

# Comparison of Freeze and Spray Drying to obtain Primaquine-Loaded Solid Lipid Nanoparticles

**Research Article****Abstract**

The spray drying and freeze drying of various nanosized Solid Lipid Nanoparticle and the physicochemical attributes of the acquired particles were examined. Primaquine loaded Solid Lipid Nanoparticles dried by the two strategies was examined. Particles were characterised by determination of size, drug loading, encapsulation efficiency and surface morphology. In vitro and kinetic drug discharge models were also considered. Preparation parameters have no impact on the molecule morphology and properties, and the main parameter deciding the molecule attributes in the drug substance of the nanoparticle, either in the spraying or in the freezing technique of drying. The drug release profile of spray dried SLN is superior to that of the freeze dried SLN.

**Keywords:** Spay drying; Freeze drying; Double emulsion; Solid lipid nano particle

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**Introduction**

Systemic delivery of therapeutic nanoparticles nano particles has as of late increased critical concern on account of its bioavailability enhancement potential ascribed to the extraordinary capacity of nanoparticles to avoid extracellular degradation to enhance selectivity in connection to the target, and to diminish dosage recurrence and also length of the treatment by means of improving the pharmacokinetic profile of the medication Omwoyo et al. [1]. Most examinations on systemic therapeutic nanoparticles utilize polymeric nano-carriers, especially poly (lactic-co-glycolic corrosive) (PLGA) and lipids, attributable to their entrenched biocompatibility and biodegradability. Particular to Solid Lipid Nanoformulation (SLN), the broad utilization of PVA nanoparticles as carriers are more apparent.

As opposed to other biocompatible and biodegradable polymers, for example, poly-caprolactone, PLGA and lipophilic nanoparticles are basically strong and thermally insensitive, to such an extent that they can be changed without the need of thorough formulation steps while protecting their physicochemical attributes, like size and drug loading. Various SLN formulations of spray dried PLGA and lipophilic nanoparticles as micro-scale circular aggregates of the nanoparticles have been presented for different therapeutic regimes from drugs Ohashi et al. [2]; Sung et al. [3]; Tomoda et al. [4] to gene Jensen et al. [5]; Takashima et al. [6] deliveries.

The drug discharge from polymeric nanoparticles relies on the rate of diffusion of the drug from delivery system, disintegration of the polymeric lattice and biodegradation of the polymer. In the event that disintegration and biodegradation are moderate process, the discharge rate is emphatically impacted by drug dissemination from nanoparticles. Factors like the association between drug and the polymer, the condition of consolidation of the drug in the carrier system, the pKa of the drug and the concentration of drug stacked in nanoparticles can affect the

dispersion rate of the drug from nanostructured framework Allen et al. [7]. The condition of fusing of the drug in the system and interaction between drug and polymer are critical variables that influence the discharge profile Joeng et al. [8]; Zhang et al. [9].

The improvement of nanostructured materials in biomedical drug delivery systems has turned out to be topical headings in cutting edge materials science as they have shown to provide uncommon properties in contrast with sub micrometer and micrometer partners Moriarty P [10]. Notwithstanding, treatment of nanoparticles is troublesome because of their volatility. A standout amongst the most stretched out courses to permit treatment of nanoparticulate systems is the generation of free-streaming agglomerates from colloidal suspensions subjected to a controlled drying process, like spray or freeze drying.

The generation of SLN, the dispersion and control of the nanoparticles is a key stride. The attributes of the suspension determine the morphology of the particles and their properties. A few investigations have revealed the scattering and security of suspensions of nano sized SLN, for example, RAPAMUNE®, EMEND®, TriCor® and MEGACE® among others as further explained in Table 1.

