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Research Article

Application of Nanoprecipitation Technique to Develop Poloxamer-407 Facilitated Solid Lipid Nanoparticles for the Controlled Delivery of Tacrolimus

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Currently, the solid lipid nanoparticles (SLNs) are utilized as a novel approach for the controlled drug delivery system (CDDS). Tacrolimus (TCM), a lipophilic drug, can easily be encapsulated in the hydrophobic core of these SLNs using nanoprecipitation technique. The current aim was to develop the controlled release Poloxamer (PLX) facilitated TCM loaded SLNs (PLX/TCM-SLNs), followed by their physicochemical evaluations, including chemical compatibility, particle size, surface charge, surface morphology, nature of SLNs, loading efficiency (LE), entrapment efficiency (EE), *in vitro* drug release studies, release kinetic modeling, and statistical evaluation. Here we also evaluate physicochemical properties of TCM and investigate solubility profile for improvement and dissolution rate of PLX/TCM-SLNs. PLX was used in the process as a polymer due to its low toxicity and weak immunogenic properties. The prepared formulation was characterized by scanning electron microscopy (SEM) images, and Fourier transform infrared spectroscopy (FTIR) has confirmed the compatibility of the selected ingredients, whereas particle size analysis showed that prepared PLX/TCM-SLNs were of nanosized (120.6 ± 9 nm) having zeta potential of −21.3 Mv. On the other hand, SEM had revealed the smooth and uniform surface of the particle, while X-ray diffraction (XRD) confirmed the uniform surface as crystalline structure of TCM in PLX/TCM-SLNs masked. A satisfactory level of EE ($94.5 \pm 2.74\%$) has also been noticed. Furthermore, *in vitro* drug release studies have explored the controlled release of drug during 8 hours, following zero order release kinetics and diffusion type of release mechanism. Outcomes of the studies have advocated the successful preparation of SLNs, as controlled release PLX/TCM-SLNs have been prepared efficiently.

1. Introduction

Poloxamer (PLX), also known by the tradename Pluronic, Supronic introduced in 1950, is an amphiphilic non-ionic surfactant of the triblock-copolymer family of PLXs. The derivatives of PLX are a family of copolymers, which are characterized by different molecular weights of building blocks and the ratio between polypropylene oxide (PPO) and polyethylene oxide (PEO) units. They are generally recognized as safe excipients and are widely used in the pharmaceutical industry. It is approved by U.S. Food and Drug Administration (FDA) for many pharmaceutical applications. It has a molecular weight of about 12.6 kDa. Owing to its low toxicity and less immunogenic properties, it is widely used as an excipient in various pharmaceutical applications [1]. Chemically PLX is an α-hydro-ω-hydroxypoly(oxyethylene)$_a$ poly(oxypropylene)$_b$ poly(oxyethylene)$_a$ block copolymer comprised of two hydrophilic chains of PEO chains, which lies alongside of one hydrophobic PPO chain having a chemical formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. The hydrophobicity of PPO at temperatures exceeding the cloud point (>15°C) and the high hydrophilicity of PEO in temperatures between 0 and 100°C clarify the point that these block copolymers show amphiphilic features accompanied by surface-active properties [2, 3].

PLX aqueous solutions usually have thermos-reversible property having sol–gel transition temperature, which is broadly used in the thermogelling system. It is available in the form of a solution below the temperature, which leads to the interaction of the copolymer segment resulting in gelation. With the rise in the temperature, PLX molecules aggregate into micelles. PLX can be used as an emulsifier, stabilizer, or solubilizing agent via incorporating in various drug delivery systems. They are non-toxic and non-irritant and hence can be used as a wetting agent in many ointments, suppository bases, and gels [4]. The utilization of amphiphilic block of copolymers (ABCs) in pharmaceutical sciences to form polymeric micelles has a long history and a fast development. The chemical flexibility of the ABCs makes feasible the creation of an almost infinite number of complex structures, but, additionally, gives the opportunity to refine and improve the physicochemical properties of these systems in order to incorporate a drug or a DNA/RNA molecule, considering the pathophysiology of the disease [5, 6]. Progressively, most of the researchers and scientists in the field of medical sciences have been working in the quest for new medications that are more secure, safe, less invasive, quicker, and with a large level of efficacy by using lower doses; however, the conveyance of highly effective therapeutic agents to target cell remains a trouble and challenge for researchers and scientists. It emerges as a better option to surpass this issue, being called as "smart" polymers because of their stimuli-sensitive properties [7, 8]. Among different PLXs, PLX-407 has been used most frequently due to its least toxicity and various other properties. It can be used in different concentrations up to 20% (w/w) with respect to the lipid system for the formation of liquid crystalline nanoparticles. The emulsification of the lipid phase in water leads to the formation of nanoparticles. These nanoparticles, not only solubilize lipophilic, but also hydrophilic and amphiphilic drug molecules, can provide controlled release of drug molecules entrapped in the nanoparticles.

