J Nanostruct 16(2): 2493-2501, Spring 2026

RESEARCH PAPER

Development and Evaluation of Solid Lipid Nanoparticles Based Gel Loaded with Anticancer Drug

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ARTICLE INFO

Article History:
Received 09 December 2025
Accepted 19 March 2026
Published 01 April 2026

Keywords:
Compritol
Lipid
Melanoma
Topical treatment
Vemurafenib

ABSTRACT

The present work was designed to develop and characterize Vemurafenib loaded solid lipid nanoparticles (SLNs) then incorporated into gel for topical treatment of melanoma to improve the therapeutic efficacy and to decrease systemic adverse effects as well as organ exposure. Vemurafenib SLNs were prepared by high energy probe ultra-sonication process employing solid lipid, Compritol 888 ATO and surfactants, Sodium Lauryl Sulfate (SLS) and Span 20. The nanocarriers were assessed for entrapment efficiency (EE%), particle size (PS), polydispersity index (PDI), zeta potential (ZP), pH, morphology by Scanning Electron Microscopy (SEM) and in vitro drug release. The optimum formula was then included in 1 % Carbopol 940 gel. All formulations showed high encapsulation efficiencies of from 84.15% to 91.43% and the greatest EE% was seen in formulation F6 (91.43 ± 2.1\%). The particles were between 103 nm and 343 nm in size and the smaller and more uniform particles were obtained at greater surfactant ratios and lower concentrations of the lipophilic Span 20, which otherwise caused matrix swelling and crystallization disturbances. The ZP values varied from −5.8 mV to −28.1 mV, indicating good colloidal stability. The in vitro release profiles revealed that the formulation F6 exhibited quick and higher drug release. The final formulation converted to gel which demonstrated a longer prolonged diffusion-controlled drug release profile due to the viscosity of the gelling polymer. The formulation of a Vemurafenib-loaded SLN gel is a promising, stable, and non-irritating transdermal administration approach that can localize the drug activity in melanoma lesions.

How to cite this article
Alaayedi M., Kadhum Z., Saeed A., et al. Development and Evaluation of Solid Lipid Nanoparticles Based Gel Loaded with Anticancer Drug. J Nanostruct, 2026; 16(2):2493-2501. DOI: 10.22052/JNS.2026.02.089

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INTRODUCTION

The topical administration method offers several benefits for treating different dermatological conditions and for cosmeceutical applications. This approach circumvents the hepatic first-pass effect, and the systemic availability of several medications [1].

The implementation of medication delivery systems for the management of dermatological disorders was established long ago. Comprehensive research has been conducted to enhance the localized treatment of many dermatological conditions, including wounds, psoriasis, microbial infections, acne, inflammation, autoimmune disorders, and skin cancer [2]. Traditional topical therapies for skin cancer, such creams, gels, and ointments, are more occlusive and thus fail to penetrate deeply into the dermal layer, remaining confined to the epidermal layer. The stratum corneum serves as a physiological barrier for the medicine included in the typical formulation. Novel carrier systems have the capability to enhance medication penetration into the dermal layer due to their reduced size and increased flexibility compared to traditional treatments [3].

Nanoparticles have novel prospects for the treatment of dermatological disorders. The skin's barrier function presents a considerable obstacle for nanoparticles to infiltrate the tissue; nevertheless, this barrier is partly disrupted in instances of damage or inflammation, such as in skin cancer. The rationale for using nanoparticles (NPs) is mostly based on their capacity to enhance the penetration of bioactive substances into the skin and tumors. This improves medication retention in the skin and tumor, leading to decreased dose, lower toxicity, and enhanced patient compliance [4, 5].

The principal nanotechnology-based drug delivery systems functioning as transdermal carriers include vesicular systems such as liposomes, niosomes, and transferosomes, as well as specialized systems like polymeric nanoparticles, dendrimers, magnetic nanoparticles, carbon nanoparticles, gold nanoparticles, and silica nanoparticles (Saeidi et al., 2023). Innovative SLN has considerable benefits, including robust penetration capability and elevated drug-loading capacity for topical administration, in comparison to alternative carriers like liposomes and nanoemulsions [6-8].

