ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Simvastatin-Loaded Lipid Emulsion Nanoparticles: Characterizations and Applications

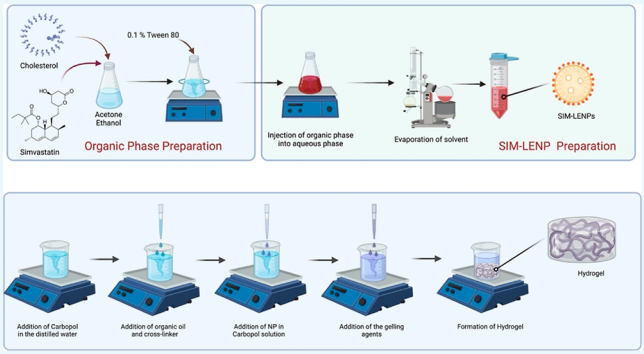
Faiz Ullah, Muhammad Farhan Ali Khan, Nazeer Hussain Khan, Muhammad Fayyaz Rehman,* Syed Sakhawat Shah, Muhammad Mustaqeem, Sami Ullah, Qidi Zhang, and Hongchao Shi*

Cite This: *ACS Omega* 2022, 7, 23643−23652

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Simvastatin (SIM) is a diet drug to treat high lipid levels in the blood. It has the drawback of being metabolized in humans' gastrointestinal tract (GIT) when taken in an oral dosage form. To enhance the role of SIM in treating hyperlipidemias and bypassing its metabolism in GIT, a biodegradable nanocarrier as a SIM-loaded lipid emulsion nanoparticle via the solvent injection method was designed. Cholesterol acts as a lipid core, and Tween 80 was utilized to stabilize the core. The optimized nanoformulation was characterized for its particle diameter, zeta potential, surface morphology, entrapment efficiency, crystallinity, and molecular interaction. Furthermore, the transdermal hydrogel was characterized by physical appearance, rheology, pH, and spreadability. In vitro assays were executed to gauge the potential of LENPs and olive oil for transdermal delivery. The mean particle size and zeta potential of the optimized nanoparticles were 174 nm and −22.5 mV 0.127, respectively. Crystallinity studies and Fourier transform infrared analyses revealed no molecular interactions. Hydrogels showed a sustained release compared to SIM-loaded LENPs that can be proposed as a better delivery system for SIM. We encourage further investigations to explore the effect of reported formulations for transdermal delivery by *in vivo* experiments.



INTRODUCTION

Nanomaterials are being widely explored in therapeutic drug delivery systems (DDSs) to manage the different biomedical pathologies.[1,2] Presently, nanotechnology is the leading research area in medical sciences with the ultimate objective to diagnose and treat health issues with no side effects. Nanomaterials are utilized as biosensors for diagnosis,[3] colorimetric sensing agents,[2] nanocarriers for targeted delivery, and nanomedicines for therapeutic purposes.[3,4] Using nanoparticles as drug carriers in DDSs has revolutionized the field of biomedicine by enhancing the drug solubility, controlled release, and site-specific delivery.[5,6] The nanomedicines and nanoparticle formulations are fine and small; therefore, they remain hidden by the immune system and carry the encapsulated drugs to target tissues.[7,8] Naturally originated with a low toxicity profile, lipid emulsion nanoparticles (LENPs) are considered the safest[9] and most effective carriers than conventional systems.[10,11] Nowadays, LENPs are gaining greater acceptance in the research community because they are biocompatible, biodegradable, stable, non-toxic, carry lipophilic and hydrophilic compounds, and are easy to prepare.[12] The LENP carrier system reduces drug degradation and improves loading capacity.[13,14] Usually, triglycerides, cholesterol, glycerides, steroids, waxes, and fatty acids are used as lipid carriers to develop LENPs.[15,16]

Because of its long safety record since its first use, simvastatin (SIM), along with many other pharmaceutical applications, is known for its anti-hyperlipidemic properties[17,18] associated with the bioavailability and aqueous solubility.[19] For better effects, SIM needs a new dosage system that can enhance its poor solubility and bioavailability. Various DDSs for enhancing the bioavailability of SIM by oral delivery have been developed.[20,21] Going through the literature, it has been shown that LENPs formulating can improve the solubility and dissolution rate of drugs.[22−24] It has also been proved that incorporating LENPs loaded with the drug for a transdermal delivery system will minimize the side effects of drugs while in systematic circulation.[25] Moreover, LENPs are compatible with the skin because of their bio-friendly origin.[26,27] By developing a transdermal delivery system, various side effects of oral

Received: April 11, 2022
Accepted: June 14, 2022
Published: June 29, 2022

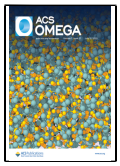


Table 1. Tabulated Presentation of the Effect of Concentrations (Surfactant and Lipid) and Temperatures on the Nanoparticle Size and Stability in Different Emulsions

emulsion	Tween 80 (%)	lipid (mg)	stirring speed (rpm)	temperature (°C)	particle size (nm)	stability
E1	0.1	40	400	60	230 ± 10.7	unstable
E2	0.3	40	400	60	230 ± 21.2	unstable
E3	0.5	40	400	60	161 ± 11.1	stable
E4	0.1	40	400	60	182 ± 13.3	stable
E5	0.1	45	400	60	242 ± 19.9	unstable
E6	0.1	50	400	60	551 ± 31.1	unstable
E7	0.1	40	400	50	177 ± 11.5	unstable
E8	0.1	40	400	55	180 ± 10.3	unstable
E9	0.1	40	400	60	182 ± 17.4	stable

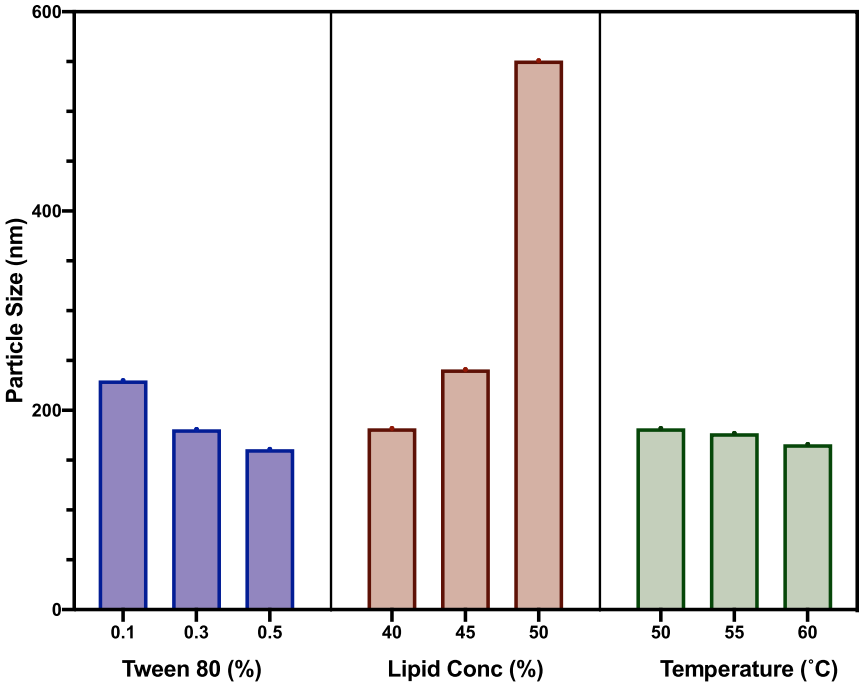


Figure 1. Association between surfactant percentage, lipid concentration, temperature, and size of nanoparticles.