TCM is a macrolide immunosuppressant (FK506) discovered in 1984, isolated from the fungus *Streptomyces tsukubaensis,* which has powerful and selective anti-T-lymphocyte activity. It is a 23-member macrolide lactone with a molecular weight of 803.5 g/mole and is effective in the prophylaxis of organ rejection after the transplantation of liver, heart, kidney, and small bowel transplantation, as well as in the therapeutic efficacy of different immune–inflammatory conditions, such as atopic dermatitis and psoriasis [9]. It has a mechanism of action similar to that of cyclosporine. It is a neutral and hydrophobic compound, possessing low water solubility and high degradation, initiating a problem in developing it as a liquid preparation [10, 11]. It also has a narrow therapeutic index, and hence important to inhibit the possible poisonous effects of the drug, when extended release dosage form is administered [12]. It is a biopharmaceutical classification system (BCS) class II drug, with low solubility (0.012 mg/mL) and high permeability. TCR has the low solubility in water and showed relatively low bioavailability of around 20% [13]. There is always a need for a new delivery system that allows the greater penetration of the lipophilic drugs like Tacrolimus (TCM) into the target sites in the body. Many delivery systems like polymer nanoparticles, polymeric micelle nanocarriers, solid lipid nanoparticles (SLNs), or nanosized lipid carriers are investigated [14, 15]. Currently, many delivery systems for TCM such as polymeric micelle nanocarriers [16], SLNs [17], and nanosized lipid carriers [18] are actively investigated. However, no reference products have yet been formulated to overcome the drawback such as low solubility and strong lipophilicity [14].

SLNs were developed in 1990s as an alternative drug delivery system to liposomes. They are synthesized by replacing liquid lipid (oil) of an oil in water emulsion (o/w) with a solid lipid in which the lipid particle matrix remains solid at room temperatures as well as body temperatures [19]. The mean particle size of SLNs lies within the submicron range, from approximately 10 to 100 nm. SLNs offer many advantages including target drug delivery, which provides an opportunity for improved bioavailability of poorly water-soluble drugs or molecules [20].

The current studies were designed with the aim for developed and characterized PLX/TCM-SLNs, by employing commonly used techniques, i.e., nanoprecipitation. Prepared particles were subjected to size analysis and surface charge, as well as drug release and release kinetics.

2. Materials and Methods

2.1. Materials. TCM was a gift from CCL Pharmaceuticals Lahore, Pakistan. Stearic acid, Tween 80, and PLX407 were purchased from Merck, Darmstadt, Germany. Potassium chloride (KCl), dihydrogen potassium phosphate (KH_2PO_4), and chloroform were purchased from Sigma-Aldrich Chemie GmbH—Schnelldorf, Germany, from commercial source.

Table 1: Composition for the fabrication of PLX/TCM-SLNs.

Formulations	TCM	PLX	Stearic acid
F1	0.1	1	1
F2	0.1	2	1
F3	0.1	2	2
F4	0.1	1	2

Quantities and volume of TCM (0.1 gm), tween 80 (0.1 ml), chloroform (50 ml), and distilled water (100 ml) were kept constant, respectively.