Solid lipid nanoparticles serve as a vehicle for the administration of medicinal medicines. Solid lipid nanoparticles (SLNs) are typically produced by integrating a solid lipid into an oil-in-water emulsion using a stabilizer, facilitating the efficient trapping of the active pharmaceutical ingredient (API) [9]. SLNs consist of physiological supermolecules, hence possessing inherent routes for lipid transport and metabolism to ensure the in vivo destiny of the carrier. These exhibit stability over prolonged durations and are comparatively easy to rescale relative to other mixture systems, making them essential for various targeting modalities. SLNs include an array of pharmaceuticals from several pharmacological classifications, including steroids, vitamins, oncological medicines, and antifungals [10].

SLNs are believed to transport medications to the site of action. They are extensively used for topical treatments. These SLN formulations provide enhanced localization, occlusiveness, regulated release, and skin affinity for improved efficacy. Solid lipid nanoparticles (SLN) are nanocarriers with a solid core, ranging from 10 to 1000 nm, that encapsulate both hydrophilic and hydrophobic active medicinal ingredients [11]. Solid lipid nanoparticles (SLNs) consist of biocompatible and biodegradable solid lipids, including mono-, di-, and triglycerides, fatty acids, waxes, and steroids, together with both lipophilic and hydrophilic emulsifying agents. The formulation of biocompatible compounds renders solid lipid nanoparticles (SLNs) one of the most effective choices for drug delivery via various administration methods, including oral administration of SLN particles [12, 13].

Vemurafenib is suggested for individuals with unresectable or metastatic melanoma. The predominant side effects of vemurafenib include arthralgia, tiredness, rash, alopecia, and photosensitivity. Vemurafenib is chemically designated as N-(3-(5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide, with the molecular formula $C_{23}H_{18}ClF_2N_3O_3S$ and a molecular weight of 489.92 g/mol, exhibiting a purity of ≥98%. Vemurafenib appears as a white to off-white powder and should be stored at -20°C. It is soluble in DMSO at 100 mg/mL, exhibits very poor solubility in ethanol and water, with a maximum solubility in plain water estimated at approximately 25-50 µM. and a LogP of 3 indicates moderate lipophilicity [14, 15]. Vemurafenib is a

chemotherapeutic agent newly sanctioned by the FDA for the treatment of melanoma. The oral route of administration of the drug typically results in significant organ damage with constrained antitumor efficacy and bioavailability. In contrast, the transdermal administration of Vemurafenib proved superior to both oral and intravenous routes in minimizing organ damage and improving antitumor efficacy [16, 17].

The aim of the study is to formulate Vemurafenib as lipid vesicle in order to improve its effect for treating melanoma topically and avoiding the systemic related exposure and consequent adverse effect.

MATERIALS AND METHODS

Materials

Vemurafenib is from . Compritol 888 ATO (solid lipid), Sodium lauryl sulfate (SLS) (hydrophilic surfactant) with Span 20 (hydrophobic surfactant), Carbapol 940, Triethanolamine.

Methods

Formulation of SLN

Vemurafenib SLN were synthesized via the high energy probe ultrasonication technique. Compritol was liquefied at a temperature 5°C above its melting point. Subsequently, Vemurafenib (1%w/v) was incorporated into the lipid phase. The combination was then combined with a warmed aqueous solution of surfactant and co-surfactant (SLS and Span) in water. The two phases underwent sonication for 3 minutes (initial sonication). This formulation constituted a nanoemulsion due to the solid lipid being in a liquid state [18]. Thereafter, the mixture was amalgamated with partly frozen water in a 1:1 ratio and subjected to sonication for an additional 7 minutes (second sonication). This procedure enabled the creation of SLNs. The formulations were stored in a refrigerator at 2-8 °C for further analysis. The formulations were created to enhance the properties of the drug [19]. The quantities of Compritol, SLS, and the time of the second sonication have been adjusted as shown in Table 1.