dosage forms can be reduced, and greater patient compliance can be achieved.[28−30]

In the present study, considering the development of an efficient DDS based on encapsulation of SIM into the LENPs will improve the solubility and enhance the bioavailability of SIM, we designed a nanocarrier system as SIM-loaded lipid emulsion nanoparticles (SIM-LENPs). The aim of the current research was to assess SIM-LENP system characteristics and their advantages for incorporation into a hydrogel to gain maximum benefits. Transdermal hydrogels have the potential to improve the therapeutic outcomes via enhancing bioavailability and reducing toxicity associated with oral delivery. Olive oil reduces triglycerides and low-density lipoproteins; hence, synergism between SIM and olive oil is beneficial against hyperlipidemia. Furthermore, we anticipated that further studies on SIM-LENP hydrogel might help overcome the issues of uncontrolled drug release and incomplete absorption in traditional dosage forms like creams, lotions, and ointments.

RESULTS

Concentration−Temperature Effect and Choice of Optimized Emulsion. To optimize the formulation, a trial-and-error method was used, varying the concentrations of different components. Changing the component concentration of nano-formulation, the most stable emulsion with the smallest particle size was selected and further characterized. Our result demonstrated that by changing the concentrations of Tween 80 (0.1, 0.3, and 0.5%) and cholesterol (40, 45, and 50 mg) in six emulsions (E1−E6), particle size and stability of the drug significantly vary. It has been noted that higher concentrations of both Tween 80 and cholesterol produced particles of smaller size, whereas low concentrations yielded bigger size particles (Table 1, Figure 1). Similarly, emulsions (E7, E8, and E9) were used to observe the effect of temperature on the particle size. It was observed that particle size does not significantly change with changing temperature (Figure 1).

Smaller nanoparticle size and the highest stability are major parameters to select the optimized emulsion. Selected optimized emulsion with smaller nanoparticle size and the highest stability was prepared at 55−60 °C temperature and 400 rpm containing 0.1% Tween 80 and 40 mg of cholesterol with 10 mg of the drug.

Characterization of SIM-LENPs. *Particle Size.* Measuring the potential and particle size of selected emulsions (LENPs and SIM-LENPs) revealed that blank nanoparticles displayed a

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

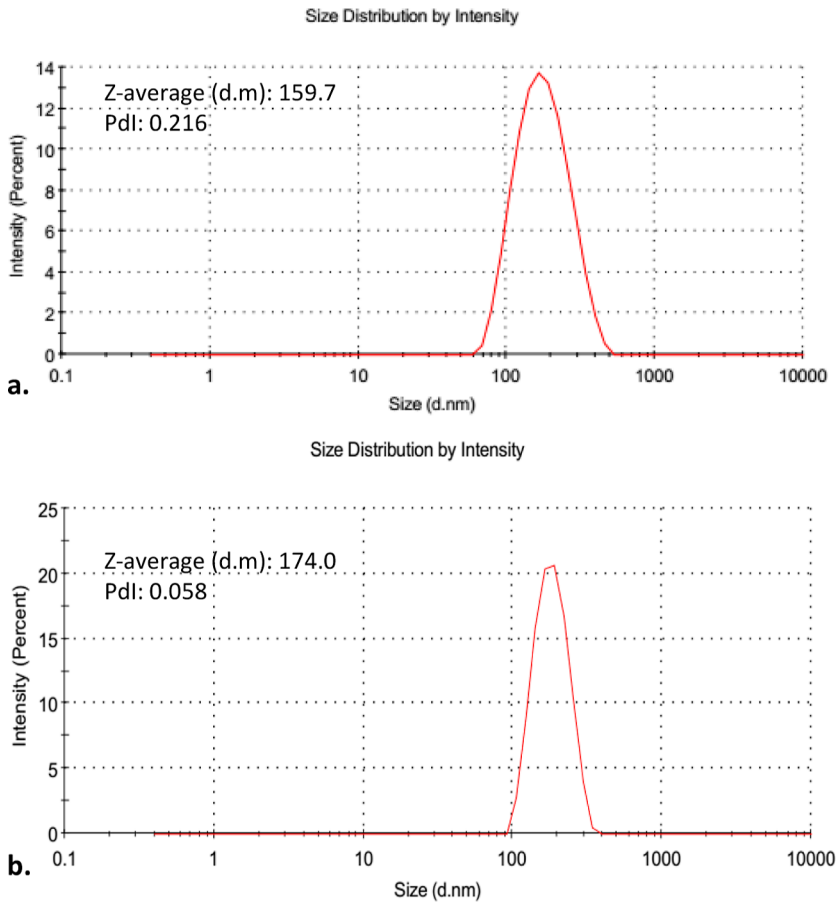


Figure 2. (a) Particle size and PDI of the selected blank nanoparticle. (b) Particle size and PDI of the selected drug-loaded nanoparticle.

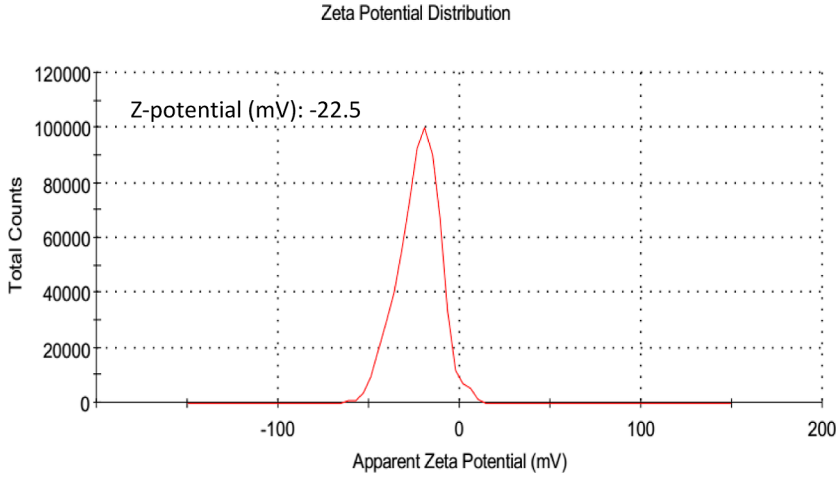


Figure 3. Zeta potential of optimized emulsion.

particle size of 159.7 nm. In comparison, SIM-loaded nanoparticles show a particle size of 174 nm. Figure 2a,b depicts the size and polydispersity index (PDI) of LENs and SIM-LENPs. Table 1 shows the effects of concentration (surfactant and lipid) and temperature on the nanoparticle size and stability in different emulsions.