2.2. Method for Fabrication of PLX Facilitated TCM Loaded SLNs. PLX/TCM-SLNs were fabricated by employing nanoprecipitation, using distilled water and chloroform as aqueous and organic vehicle. Two separate phases, i.e., aqueous and organic, were prepared separately. Organic phase was prepared by dissolving stearic acid (50 mg) followed by TCM (100 mg) in chloroform using sonicator at 37°C, till the formation of uniform solution, while for the preparation of aqueous phase, PLX and T80 were added one by one in the distilled water using same process, employed for organic phase preparation. After that, aqueous phase was subjected to stirring using hot plate magnetic stirrer, and afterward, organic phase has been poured dropwise in it with the help of syringe. Nanoprecipitation happened by a rapid interaction between particles when the polymer solution is added to the non-solvent. This results in the immediate entrapment of the drug. The resultant mixture was centrifuged in a centrifugation machine (Centurion Scientific Centrifuges Model: K241R, Daihan Labtech, Korea) for 30 minutes at 14,000 rpm. The supernatant liquid was removed, and the residue was lyophilized at −50°C and 0.013 mBar pressure using Vaco 2 Zirbus technology lyophilizer, England [15]. Lyophilized mass was stored in desiccator for further use. Initially, during pilot studies, four formulations were formulated (Table 1) and evaluated, but due to suitable findings, F2 was further processed for evaluations (Table 2).

2.3. Characterization of PLX/TCM-SLNs. All the prepared SLNs were processed further to evaluate their physicochemical properties for confirmation in terms of suitability and utility.

2.3.1. Particle Size, Zeta Potential, and Polydispersity Index. The particle size, zeta potential, and polydispersity index were detected by using a zeta-size analyzer (Zetasizer Nano ZS—Malvern Panalytical). Measurements were accomplished at an angle of 90°. A small amount of prepared formulation was added to the cuvette, and the particle size was measured.

2.3.2. Percent Entrapment Efficiency. Percent entrapment efficiency (%EE) is essential because it influences the release characteristics of the drug molecule. For calculating the %EE, the supernatant was taken from the mixture after centrifugation and added to the quartz cell, which was thoroughly washed with methanol. Quantification was done using UV–visible spectrophotometer (UV spectrophotometer UV-1800 Japan 240 V) at the wavelength of 213 nm

Table 2: Composition of selected formulation for the fabrication of PLX/TCM-SLNs.

Ingredients	Organic phase	Aqueous phase
TCM (gm)	0.1	—
PLX (gm)	—	2.0
Chloroform (ml)	50	—
Tween 80 (ml)	—	0.1
Stearic acid (gm)	1.0	—
Distilled water (ml)	—	100

[21]. Finally, the %EE was determined by using the mathematical expression:

$$\%\text{EE} = \left(\begin{array}{l} \text{Total amount of drug} \\ -\ \text{Free drug} \div \text{Total amount of drug} \end{array} \right) \times 100. \quad (1)$$

2.3.3. Morphological Study of PLX/TCM-SLNs. The surface morphology of PLX/TCM-SLNs has been studied using a scanning electron microscopy (SEM; JSM5910-JEOL, Japan). In SEM, a strong beam focused onto a solid sample scans point by point, which results in an image. SEM study also provides individual particle analysis unlike that of dynamic light scattering. Before the analysis, the samples were fixed on a sample holder followed by coating with metal. The images were then taken using SEM at an excitation voltage [22].

2.3.4. Chemical Compatibility Studies. The Fourier transform infrared spectroscopy (FTIR; FTIR-7600 FTIR Spectrometer) has been used to study the chemical compatibilities of the ingredients. This technique is based on the measurement of the absorption of electromagnetic radiation with wavelengths within the mid-infrared region (4000–400 cm^{-1}) [23]. FTIR analysis can provide further confirmation of the stability and chemical compatibilities of the PLX/TCM-SLNs. IR scan of individual component as well of prepared formulation have been recorded [14].

2.3.5. X-Ray Diffraction. X-ray diffraction (XRD) is one of the most extensively used techniques for the characterization of nanoparticles. X-ray diffractometer (JDX-3532-JEOL, Japan) has been used for this analysis. The XRD provides information related to crystalline structure, nature of the phase, lattice parameters, and crystalline grain size. The powdered samples have the advantage over other forms as the results are in statistically representative of volume averaged values [23].