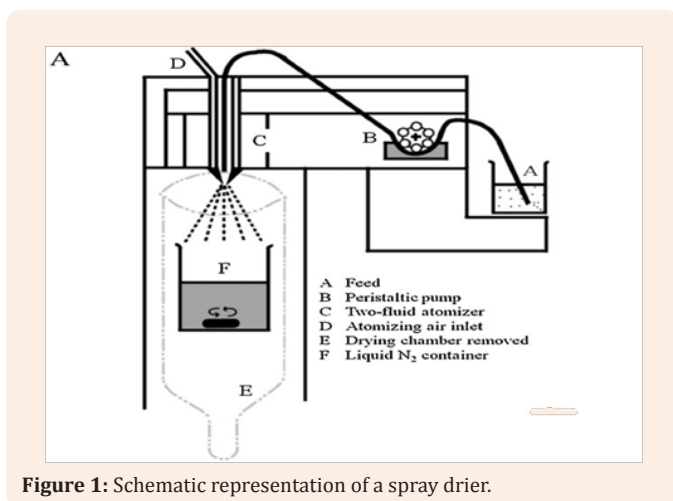
A well known technique of synthesis of nanoparticles is spray drying. Sánchez et al. [11] One favoured design in spray drying comprises on the preparation of a suspension that is delivered into the drying chamber, and atomized by pumping it at high pressure through a pressure multi-spout cluster, after that the upward spiraling beads meet hot air which is channeled through a

diffuser into the chamber (counter-current to the droplets) Negre et al. [12]. There is additionally co-current and blended systems, together with various atomization modes (rotating atomiser, pressure spouts, two-liquid spouts) Master [13]. Despite the

configuration and atomisation method of the spray dryer, it is important to prepare and optimise the nanoparticles suspensions keeping in mind the end goal to acquire homogeneous spray dried particles with high apparent density (Figure 1).

**Table 1:** Current marketed pharmaceutical products utilizing nano crystalline API.

Product	Drug Compound	Indication	Company	Product
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Elan Drug Delivery Nanocrystals®
EMEND®	Aprepitant	Antiemetic	Merck	Elan Drug Delivery Nanocrystals®
TriCor®	Fenofibrate	Treatment of hypercholesterolemia	Abbott	Elan Drug Delivery Nanocrystals®
MEGACE®	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical	Elan Drug Delivery Nanocrystals®
ES Triglide™	Fenofibrate	Treatment of hypercholesterolemia	First Horizon Pharmaceutical	Skye Pharma IDD®-P technology



**Figure 1:** Schematic representation of a spray dryer.

Another strategy for the synthesis of nanoparticles is freeze drying. This strategy is getting extraordinary consideration these days for the synthesis of nano sized particles from inorganic salts and for the produce of porous bodies by a freeze casting process. The preparation of particles by this method was created with the target of maintaining a strategic distance of pressing aids to the particle surface Lyckfedt et al. [14]. However, it is extremely restricted when contrasted with spray drying. A principle highlight of freeze drying as a nano formulation strategy is that the acquired nanoparticles have high porosity thus light granules can be produced Uchida et al. [15]; Yokota et al. [16]. The porosity and subsequently, the thickness of particles are controlled by the strong stacking of the suspensions, though the size distribution of the particles is a component of the viscosity and the solid substance of the suspension, the streaming rate utilized for spraying and the pressure of the connected gas Moritz & Nagy [17]; Rundgren et al. [18].

The present research envisaged reformulating PQ to enhance its efficacy and half-life, which may impact on its dosing regimen

by enabling lower dosage and longer frequency. These will lead to reduced toxicity and better patient compliance. The strategy employed toward this was through the synthesis of PQ-loaded Solid Lipid Nanoparticles (PQ-SLNs). The PQ-SLN that was spray dried (SD) and PQ-SLN that was freeze dried (FD) were used in order to compare the two selected methods, spray drying and freeze drying, and the physicochemical characteristics of the obtained nanoparticles such as their morphology, surface area, and size distribution as a function of the suspension preparation conditions. The influence of processing parameters such as nozzle diameter, solids content, temperature and air pressure on the nano particle characteristics were also studied.

## Materials and Methods

### Materials

All materials, reagents, chemicals, and PQ base utilized as a part of the study were provided by our partners at the Novartis, Basel, Switzerland. The stearic acid (SA), chitosan low-viscous, polyvinyl alcohol (PVA) of molecular weight 13,000-23,000 and partially hydrolyzed (87%-89%), D-lactose monohydrate, sulfanoyl, and ethyl acetate (EtOAc) were obtained from Sigma-Aldrich (Basel, Switzerland), and Pluronic® F127 Prill from BASF Corporation (Mount Olive, NJ, USA). All other synthetic items were commercially accessible and of analytical grade. In this test outline, stearic acid was the lattice; PVA and pluronic were surfactants stabilised the emulsion, and chitosan was a mucoadhesive expanding circulation time in the digestive system to enable the majority of the nanoparticles to be assimilated. Lactose improved particle size reduction, since it is a binder, while sulfanoyl was used as an antifoaming agent.