Zeta Potential (mV). Zeta potential is a very important parameter in the stability of nanoparticles. Therefore, it is compulsory to determine the zeta potential of the final formulation to observe the stability of the colloidal emulsion. High values of zeta potential represent the stability of nanoparticles. High positive and negative values (>+20 and <−20 mV) show electrostatic and steric stability. Because of the negative charge of lipid, a negative potential is displayed in Figure 3, while the drug also has a negative charge. Results explain the average potential of −22.5 mV (Figure 3).

Fourier Transform Infrared Analysis. For the chemical stability of the drug, the Fourier transform infrared (FTIR) spectrophotometer shows corresponding peaks of the OH group in the drug displayed at 3545 cm^{-1} in the SIM spectra. Due to the stretching vibration, the CH group shows peaks at 2914 and 2849 cm^{-1}. Similarly, a characteristic peak at 1732

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

cm^{-1} was also observed because of stretching vibrations of the ester group. Figure 4 shows specific peaks for blank LENPs (B-LENPs) and medication-loaded LENP (D-LENP) spectra.

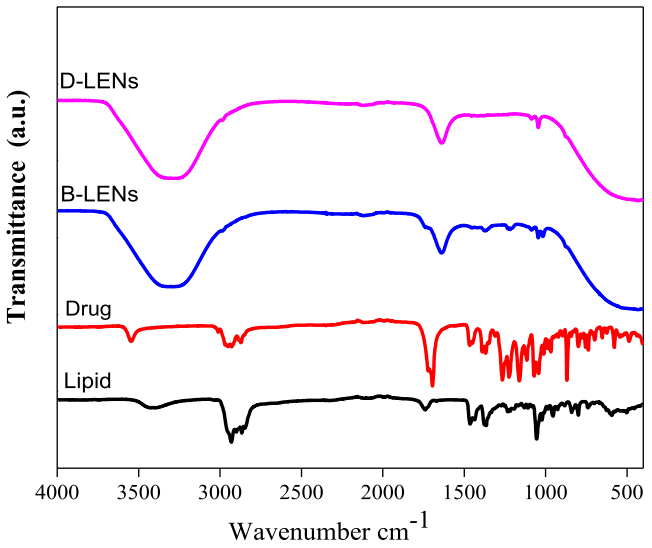


Figure 4. FTIR spectrum for both B-LENPs and medication-loaded LENPs (D-LENPs).

XRD and DSC of SIM-LENPs. To explain the crystal-like nature of the drug, SIM-LENPs were analyzed by X-ray diffraction (Figure 5). It has been observed that in SIM-

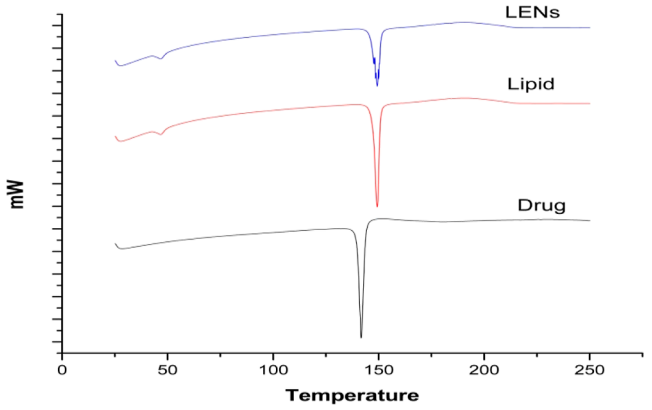


Figure 5. DSC spectrum of LENs, lipid, and drug (SIM).

LENPs, the high-intensity peak of the drug is reduced, and the drug has magnificently integrated into the lipid transporter in the amorphous form.

DSC analysis explains that the drug is less crystalline in the lipid matrix. The intensity of the drug peak and lipid significantly reduced in the SIM-LENP curve at the same temperature range. These results support the XRD spectra and explain the amorphous nature of drugs in lipid nanoparticles and the high solubility of medication. Figure 6 shows DSC spectra of LENPs, lipids, and drug (SIM).

Percentage Yield of SIM-LENPs. Percent yield is a ratio of actual to theoretical yield. It is calculated as the experimental yield divided by the theoretical yield multiplied by 100%. If the actual and theoretical yields are the same, the percent yield is 100%. Following all characterizations, the corresponding

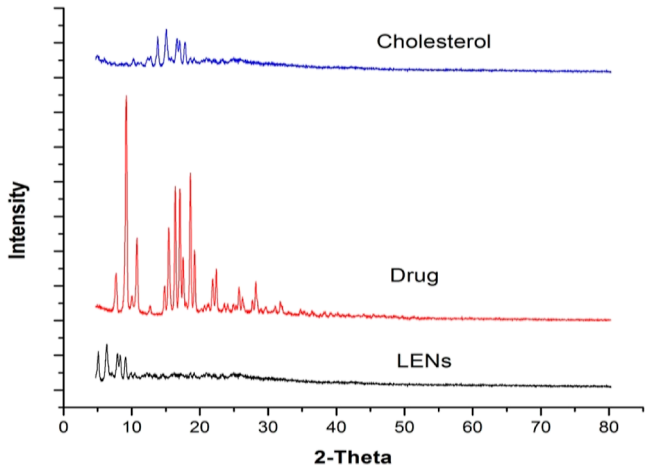


Figure 6. X-ray diffraction spectrum of LENs, lipid, and drug (SIM).

calculation revealed that experiments constructed the percentage yield of SIM-LENPs (78 ± 0.012) (Table 2).

Table 2. Percentage Yield of SIM-Loaded Nanoparticles

weight of lipid and SIM (mg)	weight of dried nanoparticles (mg)	percentage yield	average ± S.D.
50	39	78	78% ± 0.012
50	41	82	
50	37	74	

Evaluation of SIM-LENP Gel. Physical appearance explains that SIM-LENP gel was uniform, clear, and with no grittiness in texture. The final emulsion was slightly acidic, with a pH of 5.7. It is advantageous for transdermal delivery because pH in various skin surface layers remains acidic, favoring the transfer of nanoparticles through the skin. Furthermore, the rheological study of SIM-LENP gel indicates an inverse relationship between viscosity and the shear rate. Figure 7 exhibits the viscosity of SIM-LENP gel at different shear rates. When stress is applied, gel behaves like a liquid, and it changes back to the viscous form when stress is removed. The spreadability of the SIM-LENP gel was 273.2 ± 0.5 mm^2, as shown in Figure 8.

Similarly, swelling index studies of gel reveal that gel having a cross-linker exhibits a low swelling ratio compared to non-cross-linked gel (Figure 9). The physical appearance of the hydrogel did not change in terms of phase separation, color, or grittiness in 6 months, as shown in Table S1. Stability is a critical criterion for determining the efficacy of a product. Because the results of this investigation showed no significant changes, it may be assumed that hydrogels have a tendency to maintain their effectiveness (Table S1).