2.3.6. In Vitro Drug Release. To study the drug release from prepared nanoparticles, the USP-II paddle method was employed (using Dissolution Tester-DIS/6B). The drug release was investigated at 37°C in phosphate buffer pH 7.2 and potassium chloride media (KCl) medium pH 1.2 at 50 rpm. Samples were drawn and filtered using syringe filters, and similar volume of dissolution medium was added to maintain the constant volume. Analysis was performed spectrophotometrically [21]. In cellulose membrane dialysis tube, the prepared drug loaded nanoparticles were placed and dipped in 750 ml of Phosphate-buffered saline (PBS)

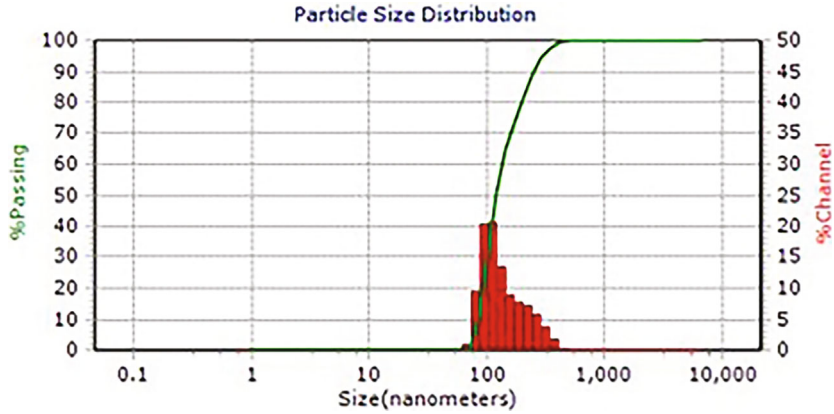

Figure 1: Particle size distribution describing the nanosized distribution (F2).

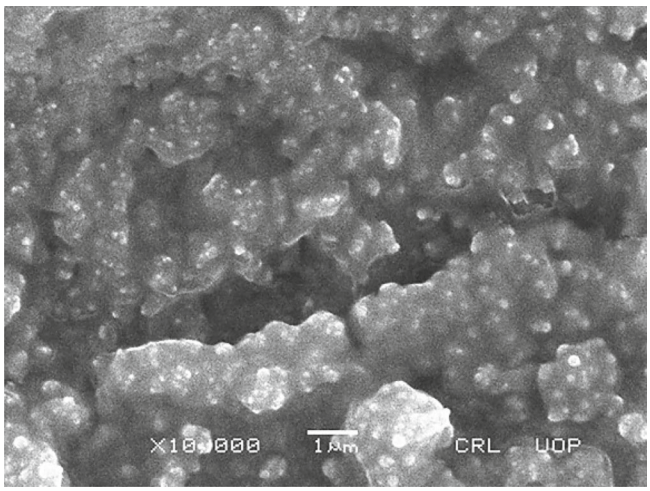

Figure 2: Representative SEM image of PLX/TCM-SLNs of formulation F2.

and KCl medium separately. Samples, each of 3 ml, were withdrawn at different time intervals (30 minutes, 1, 2, 3, 4, 5, 6r, 7, and 8 hours), followed by their analysis using spectrophotometric technique at 213 nm.

2.3.7. Release Kinetic Modeling. The drug release kinetic was applied on the drug release data to determine release patterns by model dependent methods (zero order, first order, Korsmeyer–Peppas).

3. Results and Discussions

3.1. Fabrication of PLX/TCM-SLNs. TCM has high solubility in many organic solvents like chloroform (594 mg/ml), methanol (588 mg/ml), acetone (542 mg/ml), and ethanol (370 mg/ml). But it is poorly soluble in water (0.012 mg/ml). Due to its low solubility and low bioavailability, there are several ways to enhance its solubility, which has been elaborated in previous research studies. Preparation of SLNs is one of them [24, 25].

Different evaluation parameters have confirmed that PLX/TCM-SLNs have been developed successfully, using nanoprecipitation technique. Outcomes of the studies have also confirmed that chosen composition for the preparation of SLNs was also suitable [12]. A white milky appearance of the formulation was being observed and it seemed that the lipophilic drug (TCM) has been entrapped in the hydrophobic cavity of the lipid (stearic acid).