Evaluation of the SLN formulas

Entrapment Efficiency

Entrapment Efficiency (EE) is utilized to assess the effectiveness of a nanocarrier in retaining the drug or active ingredient, ensuring the delivery of a sufficient quantity of the component to the targeted site. The entrapment efficiency of the nanoparticle was determined as follows;

Entrapment efficiency (%) = (Initial amount drug – amount of free drug)/ (Initial amount drug) × 100

Three milliliters of each Formula were deposited in an Amicon tube and centrifuged for one hour at 10,000 rpm (ultra centrifuge, Hanna Instruments Ltd. Singapore). Subsequent to separation, the lower fraction was gathered to assess entrapment effectiveness by spectrophotometry, while the suspended fraction was used to evaluate drug release [20, 21].

Dynamic light scattering

Dynamic light scattering (DLS) is a widely employed method for acquiring data on particle size (PS) and size distribution in diluted lipid-based colloidal systems (PDI), as well as measuring zeta potential (ZP), which indicates the potential difference across a particle and evaluates the aggregation propensity of nanoparticles. Values below –30 mV and above +30 mV are considered optimal for particle repulsion [22].

pH determination

The pH of the prepared SLN formulas was measured using pH meter (Hanna Instruments Ltd. Singapore).

Table 1. The composition of the SLN formulas.

Formula no.	Compritol (Solid lipid) w/w%	SLS (Surfactant) w/w%	Span 20 (Co-surfactant) w/w%	Water up 100%
F1	8	5	0	QS
F2	8	4	1	QS
F3	8	3	2	QS
F4	8	2	3	QS
F5	4	5	0	QS
F6	4	4	1	QS
F7	4	3	2	QS
F8	4	2	3	QS

In vitro drug release study

The in vitro release of vemurafenib from SLN was conducted using the dialysis membrane with Franz diffusion apparatus. The formula was placed inside a dialysis membrane (8-12 MWCO) over a distinct media of pH 6.8. The dissolving media volume was 50 ml, with release durations of 6 hours which maintained at a stirring speed of 50 rpm and a temperature of 37±0.5 ^{o}C. One milliliter samples were extracted and replenished every 30 min. The samples were examined using a UV-visible spectrophotometer at 325 nm. All experiments were conducted in triplicate for each sample [23, 24].

Scanning Electron Microscopy

The morphological characteristics of SLN optimual formula was assessed using a scanning electron microscope. This test was conducted to ascertain the morphology, dimensions, and dispersion of the particles within the ideal formulation [25].

Incorporation of SLN into Gel

Fabrication of SLN loaded gel

The optimum formula of SLN (F6) was converted into gel in order to improve the drug residence on the skin cancer area. The SLN was incorporated into carbapol 940 gel that produced using 1% the polymer in water. After getting homogenous mixture, the pH of the gel adjusted to the skin pH range using triethanolamine [26, 27].

Characterization of the gel loaded with SLN

The formulated gel was evaluated for the organoleptic properties, pH and in vitro drug release. The pH measured using pH meter to ensure the formula pH compatible with that for the skin and do not cause any irritation [28].

The gel was examined for its color, homogeneity and separation visually. The drug release from the produced SLN loaded gel was determined using Franz diffusion cell of 50mL capacity recipient part. The recipient was filled with phosphate buffer of pH 6.8. The used dialysis membrane was 8-12 MWCO that over it a one gram of the formula was placed. One milliliter from the recipient was drawn at specific time interval and then analyzed using UV spectrophotometer at the drug lambda max [29, 30].

RESULTS AND DISCUSSION

Characterization of SLN

Entrapment efficiency

The encapsulation efficiency percentage of Vemurofenib in solid lipid nanoparticles was evaluated for the formulations, with the findings shown in Table 2. All formulations exhibited excellent entrapment efficiency, ranging from 84.15% to 91.43%. This indicates that the drug was well contained inside the lipid matrix. The formulation F6 had the greatest encapsulation efficiency at 91.43%, The results data suggest that minor variations in lipid content do not significantly impede drug entrapment, as long as surfactant concentrations are sufficient to stabilize the nanoparticles. Elevated EE% across all formulations indicates that these SLNs efficiently deliver medicines rapidly, with minimum drug loss and the potential for enhanced therapeutic outcomes [31, 32].

Particle size, polydispersity index and zeta potential

The findings for PS, PDI, and ZP are shown in Table 2. The study investigates the impact of solid lipid and surfactant concentrations on PS of Vemurofenib-SLNs. Eight formulations (F1–F8) were developed by altering lipid content (4–8 w/w %), surfactant concentration (1–5 w/w %), and co-surfactant concentration (1-5%). The formulations exhibited PS values between 103 nm and 343 nm, illustrating the influence of formulation factors on

Table 2. Characterization features of the formulated SLN (n=3).