In the case of drug release studies, it was observed that ∼37% of the drug was released within 3 h in the case of SIM-LENPs, while 80% of the drug was released in the first 20 h (Figure 8). In the case of SIM-LENP gel, the initial burst release seems to be controlled where ∼21% of the drug was released within 3 h, and approximately 64% of the drug was released within 20 h (Figure 10).

DISCUSSION

A simple and more reliable technique "Solvent injection method", can synthesize the nanocarrier. LENPs are created utilizing the solvent injection method, which produces particles with a tiny size (174 nm), a low zeta potential (−22.5 mV),

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

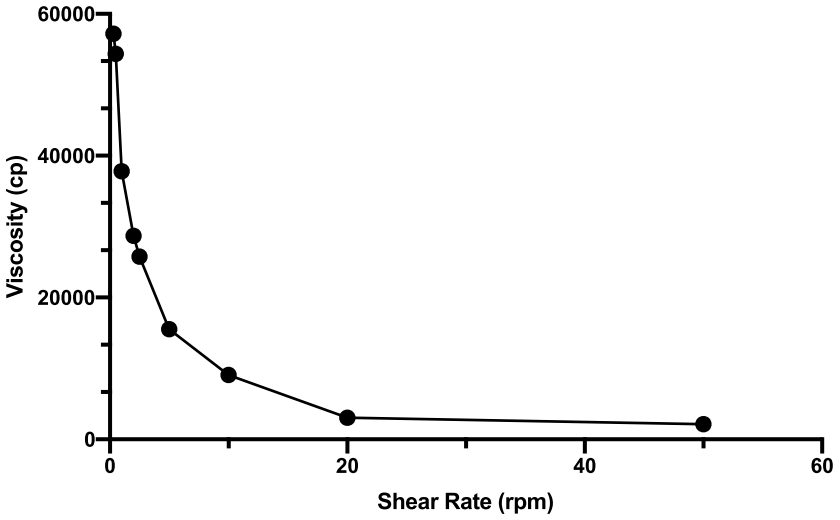


Figure 7. Viscosity of SIM-LENP gel at different shear rates.

Figure 8. Spreadability of SIM-LENP gel.

and a high PDI index, indicating the formulation's durability. The concentration of lipid and the surfactant are two main parameters to observe the size of particles. The particle size increases when we enhance the cholesterol concentration because, at high concentrations, lipid show coalesces, and van der Waal forces increase. It can also be enhanced due to the density difference between the two phases. Particle size decreased by increasing the Tween 80 concentration due to low surface tension between the aqueous and organic phases (Table 1, Figure 1). It may be due to a stabilizer, which inhibits particles' coagulation and provides stability to particles. Enlarged particle size can arise as a result of a density differential between the exterior and interior phases, or as a result of a decreased diffusion rate of solute molecules in the outer phase. It was discovered that raising the quantity of surfactant causes particle size to decrease. It might be because to a decrease in surface tension between the organic and aqueous phases.[31] The value of PDI < 0.1 represents the existence of a mono dispersing system. The system will be thermodynamically or sterically stable if the zeta potential is above ±20 mV. Zeta potential is reduced when surfactants are adsorbed on nanoparticles by shifting the shear plane of particles. Cholesterol has a negative charge, the stabilizer is also ionic, and the system has electrostatic stability. A crucial measure of stability impacting the physical stability of colloidal

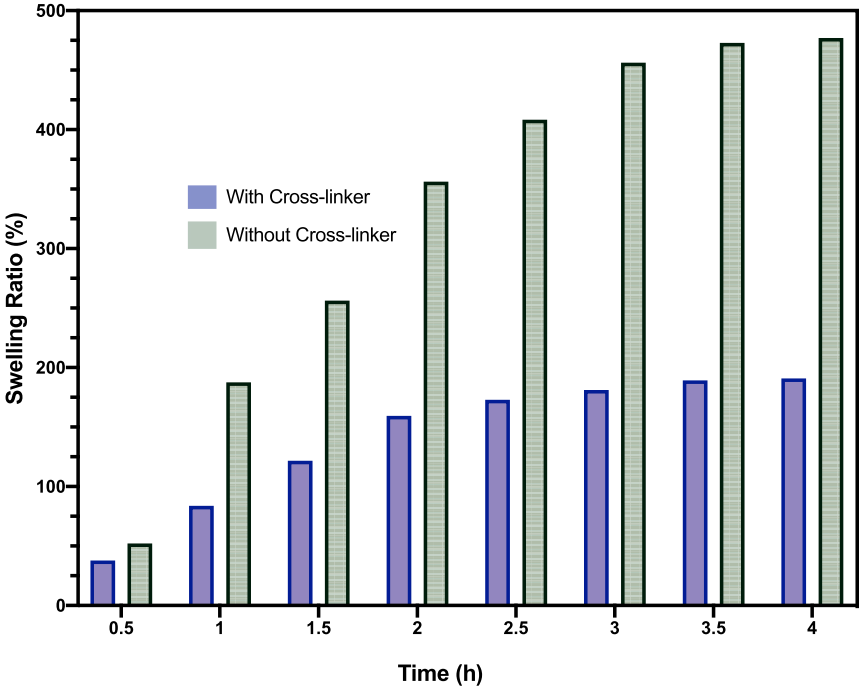


Figure 9. Swelling index of SIM-LENP gel at different time intervals.

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

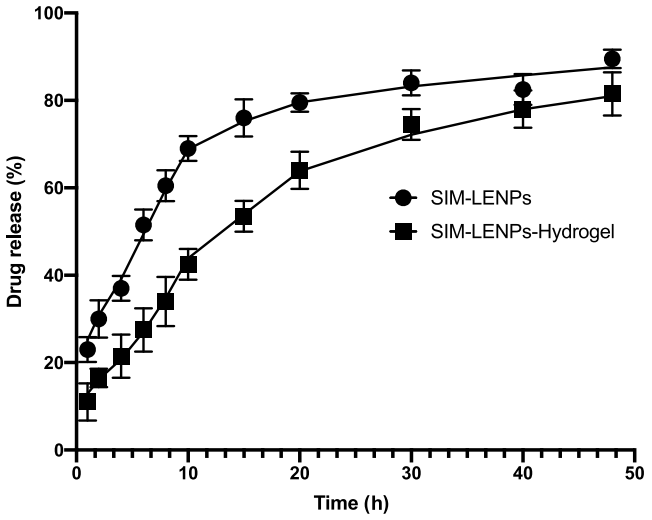


Figure 10. In vitro release profile of SIM.

dispersions is the nano particulate formulation's zeta potential. Higher zeta potential inhibits aggregation by generating electrostatic attraction between similarly charged particles, giving colloidal dispersion stability.