### Preparation of SLNs via spray drying

Nanoparticles were prepared utilizing a modified double-emulsion solvent evaporation strategy. Two millilitre of 22 polyvinyl acetate was blended for a short period with one hundred mg PQ utilizing a magnetic stirrer to make the essential

fluid stage incorporating the drug. The organic area was made by dissolving 50 mg of stearic acid in ten milliliter of EtOAc. The aqueous stage was scattered inside the organic phase by methods for a rapid homogenizer (Silverson L4R; Silverson Machines constrained, Buckinghamshire, UK), with a speed changing in the vicinity of 3,000 and 6,000 rpm for 3-6 minutes. The following water-in-oil emulsion was moved into a particular volume of an aqueous solutions made by consolidating solutions of ten milliliter of 22 polyvinyl acetate (weight/volume [w/v]), 5 mL of 0.2% (w/v), chitosan low-thick, and five milliliter of fifty (w/v) D-lactose monohydrate. A drop of sulfanoyl was added to the resultant water-in-oil-in-water (w/o/w) emulsion, and the blend was additionally emulsified for five minutes by homogenization at 8,000 rpm. The twofold emulsion (w/o/w) acquired was directly sustained into a benchtop Buchi smaller than normal spray dryer (Model B-290; BÜCHI Labortechnik ag, Flawil, Switzerland) and spray dried at a temperature running in the range of 80°C and 110°C, with an atomizing pressure fluctuating in the range of five and eight bars.

### Preparation of SLNs via freeze drying

The nanoparticles loaded with PQ were prepared using a modified multiple emulsion solvent evaporation technique followed by freeze drying. A solution of 100mg PQ was dissolved in 2m of aqueous 2% PVA to form the aqueous phase containing the drug. The organic phase was made by dissolving 50mg of stearic acid in 10ml of EtOAc. The aqueous phase was often dispersed in the organic phase by means of a high speed homogenizer (silverson L4R; Silverson machines limited, Buckinghamshire, UK), with a speed varying between 3,000 and 6,000 rpm for 3 minutes. This water-in-oil (w/o) emulsion was transferred to a specific volume of an aqueous 2% w/v PVA (mw=13000-23000), 5% of 0.2 % (w/v) chitosan low viscous, and 5 ml of 5% (w/v) D-lactose monohydrate. A drop of sulfanyl was added as a stabiliser to the resultant water-in-oil-in-water (w/o/w) emulsion and the mixture was further emulsified by homogenisation at 8,000 rpm. The water-in-oil-in-water double emulsion obtained was gently stirred overnight at room temperature to remove the organic solvent. Thereafter, drug-loaded SLNs were harvested by ultra centrifugation (37000g for 15 mins) followed by a series of wash steps with deionized water. The recovered pellets were dispersed in liquid Nitrogen before freeze drying (Heto DRYWINNER, Germany) at 0.05 mBar for 24 hours.

The nanoparticles loaded with PQ were synthesised utilizing a modified multiple emulsion solvent evaporation method followed after by freeze drying. A solution of 100mg PQ was dissolved in 2m of fluid 2% PVA to shape the aqueous phase containing the drug. The organic stage was made by dissolving 50mg of stearic acid in 10ml of EtOAc. The aqueous stage was frequently dispersed in the organic stage by a technique of fast homogenizer (silverson L4R; Silverson machines restricted, Buckinghamshire, UK), with a speed shifting in the vicinity of 3,000 and 6,000 rpm for 3 minutes. This water-in-oil (w/o) emulsion was transferred to a specific volume of an aqueous 2% w/v PVA (mw=13000-23000), 5% of 0.2 % (w/v) chitosan low thick, and 5 ml of 5% (w/v) D-lactose monohydrate. A drop of sulfanyl was added as a stabilizer to the resultant water-in-oil-in-water (w/o/w) emulsion and the blend was additionally emulsified by homogenisation at 8,000 rpm.