Formula Code	EE%	PS	PDI	ZP	pH
F1	88.21±1.3	302±11	0.450±0.01	-5.8±1.1	5.5±0.2
F2	86.34±2.4	296±21	0.364±0.03	-19.5±2.4	5.3±0.4
F3	89.42±1.9	343±23	0.263±0.02	-25±2.0	4.7±0.1
F4	84.15±3.1	340±15	0.286±0.01	-6.2±0.1	4.3±0.1
F5	90.20±2.5	152±06	0.199±0.05	-29.0±0.3	5.40.2
F6	91.43±2.1	103±03	0.110±0.02	-28.1±3.4	5.2±0.1
F7	85.63±1.7	189±07	0.317±0.01	30±3.8	6.1±0.2
F8	89.67±3.3	201±10	0.368±0.01	22±2.4	5.9±0.3

nanoparticle characteristics. The results indicated that elevated lipid concentrations correlated with an increase in PS due to the formation of bigger lipid droplets during nanoparticle production. This may be linked to the elevated viscosity and melting point of the solid lipid. Higher melting temperatures of lipids may result in less effective homogenization, thereby producing bigger particle sizes and size distributions [33, 34].

While, smaller, more uniform nanoparticles were produced with elevated surfactant concentrations, perhaps reducing interfacial tension and inhibiting aggregation. However, formulations rich in lipids and deficient in surfactant, such as F1- F5, yielded the biggest particles, but those containing enough surfactant, such F5- F8, resulted in smaller, more stable particles. The findings demonstrate the significance of the lipid-to-surfactant ratio and processing parameters in regulating the size and homogeneity of SLNs, essential for effective drug administration [35, 36].

Increasing Span 20 concentration in the formulation had a negative effect on size and uniformity of size distribution. This is due to its greater lipophilicity, Span 20 tends to embed itself more profoundly inside the lipid core rather than remaining just at the interface This integration may induce “swelling” of the lipid matrix. Moreover, it may lack enough steric stabilization relative to longer-chain or more hydrophilic surfactants, facilitating the aggregation or coalescence of particles during the cooling phase. The particle size of a solid lipid nanoparticle is significantly influenced by the stability of the original nanoemulsion created at elevated temperatures. Span 20 may be less efficient in reducing the interfacial tension between the molten lipid and the aqueous phase compared to surfactants with greater HLB values. The incorporation of Span 20 molecules in high concentration into the solid lipid matrix might disturb the ideal crystalline structure of the lipid [37].

The ZP of the SLNs formulations ranged from −5.8 to −28.1 mV, indicating a negatively charged particle surface. Formulations with high absolute zeta potential values demonstrated enhanced colloidal stability due to increased electrostatic repulsion between particles [38, 39].

The PDI of the SLNs formulations ranged from 0.110 to 0.450. Most formulations had PDI values of less than 0.3, indicating a small particle size distribution and superior homogeneity. In contrast, one formulation exhibited a markedly increased PDI (0.45), indicating considerable particle aggregation and reduced colloidal stability, likely attributable to inadequate surfactant coverage or