3.2. Particle Size, Zeta Potential, and Polydispersity Index. The results of particle size and zeta potential analysis indicated that the particle size for the formulations F1, F2 (shown in Figure 1), F3, and F4 was found to be 267 ± 13 nm, 120.6 ± 9 nm, 182 ± 11 nm, and 323 ± 17 nm with zeta potential of -26 ± 2.3 Mv, -21.3 ± 1.7, -27.4 ± 5, and -23.5 ± 2, respectively. It was observed that the concentration of PLX and stearic acid directly affected the particle size. The increased concentration of PLX produced the particles with smaller size, whereas the increased stearic acid concentration resulted in the larger particle size and zeta potential as well. This might be due to the increased stability and emulsification with increased PLX conc. Surface charge is an important and key parameter that indicates the stability of SLNs and zeta potential of above 20 is considered to be suitable for a stable colloidal dispersion [26]. The results were comparable to a recent study where author also reported zeta potential of more than 20 Mv. The SLNs having zeta potential in this range yield stable and well-dispersed formulation [27]. The particle size analysis reports also indicate homogeneity of the formulated PLX/TCM-SLNs, as the polydispersity of the formulations lies in the range of 0.2–0.4. The literature reported that homogeneous formulations were desired for achieving uniform mixing of drug content in the formulation, and for SLNs, monodispersing population is a key element [22].

3.3. Percent Entrapment Efficiency. The drug EE is known to be an important indicator and a significant parameter to evaluate, whether the prepared SLNs have the required amount of the drug, entrapped in the nanoparticles, confirming the dose required for therapeutic efficiency, and to judge their appropriateness as a drug carrier system. Findings of %EE for PLX/TCM-SLNs have exhibited maximum amount of entrapped drug in F2 (95.8%). Such a considerable entrapped amount was advocating the suitability of designed

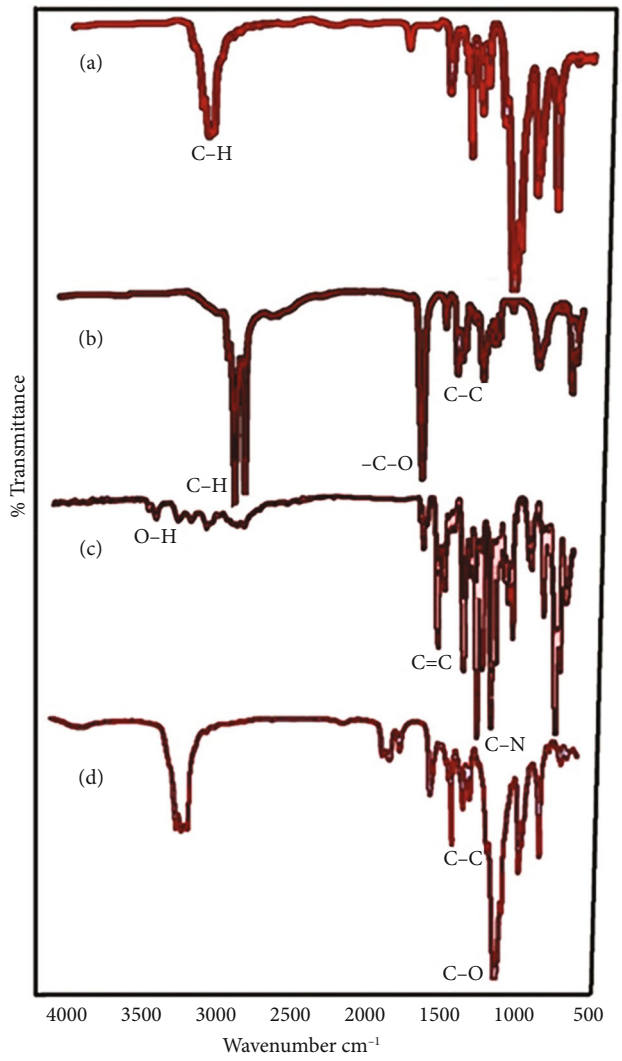

Figure 3: FTIR scans of (a) PLX, (b) stearic acid, (c) TCM, and (d) PLX/TCM-SLNs, exhibiting chemical compatibility of the ingredients.