The water-in-oil-in-water twofold emulsion got was delicately blended overnight at room temperature to expel the organic solvents. Drug loaded SLNs were collected by ultracentrifugation (37000g for 15 mins) followed by a progression of wash steps with deionized water. The recovered pellets were scattered in fluid Nitrogen before freeze drying (Heto DRYWINNER, Germany) at 0.05 mBar for 24 hours.

### Particle characterisation

#### Determination of Size and $\zeta$ -Potential

A Zetasizer Nanoseries (Malvern Instruments, Malvern, UK) was utilized to estimate particle size, poly dispersity index(PDI) and  $\zeta$ -potential of all the two sorts of particles by dynamic light scattering (DLS) or photon correlation rule. All scattering-samples were diluted 1:500 in ultra-pure water, vortex and sonicated for determination of the, PDI and  $\zeta$ -potential. Three replicates of each were measured at room temperature. Results are presented as mean±standard deviation.

### Stability study and pH determination

To guarantee stability of the formulations over some stretch of time, scatterings in water (0.5 mg/ml) were checked for up to 2 months after processing of SLN with respect to particle size, PDI,  $\zeta$ -potential, and pH. For the pH deduction a calibrated potentiometer (Model AZ-8306: AZ Instruments Corp., Taichung City, Taiwan) was utilized. pH values were measured by the direct immersion of the electrode in the undiluted dispersion at 10% (w/v). The samples were stored in amber glass flasks at 25°C.

### Drug loading and encapsulation efficiency

Drug content was broke analyzed after a modified form of the technique outlined by Fontana et al. [19] EE% was resolved utilizing both the direct and indirect strategy. In the indirect strategy, 20 mg of the synthesised nanoparticles were scattered in 10 mL of water and vortexed in falcon tubes until until completely dispersed. The resultant solution was then ultra-centrifuged at 15,000 rpm for 20 minutes at 4°C. The supernatant was then taken for ultraviolet-visible (UV-VIS) investigation at wavelengths between 400 nm and 200 nm. For the direct technique, the precipitate was taken and disintegrated in a predetermined amount of EtOAc. Water was then added to the solution and left overnight. The aqueous stage was then isolated by means of a separating funnel and examined for PQ concentration. The concentration of the drug was calculated by methods for a standard curve as separated from UV-VIS spectrometry examination by utilizing diverse known concentrations of the drug. The EE% and DL% were ascertained utilizing the equations underneath:

$$EE\% = (\text{drug in precipitate}/\text{total added drug}) \times 100 \quad (1)$$

$$DL\% = (\text{drug in precipitate}/\text{drug in precipitate} + \text{added excipients}) \times 100 \quad (2)$$

Where “drug in precipitate”=total drug added-free drug after ultra-centrifugation (indirect method) and “added excipients”=lipids+surfactant mixtures+other ingredients used.

### Surface morphology

Scanning electron microscopy was utilized to give an approach

to specifically observe the morphological appearance of the nanoparticles. The particles were first covered in gold to limit the impact of heat amid high-power amplification and were then run through a scanning electron microscope instrument (SU1510 model; Hitachi Ltd., Tokyo, Japan) where photos of the nanoparticles were taken. Fourier change infrared spectroscopy (FTIR) was likewise used to decide the useful gatherings exhibit on the surface of the nano particle.

### In vitro release experiment

In vitro release studies were performed utilizing the strategy outlined by Mühlen and Mehnert, with slight modification. To decide if the encapsulation procedure brings about a sustained release of drug was performed in phosphate buffered saline (0.1 M PBS, pH 7.4). in this strategy, three replicates of each sample containing nanoparticles of a known concentration of PQ-stacked nanoparticles both framed by Spray drying (SD) and Freeze Drying (FD) strategies were set in a dialysis film and immersing dialysis film into in 20 ml of PBS arrangement in a shaker at 37°C, at a predetermined interim 100 µL of sample were analysed by HPLC utilizing the technique adapted from Mohan et al. 2003, with minor alterations. For positive controls, 10 mg of free PQ drug was dialysed into 20 ml of PBS sample. The investigation gave the amount of drug discharged from the nanoparticles with time.