FTIR spectra confirm the deficiency of any electrostatic and chemical interaction in SIM and nanoparticles. Characteristic peaks of drug maintained in the entire LENP. The lack of new peaks exhibits the absence of any new functional group; therefore, no interaction between constituents was observed. Reports of other studies also support the conclusion derived from FTIR analysis.[32] The permeation enhancer may not have been damaging to the skin, according to FTIR spectra. Olive oil-induced intercellular penetration may be the cause of the little disturbance found in spectra. These alterations are slight, and the skin may recover from them because to its elasticity and regeneration abilities. Lack of any new peak or functional group indicate there has been no interaction between the elements. Regular bands may be seen in the FTIR spectra of LENs produced using this method. The present results recommend the formulation as harmless and encourage further studies to use this as a transdermal delivery system.

XRD analysis of drug, cholesterol, and SIM-loaded nanoparticles represents that the drug was in a crystalline, free state, but its crystallinity decreased when encapsulated in nanoparticles. A sharp peek between 10 and 30 in drug XRD spectra represents the crystalline nature of the medication. There is no such peak after encapsulation in a nanoparticle that confirms the decreased crystalline nature of the drug in a carrier. Change in the nature of the drug is due to the adsorption of stabilizers on the surface of SIM-LENPs (Figure 6) within this range. Before and after drug loading, Precirol remained crystallised that seems consistent with past research since the drug's nature shifted from crystalline to amorphous but its lipid nature remained same. Crystallinity may have decreased as a result of surfactant absorption on LEN's surface. The results are consistent with earlier studies showing SIM in an amorphous form inside a solid lipid core.[33]

A hydrogel based on Carbopol may help SIM-LENPs to cross the skin easily. A secondary carrier (hydrogel) is necessary to prevent the burst release of the drug. As shown in Figure 10, SIM-LENP gel showed a controlled initial burst release, where in the first hour, 11% of the drug was released compared to SIM-LENPs, where 23% drug release was observed. Olive oil is expected to enhance the permeation[34] of a DDS, and it also has an anti-hyperlipidemic effect. In the transdermal DDS (TDDS), a skin barrier is an important factor, and the use of olive oil enhances the permeation of drugs through the transdermal route.[35] The permeation enhancer has no toxicity and is non-reactive and biocompatible. The hydrogel was smooth in texture with no grittiness and was uniform and clear. The normal pH of the skin ranges from 4−6, whereas the pH of transdermal hydrogel was 5.7, indicating a slightly acidic nature. It is beneficial for transdermal formulation because pH at the skin surface and within different layers remains acidic, favoring intact delivery of nanoparticles across the skin. Such DDSs might be suitable for transdermal drug delivery.[36,37]

The rheological study of the hydrogel is important to know the retention time of gel on the skin and force of adhesive with the skin. Various shear rates of hydrogels were calculated for rheological studies of the hydrogel. There is an anti-relation between the shear rate and viscosity. During the stress, "shear thinning gels" show such behavior. These gels can be easily applied to the skin by a small force. This behavior was observed during the thixotropic study of hydrogels.[38] The viscosity of the hydrogel and the shear rate are inversely related. By increasing shear rate, hydrogel viscosity will be lowered, and vice versa. The hydrogel's behaviour is comparable to that of shear thinning gels, which, while under stress, act like liquids before changing to viscous form. Shear thinning is the term for this type of stress-related behaviour. Shear thinning is thought to be the result of minute structural changes within the fluid, which cause the fluid's microscale geometries to reorganise to enable shearing, even if the exact source of this phenomenon is not entirely known. Rheological qualities are crucial for determining adhesive capacity and skin retention duration. It is clear from the swelling index results that the hydrogel has a higher value of the swelling index without a cross-linker. The cross-linker swelling index is reduced because gel diffuses and creates ample space for water in the matrix without a cross-linker. The cross-linker also provides strength to gel and controls burst release of the drug. Glutaraldehyde cross-linked effects were studied by Mirzaei et al. for chitosan hydrogel during TDDS.[39]

The spreadability of the hydrogel was also measured after studying all these factors, and analysis shows that it is the easy and more comfortable spreading of the hydrogel on the skin surface. Spreadability and ease of application are crucial formulation properties for consistent medication administration. Additionally, it increases patient adherence. Studies on spreadability attested to the ease of spreading on the skin's surface.[40] These results agreed with former studies as values are in the satisfactory range (Figures 7−9).[41] The carrier of the natural product (lipid) is suitable, non-toxic, and non-reactive. Nanoparticles release drugs slowly and in the controlled way; hence, half-life and stability of the drug can be increased.[42]

CONCLUSIONS

The current study demonstrates the designing of a well characterized, stable formulation of SIM-LENPs loaded hydrogel. The hydrogel with olive oil and NPs, formulated with biodegradable and biocompatible ingredients, is a suitable candidate for transdermal delivery. Furthermore, the uniform particle size distribution and morphology of loaded SIM-LENs define the high encapsulation efficiency, better retention time, increased permeability and sustained drug release. This

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

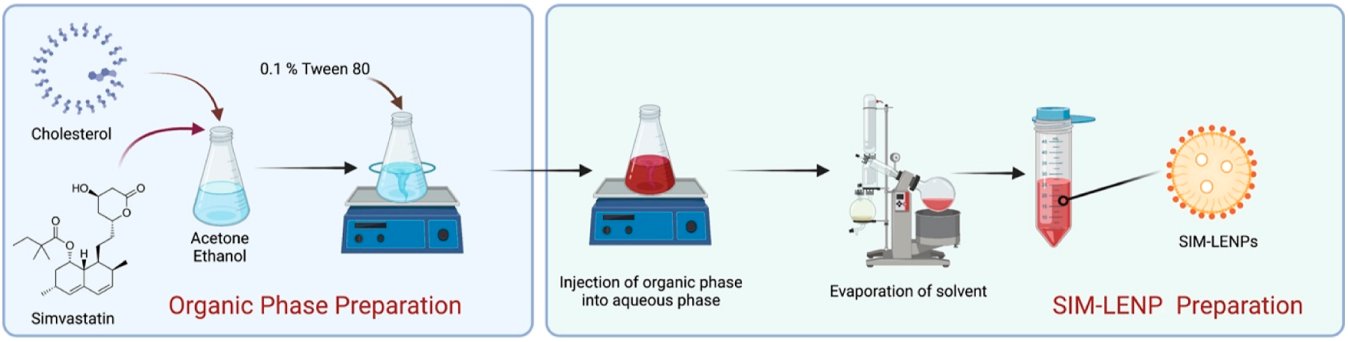


Figure 11. Fabrication of drug (SIM)-loaded LENPs.