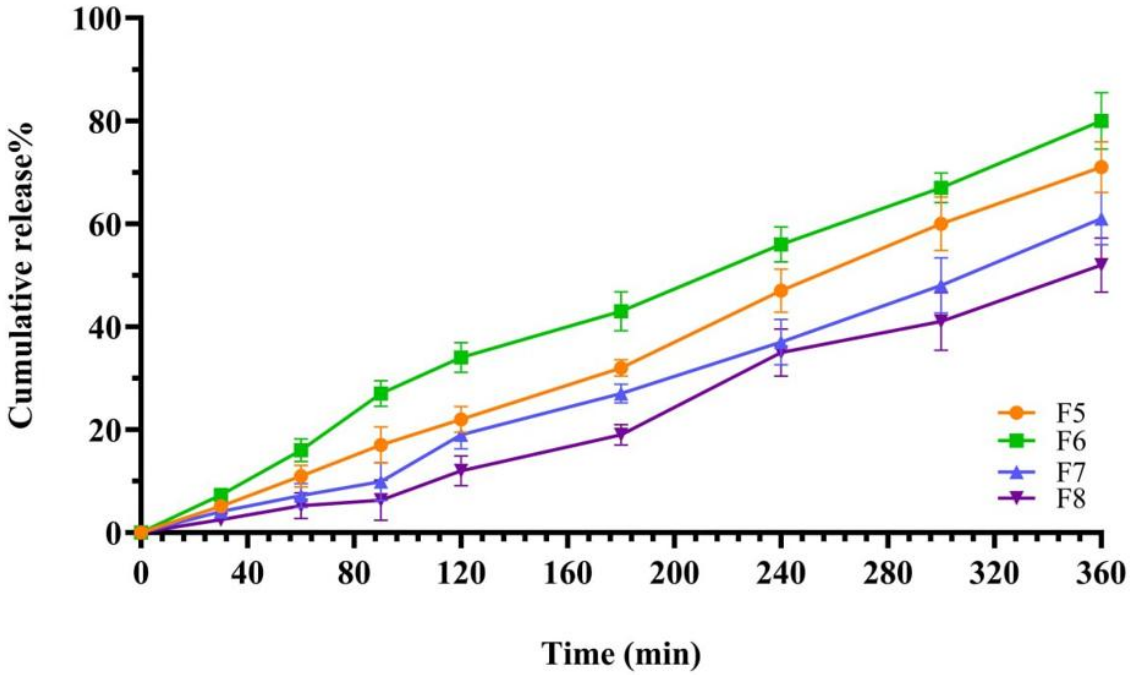

Fig. 1. In vitro drug release.

lipid recrystallization. The decreased PDI values mostly corresponded with formulations displaying increased ZP, highlighting the synergistic effect of electrostatic and steric stabilization on the uniformity of SLNs [40].

pH determination

The pH of the formulas showed a range of 4.7 to 5.5. The skin can afford pH range between 3-10, therefore the formulas pH is within the acceptable range for the skin and do not cause problems [41].

In vitro drug release

The in vitro release characteristics of the selected formulations F5-F8 exhibited a distinct correlation with lipid content. formula F8 had the slowest drug release, while F6, displayed the most rapid release.

Prior researches suggests that this behavior may be ascribed to variations in the crystalline structure of the lipid in presence of increasing concentration of lipophilic co-surfactant. At low lipid concentration of co-surfactant (F6) the drug release was better than in higher concentration (F7 and F8) since lipid molecules may arrange into a highly structured, densely packed crystalline lattice, yielding a compact, rigid SLN core. This configuration confines the drug more profoundly inside the nanoparticles and diminishes matrix porosity, therefore restricting water infiltration and decelerating drug diffusion. In addition, formula F6 had the faster and higher drug release due to