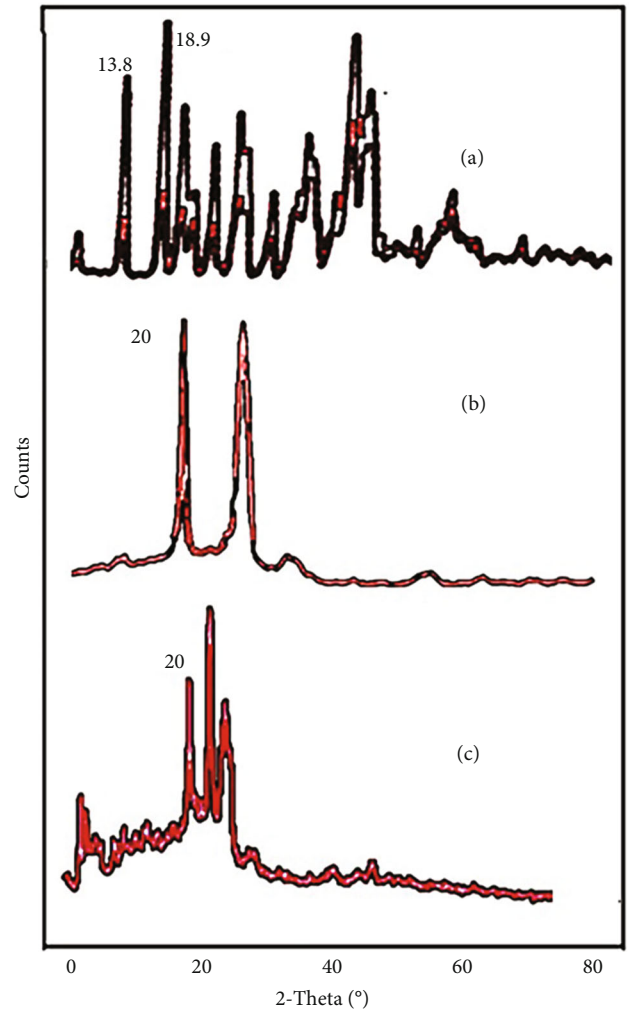

Figure 4: XRD diffraction pattern of (a) TCM, (b) PLX, and (c) PLX/TCM-SLNs.

formulation composition and the selected method of fabrication. The increased EE in case of F2 compared to other formulations is due to the highest amount of PLX, which provided the increased emulsification of TCM leading to the increased entrapment in the lipid core. The findings were similar to a recent study that aimed to develop SLNs using beta cyclodextrin (βCD). In nanotechnology, drug entrapment in the polymeric nanoparticle is one of the biggest challenges, and for achieving this aim, selection of excipients is a key factor. The literature reported that stearic acid is an extensively used excipient in the preparation of SLNs because it is good to entrap the drug especially lipophilic drugs and combination of PLX and stearic acid made it possible to achieve more than 95% EE [27].

3.4. Morphological Studies. The morphological study of PLX/TCM-SLNs has revealed that synthesized SLNs were of smooth, uniform surface, and nanosized. Particles were distributed uniformly, describing acceptable Dots per Inch (PDI) (Figure 2). As indicated in particle size analysis, SEM images also showed uniform mixing of drug in SLNs. Superficially, Figure 1 depicts spherical shape and smooth surface, advocating the appropriateness of excipients used and also the nanoprecipitation method, which was used in the preparation of SLNs. The benefit of SEM analysis instead of transmission electron microscopy is to observe the surface of nanoparticles [22].

FTIR spectra of pure PLX 407, pure stearic acid, pure TCN, and PLX/TCM-SLNs were recorded in the range of 500–4000 cm^{-1} The outcomes of the studies have confirmed that selected ingredients are compatible with each other, as no interacting peaks have been noticed (Figure 3).

The FTIR studies were carried out to confirm the stability and crystallinity of prepared nanoparticles and to check any interaction between TCM, PLX, and stearic acid. In the FTIR spectra of crystalline TCM, absorption bands of C–H stretching vibration at 700–800 cm^{-1}, and another peak of C–N stretch was observed at 1180 cm^{-1} due to aliphatic amines. At 1250 cm^{-1} and 1310 cm^{-1}, a sharp peak is observed due to C–O bond indicating the presence of alcohols and carboxylic acids, C=O (ketoamide) and C=C