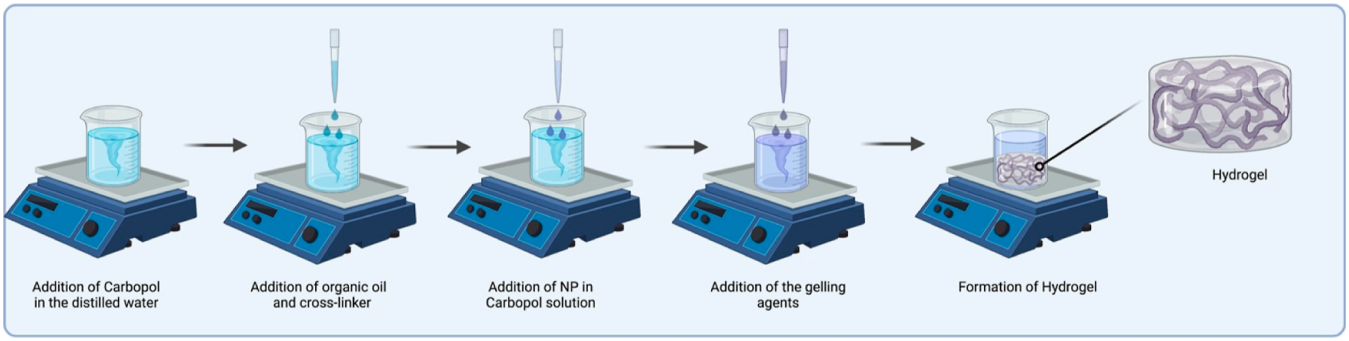


Figure 12. Fabrication of SIM-loaded hydrogels.

composite of nanoparticles in hydrogel form might significantly enhance bioavailability. Given the mentioned advantages, of SIM-LENPs hydrogel could be promising nano carriers to enhance therapeutic potential of drugs suffering from gastrointestinal problems and low bioavailability. Considering the pharmacological and clinical advantages of the formulated hydrogel, we anticipate that findings of our study will stimulate the esteemed reader-researcher community of prestigious target journal for further exploration in the *in vivo* experiments and its future application of SIM-LENPs hydrogel in nanomedicine formulation.

EXPERIMENTAL SECTION

Fabrication of SIM-LENs. To synthesize the SIM-LENPs, the organic phase was prepared by mixing cholesterol with ethanol and acetone (3:1). First, blank nanoparticles (without SIM) were fabricated by injecting 10 mg of 0.1% Tween 80 solution into the organic phase with continuous stirring. To optimize the formulation (SIM-LENs), a trial-and-error method was used, varying the concentrations of different components. To fabricate the SIM-LENs, the same optimized procedure was applied after mixing 10 mg of SIM in the organic phase. The blue tin-colored lipid nanoparticles were collected after drying the organic phase with the help of a rotary evaporator. Figure 11 describes the procedure for preparing LENPs.

Optimization of SIM-LENPs. The trial and error methods were used to optimize SIM-LENPs by changing the concentration of different emulsion components: Tween 80 ranges between 10 and 40 mg, and lipid ranges between 10−50 mg. To determine the particle size and stability of the nanocarrier, 21 trials were run. With better stability, small-sized nanoparticle emulsion was selected as a target-finalized emulsion. Table 1 represents various trials conducted for the optimization of lipid nanoparticles. Small size emulsions with maximum stability were further characterized in terms of temperature, magnetic stirrer speed, and injection rate.

SIM-LENP-Loaded Hydrogels. Carbopol 934 was utilized to prepare the transdermal hydrogel (Figure 10). Briefly, a 1% Carbopol solution was prepared by dissolving it in distilled water with stirring at 300 rpm, followed by SIM-SLN addition to the solution. Glutaraldehyde (0.5%) was added as a cross-linker during stirring. In the end, triethanolamine (0.5%) as a gelling agent was added to neutralize the pH of the medium. The hydrogel having a penetration enhancer was prepared in the same manner by adding olive oil (1 mL) before incorporating triethanolamine hydrogel (Figure 12).

Characterization of SIM-LENPs and Blank. For further evaluation, the most stable and small-sized emulsions with and without drugs were characterized.

Zeta Potential of Lipid Nanoparticles. The size of particles and zeta potential of samples were measured by Zeta Sizer Nano ZS 90. For this purpose, 10 μL of the sample was mixed with 1 mL of deionized water, vortexed for 2 min, and analyzed using a zeta sizer. Each result displayed was measured in triplicate.

FTIR Spectroscopy. To check the chemical stability of the drug in nanoparticles, FTIR spectra of emulsion were obtained using a Bruker spectrophotometer. Spectra were scanned between 500 and 3500 cm^{-1}.

XRD and DSC Analyses. DSC and XRD analyses were performed at room temperature to know the amorphous or crystalline nature of SIM inside the nanocarrier. The absolute intensity was recorded in the range of 2−θ. DSC clearly explains the exothermic or endothermic process when a drug changes its nature in the nanoparticle.

Yield (%) of Nanoparticles. Percentage yield is necessary to prepare large-scale production of the desired compound at

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

the industrial level. To determine yield (%), the total mass of lyophilized nanoparticles was divided by the sum of the total mass of lipid and drug.

$$\% \text{ yield} = \frac{\text{Mass of lyophilized nanoparticles}}{\text{Mass of drug + lipid}} \times 100$$

Physicochemical Evaluation of SIM-Loaded Gels. To study the physicochemical properties of the drug-loaded hydrogel, transparency, softness, homogeneity, pH, spreadability, and swelling index were observed and analyzed.

For the spreadability of the SIM-loaded gel, the glass slide-weight method was utilized[43] with a spreading equation to measure the diameter of the drug spread on pressing with a slide.

$$A = D^2 \times \frac{\pi}{4}$$

A = spreading area; D = gel diameter.

Similarly, a gravimetric method was utilized to measure the swelling index of the hydrogel.[44] To achieve this target, gel after lyophilizing was placed in a buffer solution of pH 5.5. In the end, the weight of swollen hydrogel was checked in different time periods, and swelling % was measured.

$$\text{Swelling } \% = \frac{M2 - M1}{M1} \times 100$$

where $M1$ = initial mass of gel and $M2$ = mass after placing in buffer solution.

In vitro drug release profile for SIM was studied for 48 h. SIM-LENPs and prepared SIM-LENP hydrogels were individually placed in a dialysis membrane (14 kDa cutoff size). The release was studied in a shaking water bath where 1 mL of the sample was analyzed at a wavelength of 238 nm at different time intervals using a spectrophotometer.

Stability tests for hydrogels were carried out in accordance with ICH recommendations.[45] At a temperature of 25 °C and relative humidity of 60%, accelerated experiments were conducted for 6 months (1, 3, and 6 months). Changes in pH and physical appearance were used to test the hydrogel.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02242.