### Mathematical modeling of PQ loaded nanoparticles

The PQ discharge information was utilized to study the mechanism of drug discharge. They were fitted using the numerical models of Zero-arrange, First-arrange, Higuchi 's demonstrate, Hixon-Crowell's model and Korsmeyer-Peppas show Barzegar-Jalali et al. [20]. Equations of the mathematical models are showed in Table 2. Data were fitted and the relapse direct of the scientific models was assessed utilizing R2 (squared relationship coefficient). The linear regression was applied in the range of 6 to 400 h.

**Table 2:** Applied mathematical models to the data release of the PQ loaded in solid lipid nanoparticles.

Mathematical Models	Equation
Zero order	$F=k_0t$
First order	$\ln(1-F)=-k_1t$
Higuchi	$F=k_H t^{1/2}$
Hixon-Crowell	$1-(1-F)^{1/3}=k_{1/3}$
Korsmeyer-Peppas	$F=k_k -Pt^n$

F denotes fraction of drug released up to time t.  $k_0$ ,  $k_p$ ,  $k_H$ ,  $k_{1/3}$  and  $k_{k,p}$  are constants of the mathematical models. n is the release exponent of the Korsmeyer-Peppas model.

## Results and Discussion

### Particle characterisation

**Particle size, size distribution and zeta potential:** The measure of nanoparticles was optimized against a benchmark of 250 nm as it is accounted for smaller particles (normal size <250

nm) undergo passive diffusion through hepatocytes. Different parameters were optimized to acquire an average particle size ranging between 230 and 250 nm and an average polydispersity index of 0.1to 0.2. The expansion of shear rate by expanding the speed of homogenizer caused a lessening in particle size.

All particles demonstrated a positive zeta potential. The added drops of chitosan to give positive surface charge brought about micro particles. The sizes measured for the two unique sorts of particles went between ~250-260 nm (Table 1). FD gave rise to a generally larger size when contrasted to SD. This can be explained by the presence of the oil phase (U.M.A., 2009) prompting a core-and-shell structure for FD rather than a matrix system in the spray dried (SD). All nanoparticles had a PDI in the range of 23.48 and 15.50 affirming a homogeneous size appropriation. The ζ-Potential of every one of the two sorts of NPs was positive, extending from 17.0 to 19.5 mV. This positive potential is in all likelihood caused by the polymeric divider made by the lipids. The strength and stability of the particles is because of steric obstruction of the surfactant between the two phases counteracting mixture preventing coalescence (Table 3).

### Stability study

Stability of the NPs in suspension was tested for a period of 3 months in terms of size, poly dispersity, ζ-potential, and pH (Table 2). After this period a slight increment in particle size was noted, probably as a result of aggregation or agglomeration. However, this effect was minimal and negligible. The ζ-potential varied marginally over time with no general trend observed. The pH study demonstrated that the pH values obtained were suitable for application on the skin over the entire period of three months, as the pH stayed between pH 5.1-6.1. A slight reduction in pH was observed, but still remained adequate for topical application. This effect has previously been explained as a possible degradation of the polymer due to a release of free PQ, as well as a hydrolysis of the medium chain triglycerides, leading to an increase of free fatty acids Abdelwahed et al. [21]. Thus, all measurements confirmed that no noteworthy changes in size, polydispersity, ζ-potential, or pH occurred over time (Table 4).

### Drug loading and encapsulation efficiency

The PQ content measured approximately 0.5 mg/ml for all two nano carriers, showing that 40 to 30% drug were lost during the preparation step for FD or SD. Moreover, the encapsulation efficiency (EE %) measured was close to 60 to 78%, regardless of the type of particle for exact values please refer to Table 1. Hence, no significant differences regarding the ability to encapsulate the drug were observed between FD and SD, although the preparation processes and components used were slightly different.

### Surface morphology

Scanning electron microscopy (SEM) analysis was feasible for all two types of particles (Figure 2a & 2b).

However, for FD the imaging was more difficult, most likely due to the presence of the organogel. Both methods confirmed the expected morphology. All particles were spherical in shape, revealed a smooth surface, and a homogeneous size distribution. Figure 1a and b displays SEM images of all two particles (FD and SD) respectively.

**Table 3:** Size distribution, PDI values, and  $\zeta$ -potential of nanoparticles (NP) using dynamic light scattering (DLS) analysis; mean $\pm$ standard deviation.