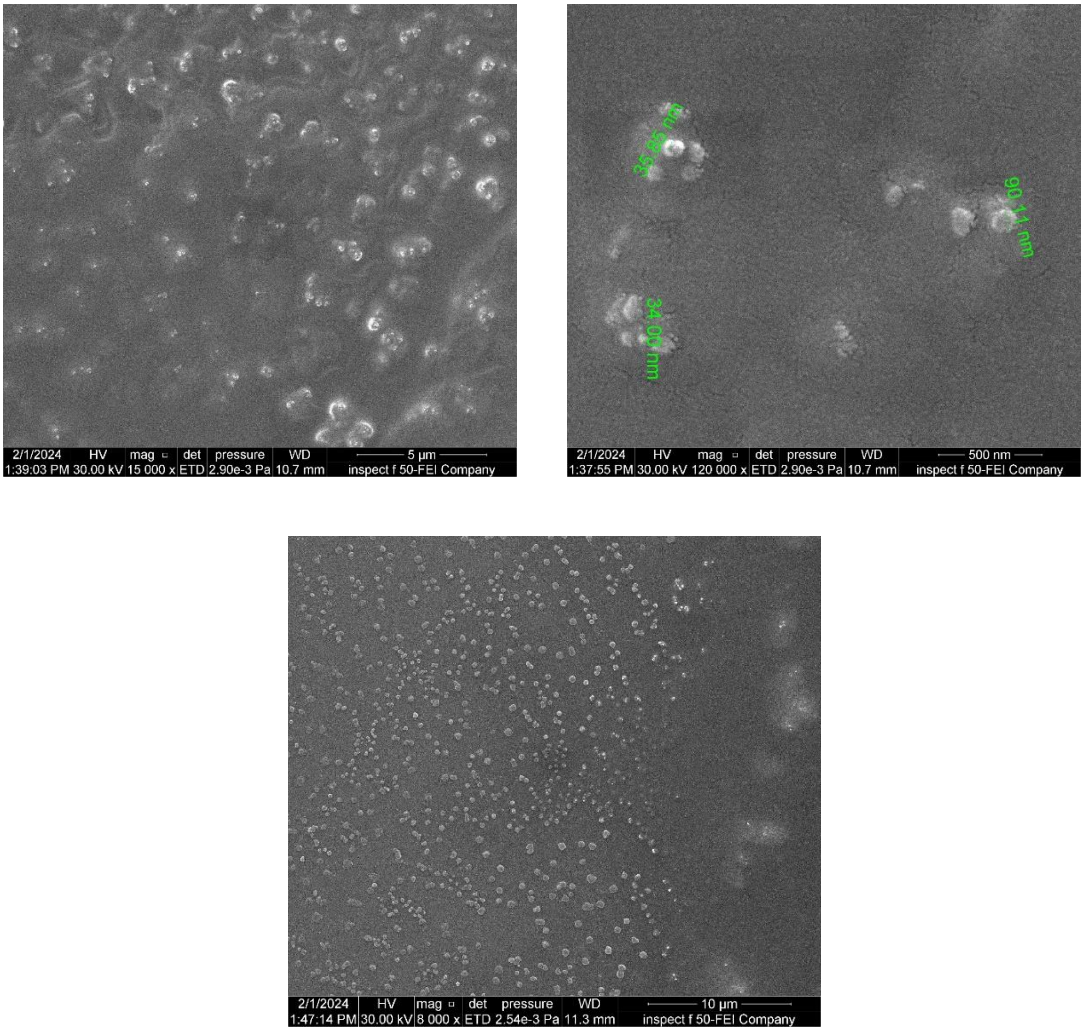

Fig. 2. SEM image of the optimal Vemurafenib SLN.

the smaller particle size of the nanoparticles as the surface area increase then the drug solubility and release [42].

Formula F5 contained only surfactant without co-surfactant gave better release than formulations of higher co-surfactant concentration (F7 and F8) due to the same reason of elevated the concentration may facilitate suboptimal crystallization as a result of lipid chain congestion during solidification. The low and absence of span 20 led to a disordered, defect-laden lipid matrix characterized by increased porosity and enhanced diffusion pathways, enabling the dissolving media to infiltrate more readily and promoting accelerated drug release. Consistent with prior research, it has been shown that the disparities among the formulations were more evident at pH 6–7, when lipid matrix and diffusion-controlled release predominate. At this juncture, the disordered lipid configuration of F6 enabled fast drug diffusion, whereas the highly crystalline matrix of F8 preserved the drug, leading to prolonged release [43-45].

SEM of the optimal SLN formula

SEM is a kind of electron microscopy that use high-energy electrons to systematically examine a sample's surface for its features. This method offers a comprehensive visual examination of the nanostructure of materials, including thin films and powders. Additionally, signals produced by the sample allow the collection of data on the dimensions, form, and surface appearance of Vemurofenib SLN, together with their physical and structural properties. SEM examination was conducted to characterize the size, shape, and surface morphology of the particles and to provide a three-dimensional representation for the best formulation of SLN (F6). The SEM images of the optimal formula exhibited uniformity and a sample characterized by high dispersion and a spherical morphology (as seen in Fig. 2). The SEM data corroborate the successful fabrication of SLN with uniformly distributed nano-sized particles [46].