Stability studies of hydrogels in terms of pH and physical appearance (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Muhammad Fayyaz Rehman − *Institute of Chemistry, University of Sargodha, Sargodha 40100, Pakistan;* orcid.org/0000-0003-2901-7212; Email: fayyaz9@gmail.com

Hongchao Shi − *Department of Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong, University School of Medicine, Shanghai 200025, China;* Email: hongchaoshigh@yeah.net

Authors

Faiz Ullah − *Department of Chemistry, Quaid-i-Azam University, Islamabad 15320, Pakistan*

Muhammad Farhan Ali Khan − *Department of Pharmacy, Quaid-i-Azam University, Islamabad 15320, Pakistan*

Nazeer Hussain Khan − *Henan International Joint Laboratory for Nuclear Protein Regulation, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China; School of Life Sciences, Henan University, Kaifeng 475004, China*

Syed Sakhawat Shah − *Department of Chemistry, Quaid-i-Azam University, Islamabad 15320, Pakistan*

Muhammad Mustaqeem − *Department of Chemistry, Thal University, Bhakkar 30000, Pakistan*

Sami Ullah − *Department of Zoology, Government College University, Faisalabad 54000, Pakistan*

Qidi Zhang − *Department of Gastroenterology, Shanghai General Hospital, Shanghai Jiao Tong, University School of Medicine, Shanghai 200025, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c02242

Funding

This work was supported by grants from the Higher Education Commission of Pakistan and Quaid-i-Azam University (QAU), Islamabad, Pakistan.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance and motivation energy of Dr. Muhammad Sarfaraz to accomplish this manuscript.

■ REFERENCES

(1) Kanwal, F.; Ma, M.; Rehman, M. F. U.; Khan, F.-U.; Elizur, S. E.; Batool, A. I.; Wang, C. C.; Tabassum, T.; Lu, C.; Wang, Y. Aspirin Repurposing in Folate-Decorated Nanoparticles: Another Way to Target Breast Cancer. *Front. Mol. Biosci.* **2022**, *8*, 788279.

(2) Irfan, M. I.; Amjad, F.; Abbas, A.; Rehman, M. F. u.; Kanwal, F.; Saeed, M.; Ullah, S.; Lu, C. Novel Carboxylic Acid-Capped Silver Nanoparticles as Antimicrobial and Colorimetric Sensing Agents. *Molecules* **2022**, *27*, 3363.

(3) Nagraik, R.; Sharma, A.; Kumar, D.; Mukherjee, S.; Sen, F.; Kumar, A. P. Amalgamation of biosensors and nanotechnology in disease diagnosis: Mini-review. *Sens. Int.* **2021**, *2*, 100089.

(4) Patra, J. K.; Das, G.; Fraceto, L. F.; Campos, E. V. R.; Rodriguez-Torres, M. d. P.; Acosta-Torres, L. S.; Diaz-Torres, L. A.; Grillo, R.; Swamy, M. K.; Sharma, S.; et al. Nano based drug delivery systems: recent developments and future prospects. *J. Nanobiotechnol.* **2018**, *16*, 71.

(5) Zhou, S.; Shang, Q.; Wang, N.; Li, Q.; Song, A.; Luan, Y. Rational design of a minimalist nanoplatform to maximize immunotherapeutic efficacy: Four birds with one stone. *J. Controlled Release* **2020**, *328*, 617−630.

(6) Zhang, M.; Qin, X.; Xu, W.; Wang, Y.; Song, Y.; Garg, S.; Luan, Y. Engineering of a dual-modal phototherapeutic nanoplatform for single NIR laser-triggered tumor therapy. *J. Colloid Interface Sci.* **2021**, *594*, 493−501.

(7) Silva, E.; Barreiros, L.; Segundo, M. A.; Costa Lima, S. A.; Reis, S. Cellular interactions of a lipid-based nanocarrier model with human keratinocytes: Unravelling transport mechanisms. *Acta Biomater.* **2017**, *53*, 439−449.

(8) Zeb, A.; Arif, S. T.; Malik, M.; Shah, F. A.; Din, F. U.; Qureshi, O. S.; Lee, E.-S.; Lee, G.-Y.; Kim, J.-K. Potential of nanoparticulate carriers for improved drug delivery via skin. *J. Pharm. Invest.* **2019**, *49*, 485−517.