Type of Particle	Size (nm)	PDI	$\zeta$ -potential (mV)	PQ DL(%)	Encapsulation Efficiency (%)
FD	267.6 $\pm$ 3.7	0.13 $\pm$ 0.02	17.17 $\pm$ 1.11	23.48 $\pm$ 0.02	78.46 $\pm$ 1.0
SD	256.4 $\pm$ 2.9	0.18 $\pm$ 0.02	19.0 $\pm$ 2.8	15.50 $\pm$ 0.01	64.1 $\pm$ 0.8
FD(placebo)	228 $\pm$ 2	0.17 $\pm$ 0.02	13.59 $\pm$ 0.73	-	-
SD(placebo)	217 $\pm$ 11	0.15 $\pm$ 0.01	14.42 $\pm$ 1.09	-	-

**Table 4:** Physiochemical characteristics of Freeze Dried (FD and Spray Dried (SD) tracked for 2 months; mean $\pm$ SD (size measured using DLS analysis).

Type of Particle	Month	Size (nm)	PDI	$\zeta$ -Pot (mV)	pH
SD	0	258 $\pm$ 2	0.09 $\pm$ 0.02	19.40 $\pm$ 1.75	6.12 $\pm$ 0.23
	1	269 $\pm$ 1	0.12 $\pm$ 0.03	18.90 $\pm$ 1.59	5.86 $\pm$ 0.13
	2	267 $\pm$ 9	0.14 $\pm$ 0.05	18.47 $\pm$ 1.84	5.53 $\pm$ 0.26
FD	0	295 $\pm$ 4	0.08 $\pm$ 0.02	17.10 $\pm$ 1.93	5.99 $\pm$ 0.23
	1	218 $\pm$ 3	0.16 $\pm$ 0.02	16.30 $\pm$ 1.71	5.92 $\pm$ 0.19
	2	208 $\pm$ 4	0.13 $\pm$ 0.03	15.63 $\pm$ 0.65	5.42 $\pm$ 0.12

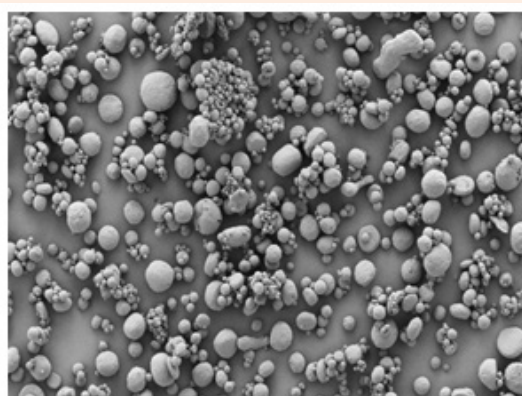


Figure 2a

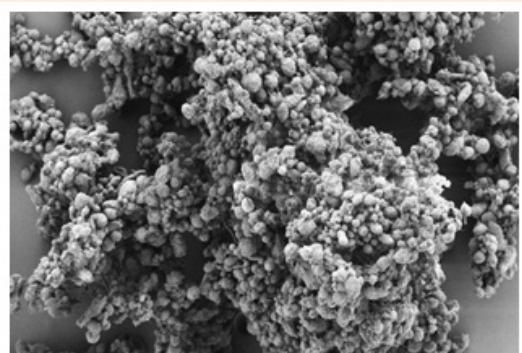


Figure 2b

**Figure 2:** Scanning electron microscopy (SEM) analysis.

### In vitro release studies

To determine whether the encapsulation process results in a sustained release of drug, the dialyzer dialysis membrane method was applied. The release profiles of the two different SLNs in suspension (FD, SD) vs. free drug in a PBS solution as a control are depicted in Figure 2. A noteworthy issue amid the work with lipid nano pellets has been the burst discharge seen with these systems. At the point when not washed properly, PQ-SLNs could demonstrate a burst discharge due to unencapsulated drug. An extended drug discharge has been acquired when contemplating the consolidation of prednisolone. As can obviously be found in Figure 3, no significant differences were observed between the release profiles of the two nano carriers FD, or SD ( $p > 0.05$ ). However, as was anticipated, all the two PQ-loaded particles showed a sustained discharge of the drug, as following 24 hours just around half of the typified drug was discharged for each of the three carriers. Indeed, even toward the finish of a 72h period, the mean concentration of discharged drug still stayed beneath 80%. Free drug, conversely, showed a quick discharge profile with ~80% of PQ as of now being distinguished after just 5h.