Evaluation of the gel

The produced gel was semitranslucent, colorless to off-white, it was homogenous with no separation. The gel pH was adjusted to 6.5 to be compatible with skin pH and enhance the sustained release of the drug. The drug release from the gel (Fig. 3) was more sustained in comparison with F6 formula of SLN due to the high viscosity of the gel

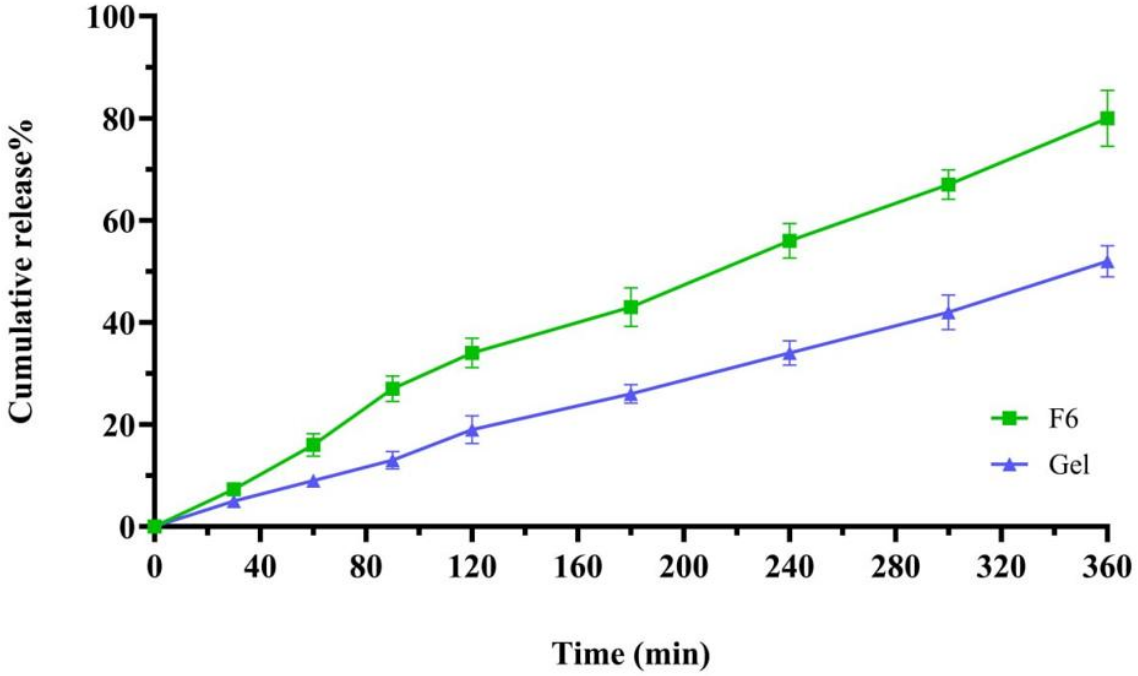

Fig. 3. The in vitro release of the Gel.

that related to the presence of the gelling agent, carbapol [26, 29, 47, 48].

CONCLUSION

The present work effectively demonstrates the development of a new transdermal drug delivery system for Vemurafenib employing SLNs embedded in Carbopol 940 gel matrix. Optimizing the ratio of solid lipid (Compritol 888 ATO) and surfactant system (SLS and Span 20) yielded stable nano-sized particles. The best formulation F6, showed high encapsulation effectiveness of 91.43%, smallest particle size of 103 nm and good colloidal stability. Morphological and structural studies confirmed the highly distributed and homogenous spherical nanostructures that promote enhanced drug delivery channels. The inclusion of these improved SLNs in a topical hydrogel led to a semitranslucent, homogeneous and stable system with a skin friendly pH of 6.5. The gel framework was able to modify the burst release seen in the raw SLN solution into a continuous controlled release profile mediated by the polymeric network of Carbopol. Collectively, this formulation approach offers a clinically feasible alternative to conventional oral administration, maximizing the local therapeutic retention at the site of skin tumor while substantially reducing the systemic exposures and organ toxicities typically associated with conventional vemurafenib regimens.

ACKNOWLEDGMENT

The authors would like to thank University of Kerbala (https://uokerbala.edu.iq/en/), Ahl Al Bayt University (https://www.abu.edu.iq/en), University of AlKafeel (https://en.alkafeel.edu.iq/) and Mustansiriyah University (www.uomustansiriyah.edu.iq), for supporting this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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