(9) Huang, Z.-r.; Hua, S.-c.; Yang, Y.-l.; Fang, J.-y. Development and evaluation of lipid nanoparticles for camptothecin delivery: a comparison of solid lipid nanoparticles, nanostructured lipid carriers, and lipid emulsion. *Acta Pharmacol. Sin.* **2008**, *29*, 1094−1102.
(10) Escobar-Chávez, J. J.; Díaz-Torres, R.; Rodríguez-Cruz, I. M.; Domínguez-Delgado, C. L.; Morales, R. S.; Ángeles-Anguiano, E.; Melgoza-Contreras, L. M. Nanocarriers for transdermal drug delivery. *Res. Rep. Transdermal Drug Delivery* **2012**, *1*, 3−17.
(11) Makled, S.; Nafee, N.; Boraie, N. Nebulized solid lipid nanoparticles for the potential treatment of pulmonary hypertension via targeted delivery of phosphodiesterase-5-inhibitor. *Int. J. Pharm.* **2017**, *517*, 312−321.
(12) Yucel, U.; Elias, R. J.; Coupland, J. N. Emulsions, Nanoemulsions and Solid Lipid Nanoparticles as Delivery Systems in Foods. In *Food and Industrial Bioproducts and Bioprocessing*; Wiley, 2012; pp 167−184.
(13) Sawant, K.; Dodiya, S. Recent advances and patents on solid lipid nanoparticles. *Recent Pat. Drug Delivery Formulation* **2008**, *2*, 120−135.
(14) Palmer, B.; DeLouise, L. Nanoparticle-enabled transdermal drug delivery systems for enhanced dose control and tissue targeting. *Molecules* **2016**, *21*, 1719.
(15) Silva, A. C.; González-Mira, E.; García, M. L.; Egea, M. A.; Fonseca, J.; Silva, R.; Santos, D.; Souto, E. B.; Ferreira, D. Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. *Colloids Surf., B* **2011**, *86*, 158−165.
(16) Kurakula, M.; Ahmed, O. A. A.; Fahmy, U. A.; Ahmed, T. A. Solid lipid nanoparticles for transdermal delivery of avanafil: optimization, formulation, in-vitro and ex-vivo studies. *J. Liposome Res.* **2016**, *26*, 288−296.
(17) Pedersen, T. R.; Tobert, J. A. Simvastatin: a review. *Expert Opin. Pharmacother.* **2004**, *5*, 2583−2596.
(18) Tong, X.-K.; Trigiani, L. J.; Hamel, E. High cholesterol triggers white matter alterations and cognitive deficits in a mouse model of cerebrovascular disease: benefits of simvastatin. *Cell Death Discovery* **2019**, *10*, 89.
(19) Korani, S.; Bahrami, S.; Korani, M.; Banach, M.; Johnston, T. P.; Sahebkar, A. Parenteral systems for statin delivery: a review. *Lipids Health Dis.* **2019**, *18*, 193.
(20) Meola, T. R.; Schultz, H. B.; Peressin, K. F.; Prestidge, C. A. Enhancing the oral bioavailability of simvastatin with silica-lipid hybrid particles: The effect of supersaturation and silica geometry. *Eur. J. Pharm. Sci.* **2020**, *150*, 105357.
(21) Kong, R.; Zhu, X.; Meteleva, E. S.; Chistyachenko, Y. S.; Suntsova, L. P.; Polyakov, N. E.; Khvostov, M. V.; Baev, D. S.; Tolstikova, T. G.; Yu, J.; et al. Enhanced solubility and bioavailability of simvastatin by mechanochemically obtained complexes. *Int. J. Pharm.* **2017**, *534*, 108−118.
(22) Vyas, A.; Saraf, S.; Saraf, S. Encapsulation of cyclodextrin complexed simvastatin in chitosan nanocarriers: A novel technique for oral delivery. *J. Inclusion Phenom. Macrocyclic Chem.* **2010**, *66*, 251−259.
(23) Savjani, K. T.; Gajjar, A. K.; Savjani, J. K. Drug Solubility: Importance and Enhancement Techniques. *ISRN Pharm.* **2012**, *2012*, 195727.
(24) Thangamani, S.; Mohammad, H.; Abushahba, M. F.; Hamed, M. I.; Sobreira, T. J.; Hedrick, V. E.; Paul, L. N.; Seleem, M. N. Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. *Sci. Rep.* **2015**, *5*, 16407.
(25) Jahangirian, H.; Ghasemian lemraski, E.; Webster, T. J.; Rafiee-Moghaddam, R.; Abdollahi, Y. A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. *Int. J. Nanomed.* **2017**, *12*, 2957.
(26) Vitorino, C.; Almeida, A.; Sousa, J.; Lamarche, I.; Gobin, P.; Marchand, S.; Couet, W.; Olivier, J.-C.; Pais, A. Passive and active strategies for transdermal delivery using co-encapsulating nanostructured lipid carriers: in vitro vs. in vivo studies. *Eur. J. Pharm. Biopharm.* **2014**, *86*, 133−144.
(27) Kakadia, P.; Conway, B. Lipid nanoparticles for dermal drug delivery. *Curr. Pharm. Des.* **2015**, *21*, 2823−2829.
(28) Fernández-Colino, A.; Bermudez, J. M.; Arias, F.; Quinteros, D.; Gonzo, E. Development of a mechanism and an accurate and simple mathematical model for the description of drug release: application to a relevant example of acetazolamide-controlled release from a bio-inspired elastin-based hydrogel. *Mater. Sci. Eng., C* **2016**, *61*, 286−292.
(29) Azarmi, S.; Roa, W.; Löbenberg, R. Current perspectives in dissolution testing of conventional and novel dosage forms. *Int. J. Pharm.* **2007**, *328*, 12−21.
(30) Lau, E. T. L.; Steadman, K. J.; Cichero, J. A. Y.; Nissen, L. M. Dosage form modification and oral drug delivery in older people. *Adv. Drug Delivery Rev.* **2018**, *135*, 75−84.
(31) Shah, M.; Pathak, K. Development and statistical optimization of solid lipid nanoparticles of simvastatin by using 2 3 full-factorial design. *AAPS PharmSciTech* **2010**, *11*, 489−496.
(32) Jiang, T.; Han, N.; Zhao, B.; Xie, Y.; Wang, S. Enhanced dissolution rate and oral bioavailability of simvastatin nanocrystal prepared by sonoprecipitation. *Drug Dev. Ind. Pharm.* **2012**, *38*, 1230−1239.
(33) Harisa, G. I.; Alomrani, A. H.; Badran, M. M. Simvastatin-loaded nanostructured lipid carriers attenuate the atherogenic risk of erythrocytes in hyperlipidemic rats. *Eur. J. Pharm. Sci.* **2017**, *96*, 62−71.
(34) Hussain, A.; Khan, G. M.; Jan, S. U.; Shah, S. U.; Shah, K.; Akhlaq, M.; Rahim, N.; Nawaz, A.; Wahab, A. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer. *Pak. J. Pharm. Sci.* **2012**, *25*, 365.
(35) Hussain, A.; Khan, G. M.; Jan, S. U.; Shah, S. U.; Shah, K. U.; Akhlaq, M.; Rahim, N. A.; Nawaz, A.; Wahab, A. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer. *Pak. J. Pharm. Sci.* **2012**, *25*, 365−369.
(36) Ali, S.; Yosipovitch, G. Skin pH: from basic science to basic skin care. *Acta Derm.-Venereol.* **2013**, *93*, 261−267.
(37) Lee, E.-A.; Balakrishnan, P.; Song, C.-K.; Choi, J.-H.; Noh, G.-Y.; Park, C.-G.; Choi, A.-J.; Chung, S.-J.; Shim, C.-K.; Kim, D.-D. Microemulsion-based hydrogel formulation of itraconazole for topical delivery. *J. Pharm. Invest.* **2010**, *40*, 305−311.
(38) Li, X.; Yang, Q.; Zhao, Y.; Long, S.; Zheng, J. Dual physically crosslinked double network hydrogels with high toughness and self-healing properties. *Soft Matter* **2017**, *13*, 911−920.
(39) Mirzaei, B. E.; Ramazani, A.; Shafiee, M.; Danaei, M. Studies on Glutaraldehyde Crosslinked Chitosan Hydrogel Properties for Drug Delivery Systems. *Int. J. Polym. Mater. Polym. Biomater.* **2013**, *62*, 605−611.
(40) Zagórska-Dziok, M.; Sobczak, M. Hydrogel-Based Active Substance Release Systems for Cosmetology and Dermatology Application: A Review. *Pharmaceutics* **2020**, *12*, 396.
(41) Gangurde, A. B.; Amin, P. D. Microencapsulation by spray drying of vitamin A palmitate from oil to powder and its application in topical delivery system. *J. Encapsulation Adsorpt. Sci.* **2017**, *7*, 10.
(42) Fernández-Colino, A.; Bermudez, J. M.; Arias, F. J.; Quinteros, D.; Gonzo, E. Development of a mechanism and an accurate and simple mathematical model for the description of drug release: Application to a relevant example of acetazolamide-controlled release from a bio-inspired elastin-based hydrogel. *Mater. Sci. Eng., C* **2016**, *61*, 286−292.
(43) Dantas, M. G. B.; Reis, S. A. G. B.; Damasceno, C. M. D.; Rolim, L. A.; Rolim-Neto, P. J.; Carvalho, F. O.; Quintans-Junior, L. J.; Almeida, J. R. G. d. S. Development and Evaluation of Stability of a Gel Formulation Containing the Monoterpene Borneol. *Sci. World J.* **2016**, *2016*, 7394685.
(44) Gupta, N. V.; Shivakumar, H. G. Investigation of Swelling Behavior and Mechanical Properties of a pH-Sensitive Superporous Hydrogel Composite. *Iran. J. Pharm. Sci.* **2012**, *11*, 481−493.
(45) ICH Harmonised Tripartite Guideline. Stability testing of new drug substances and products. Q1A (R2). *International Conference on*

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003; Vol. 4, pp 1−24.

https://doi.org/10.1021/acsomega.2c02242
ACS Omega 2022, 7, 23643−23652