### Release kinetics

A few scientific models were utilized to examine the mechanism of the PQ discharge from solid lipid nanoparticles Barzegar-Jalali et al. [20]; Tanaka et al. [22]. The drug discharge relies on: adsorption through the nanoparticles matrices, dispersion through the nanoparticles matrices, particles disintegration, a consolidated disintegration and diffusion process and polymer degradation (chemical or enzymatic hydrolysis). The utilization of the right scientific model permitted analysis about discharge rate, points of disintegration change and mechanisms of drug discharge. The squared correlation coefficients ( $R^2$ ), slope (a), linear coefficient (b), rate constant (k) got after regression

linearity using scientific models are displayed in Tables 5 & 6. Figure 3 demonstrates the direct linearity got using Higuchi's model Higuchi [23] that gave the most noteworthy estimation of squared correlation coefficient ( $R^2$ ).

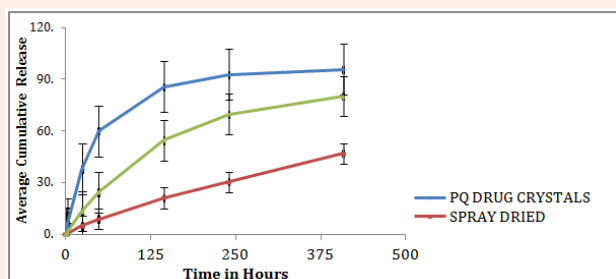
**Table 5:** Squared correlation coefficient ( $R^2$ ) and coefficients obtained after linear regression of the release data utilizing five mathematical models

Mathematical Model	R2	a	b	k	n
Zero order	0.9706	0.08	14.098	0.08 (h-1)	-
First order	0.9815	0.0015	0.0911	0.0015 (h-1)	-
Higuchi	0.9932	2.5619	2.9378	2.5619 (h-1/2)	-
Hixson-Crowell	0.9789	0.0004	0.0371	0.0004 (h-1/3)	-
Korsmeyer-Peppas	0.9931	0.4977	0.3925	2.5044 (h-n)	0.4978

$R^2$ -squared correlation coefficient.  $y=ax±b$  is an equation obtained after linear regression: a-slope and b- linear coefficient. k- Release rate constant of the mathematical models. n- release exponent of the Korsmeyer-Peppas model.

**Table 6:** Best-fit values of cumulative drug release from PQ Loaded SLN (curves are shown in Figure 3).

Fitted Parameters	Freeze Dried	Spray Dried
A (% release)	24±2	38±2
K1 (day <sup>-1</sup> )	0.38±0.08	0.29±0.04
B (% release)	80±5	59±3
K2 (day <sup>-1</sup> )	0.044±0.004	0.060±0.006
T50 (day)	64±3	33±3
R <sup>2</sup>	0.9755	0.9709



**Figure 3:** In-vitro release study of PQ loaded SLN in PBS pH 7.4, in 37 C water bath. PQ Drug Crystals were used as control. Data are expressed as mean ± SD (n=3). Lines drawn represent non-linear regression fit of the data.

Squared correlation coefficients ( $R^2$ ) acquired with the Zero-order model was 0.9706. This model can be utilized to portray the drug discharge from a few sorts of delivery systems, such as, matrix tablets for drugs with low solvency Varelas et al. [24] and osmotic systems, where drug discharge would directly correspond to the time. First-order kinetics model Gibaldi & Feldman [25]; Wagner [26] produced a  $R^2$  of 0.9815. First-order kinetics model can portray the discharge profile from the delivery system containing hydrophilic drugs dispersed in permeable matrices, where drugs would be discharged at the rates corresponding to the concentration of drug staying in the inside of the delivery system Mulye & Turco [27]. Hixson-Crowell's cube root model was applied in the discharge data and it gave a  $R^2$  of 0.9789. This