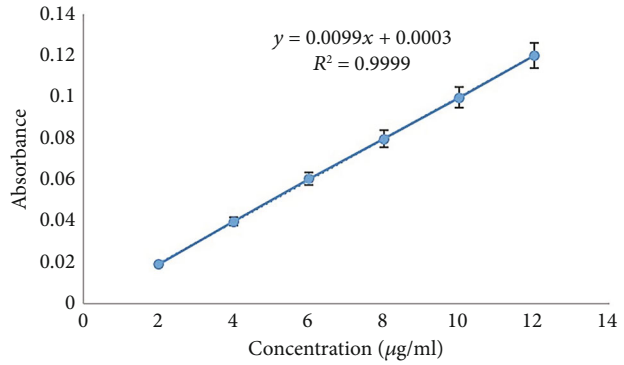

Figure 5: Calibration curve of TCM, indicating good linearity behavior in the concentration range of 2–12 μg/ml.

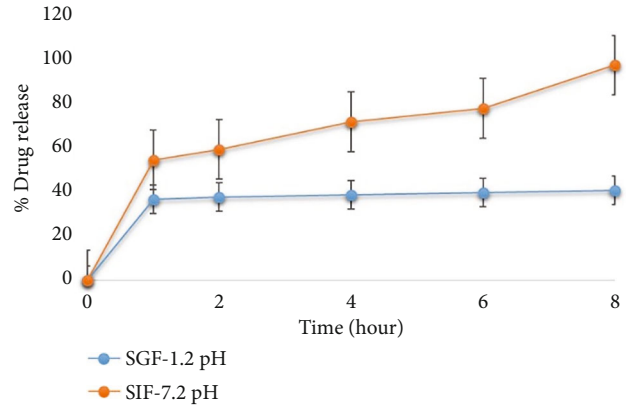

Figure 6: The % drug release of TCM, exhibited by PLX/TCM-SLNs in SGF-1.2 pH and SIF-7.2 pH.

stretching vibration at 1637 cm^{-1}, C–O–C (ether) stretching vibrations at 1176 cm^{-1} and 1094 cm^{-1} were observed. Strong infrared absorption at 3440 cm^{-1} was also seen confirming the presence of O–H [18]. The result provides an evidence for the complete entrapment of TCM and its interactions with the excipients. The peak at region 3440 cm^{-1} did not overlap peaks with other excipients [14, 17]. The FTIR spectrum of PLX showed stretching region of functional group C–H ranges from 2810 to 2889 cm^{-1}. Prominent peaks of alcohols, carboxylic acids, and ethers were observed at 1075 cm^{-1}, 1100 cm^{-1}, and 1120 cm^{-1}, respectively. A functional group of alkanes, C–H, was also observed at 2890 cm^{-1}. Another peak of O–H group that was observed at 873 cm^{-1} depicts the presence of carboxylic acids. FTIR spectrum of stearic acid showed characteristics peak at 2933 cm^{-1} assigned to the C–H stretch in alkanes, and a peak of 1700 cm^{-1} is assigned to the –C–O stretch indicating unsaturated aldehydes. Peak at 1306 cm^{-1} in the Figure 3 was due to C–H stretching vibration in alkanes. Another peak at 1441 cm^{-1} was the indication of C–C group in aromatics. The FTIR spectrum of resultant formulation of PLX/TCM-SLNs was scanned. The stretching region of functional group O–H ranges from 910 to 990 cm^{-1} depicting carboxylic acids. Bands between 2790 and 2820 cm^{-1} showed H–C=O: C–H stretch confirming aldehydes. Peak at 1370 cm^{-1} was due to C–H vibrations in alkanes. The stretch of C=O observed at 1710 cm^{-1} confirms the presence of α, β unsaturated aldehydes, and ketones. From these results, it was confirmed that there was no interaction between drug and excipients in the resultant formulation [28, 29].

3.5. XRD Method. XRD spectrum indicated that the TCM is highly crystalline in nature, and characteristic diffraction peaks appeared between the region of 10° and 35°. The main intense sharp peaks, at 13.8°, 18.9°, and 20.1°, confirmed the crystalline forms of TCM. The patterns of sharp peaks of PLX were noticed at 20° and 29°, while in PLX/TCM-SLNs, the intensity of the peaks appeared to depict that the crystalline nature of TCM changed to very less crystalline (Figure 4). However, the presence of few peaks attributed to the presence of unbound drug or drug present at the surface.

