD 402) and Table 8 shows results of Skin Irritation Test (OECD 404). Finding Shows well-tolerated and does not induce significant skin irritation, making it suitable for further clinical development as a topical delivery system for TAF.

CONCLUSION

The design and evaluation of Tenofovir Alafenamide (TAF)-loaded solid lipid nanoparticles (SLNs) gel for enhanced transdermal delivery demonstrated promising results. The pre-formulation studies confirmed the drug's purity, with a λ max of 260 nm and a linear calibration curve ($R^2 = 0.9999$), ensuring reliable quantification. The melting point of TAF at 119°C, along with a moisture content of 1.17±0.19% and water activity of 0.124±0.01, highlighted its suitable physical properties for formulation.

Tristearin (Dynasan 118) and Span 80 were identified as optimal excipients for TAF, with compatibility studies (FTIR and TGA) showing no adverse interactions. The lipid's high drug solubility (10510 mg/gram) and surfactant's favorable solubility (50 mg per 5 ml) were key factors in formulation success.

The TAF-loaded SLNs exhibited a particle size range of 125.8 ± 2.0 nm to 274 ± 2.5 nm, with a PDI of 0.192 ± 0.04 to 0.214 ± 0.06 and zeta potential ranging from -18.2 ± 4.1 to -26.6 ± 3.2 mV, which were optimized using a Plackett-Burman factorial design. The formulation (A7) demonstrated a high entrapment efficiency of 96.42%. DSC, SEM, TEM, and AFM analyses confirmed the drug's molecular dispersion in the lipid matrix and the nanoparticles' spherical morphology, making them suitable for drug delivery.

The TAF-loaded SLN gel exhibited a clear, smooth, and homogeneous appearance with a pH of 6.02–6.15. The *ex-vivo* permeation studies indicated a cumulative drug permeation of 45.2 µg/cm² after 24 hours, and *in-vitro* release studies showed 71.4% cumulative drug release over 12 hours. The gel demonstrated desirable characteristics, including excellent spreadability (7.2 cm) and extrudability (4.8–5.5 N), while maintaining good stability over 3 months.

Safety evaluation through acute dermal toxicity (OECD 402) and skin irritation (OECD 404) studies showed no mortality or morbidity, with minimal erythema and edema, classifying the formulation as a mild irritant (PII: 0.44). These findings collectively support the potential of the TAF-loaded SLN gel as an effective transdermal drug delivery system, with sustained release, high entrapment efficiency, and promising safety profiles, making it a strong candidate for clinical development in transdermal drug delivery applications.

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