model can be connected to the delivery systems whose drug discharge rate is corresponding to the surface area of the systems, for instance, the disintegration dependent discharge systems Hixson & Crowell [28]; Yan et al [29]; Costa & Lobo [30]. Higuchi's model Higuchi [23] has been founded on the Fick's Law where the discharge happens by the dispersion of drugs inside the delivery systems. For this situation, the total discharged concentration of the drug is relatively promotional to the square root of time. The correlation can be utilized to portray drug disintegration from different sorts of modified discharge of pharmaceutical dose forms Mathew et al. [31]. In the event that the correlation of squared root of time versus the yield of cumulative concentration of drug discharged (Table 2) a straight line then the specific dose form is thought to take after Higuchi kinetics Mathew et al. [32]. Under some test circumstance the discharge component can stray from Fickian diffusion, following a peculiar transport (non-Fickian discharge) Mathew et al. [32]. In these cases, a more nonexclusive equation can be utilized. Korsmeier-Peppas et al. [32]; Mathew et al. [32] developed a scientific model relating exponentially to the drug discharge to the elapsed time. The model is depicted in Table 2. Pappas Mathew et al. [32]; Peppas [32] utilized the discharge exponent (n) with a specific end goal to describe diverse discharge system. In the event that the n value is 0.5 or less, the discharge component takes after Fickian dispersion (Higuchi display), and higher values  $0.5 < n < 1$  for mass exchange take after a non-Fickian model denominates peculiar transport. The drug discharge takes after Zero-order drug discharge or Case-II transport if the n values are 1. For the estimates of n higher than 1 ( $n > 1$ ), the mechanism of drug discharge is viewed as super Case-II transport Mathew et al. [32]; Peppas [32]. This model is utilized to analyse the discharge of pharmaceutical polymeric concentration forms when the discharge system is not finite or when more than one sort of discharge phenomena was involved Mathew et al. [30]. This model is restricted to the initial 60% of the cumulative concentration of drug discharge. The n values could be gotten from slope (a) of the straight line of log cumulative concentration of drug discharged (%) versus log time Mathew et al. [30]. For the models of Zero-order, First-order, Higuchi and Hixson-Crowell, the rate constant (k) was derived from the slope (a) of the straight line (Table 5). The rate constant (k) for the Korsmeyer-Peppas model was resolved utilizing the discharge exponent (n) and the equation depicted in Table 2. As appeared in Table 5, Higuchi's model Higuchi [23] and Korsmeyer-Peppas

model Carriazo et al. [33]; Peppas [32] gave the most noteworthy estimations of squared correlation coefficient ( $R^2$ ). In this manner, these scientific models would be the best fit models to depict the Primaquine discharge from SLN Carriazo et al. [33]. Both Higuchi and Korsmeyer-Peppas models are generally used to describe the discharge mechanisms. In Higuchi approach, the part of drug discharged is relative to the square root time. The rate constant ( $k$ ) is a consistent of the formulation Carriazo et al. [33]. For Korsmeyer-Peppas,  $k$  is additionally the rate constant and  $n$  is the discharge exponent describing the diffusion system. For  $n=0.5$ , the Korsmeyer-Peppas model is indistinguishable with Higuchi model Carriazo et al. [33]; Karewicz et al. [34]. This reality can be seen in our experiments. The polymer hydrolysis and polymeric grid disintegration could impact in the drug discharge from nanoparticles, however, these procedure are moderately slow. The outcome presupposes that the release of PQ from SLN is controlled by diffusion. The mechanism of the drug discharge from SLN can be considered as one that takes after: water enters into polymeric lattice of the nanoparticles through small permeable and channels; gradually dissolving the drug and primaquine is discharged by dissemination to acceptor solution [35-45].

## Conclusion

The FD SLN had a higher encapsulation efficiency but was not easy to optimise in terms of size, zeta potential and PDI. Both FD and SD nanoparticles were stable whereas the SD SLN had smooth morphology compared to the FD nanoparticle.

Release studies showed that both SD and FD SLN exhibited a sustained release with kinetic obeying Higuchi's model. Korsmeyer-Peppas model corroborates the results obtained with Higuchi's model. The results show that Solid Lipid nanoparticles are promising sustained release system for Primaquine.

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## Conflicts of Interest

The authors report no conflicts of interest in this work.

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