3.6. Qualitative Analysis of TCM. The calibration curve was drawn between the concentration and absorbance, and it was noticed that in selected concentration range, drug has shown good linearity behavior. The slope was 0.0099, the intercept was 0.0003, and the value of R^2 was 0.9999, indicating significant linearity. The drawn curve was used for quantitative analysis of the drug in prepared SLNs (Figure 5).

3.7. In Vitro Drug Release Study. Different factors that affected the drug release during dissolution are the nature of the polymer matrix, porosity of release unit, solubility of the drug, and pH of the media. The formulations showed the abrupt release of drug during first hour. This is due to rapid solubilization of the drug that is present on the surface of nanoparticles. The formulations showed a sustained release of drug in PBS over a period of 8 hours. The formulation showed 90% drug release in 8 hours. With respect to second media (KCl 1.2 pH) used for dissolution, formulation showed more sustained effect over release of drug (40 ± 5.98%). Greater release of the drug in basic medium might be due to PLX having better solubility at pH higher than 5, and possibly, this factor has contributed in greater release of drug at pH 7.2. Similarly, the absorption of TCM was found to be better at intestinal pH, rather than gastric one [30]. Therefore, the findings of current studies suggested that a sustained release formulation, with better opportunity for the drug to get absorbed at its absorption window, could be developed by the use of selected ingredients. Hence considering these features, suitable formulation with better release and absorption profile could be designed to improve the oral bioavailability of TCM, leading to improved patient compliance (Figure 6).

3.8. Kinetic Modeling of Release Data. In literature, numerous mechanisms have been reported by which drug was released from SLNs, including diffusion, desorption, matrix erosion, and erosion–diffusion process [31]. In the current study, data obtained from dissolution analysis have been

processed by using DD solver to employ different kinetic models. The highest value of (R^2) for PLX/TCM-SLNs in KCl 1.2 pH was 0.9761 for Korsmeyer–Peppas model. The value of "n" is 0.683, which was less than 0.89. The study reports the best fit model as Korsmeyer–Peppas, which indicated drug would be released through diffusion mechanism and following non-Fickian type of diffusion pattern.

4. Conclusions

TCM has been successfully loaded in SLNs and evaluated for different characterizations. The outcomes have confirmed that chemically compatible, nanosized uniformly distributed SLNs allow controlled and sustained release of drug with diffusion mechanism. The particle size of optimized formulation was considerable (120 nm). The prepared formulation would be a great contribution for the patients who need to suppress the immunity to avoid transplant rejection. Furthermore, it would be recommended to perform the *in vivo* experimentation in suitable animal model and later on in human to confirm its biological applications.

Data Availability

All the data has been presented in the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Conceptualization: Muhammad Zaman and Asma Mumtaz; data curation: Asma Iqbal and Muhammad Shahid Riaz; formal analysis: Asma Iqbal, Muhammad Hammad Butt, Asma Mumtaz, and Hafiza Yusra Nazeer; funding acquisition: Muhammad Zaman, Abdulrahman Alshammari, and Muhammad Shahid Riaz; investigation: Asma Iqbal, Muhammad Hammad Butt, Muhammad Omer Iqbal, Naveed Nisar, AsmaMumtaz, and Muhammad Shahid Riaz; methodology: Muhammad Zaman, Hafiza Yusra Nazeer, and Abdulrahman Alshammari; project administration: Muhammad Zaman and Abdulrahman Alshammari; resources: Muhammad Hammad Butt, Muhammad Omer Iqbal, Hafiza Yusra Nazeer, and Muhammad Shahid Riaz; software: Asma Iqbal, Muhammad Hammad Butt, and Hafiza Yusra Nazeer; supervision: Muhammad Zaman and Naveed Nisar; validation: Muhammad Omer Iqbal, Asma Mumtaz, Abdulrahman Alshammari, and Muhammad Shahid Riaz; visualization: Muhammad Hammad Butt; writing—original draft: Muhammad Zaman, Asma Iqbal, Muhammad Hammad Butt, Asma Mumtaz, and Hafiza Yusra Nazeer; writing—review and editing: Hafiz Shoaib Sarwar, Muhammad Omer Iqbal, Naveed Nisar, Abdulrahman Alshammari, and Muhammad Shahid Riaz. All authors have read and agreed to the published version of the manuscript.

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