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DESIGN, EVALUATION, AND PHARMACOKINETIC STUDIES OF PALIPERIDONE SOLID LIPID NANOPARTICLES FOR BIOAVAILABILITY ENHANCEMENT

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ABSTRACT

The purpose of the study was to develop and assess paliperidone (PPD) loaded solid lipid nanoparticles (SLNs) for the treatment of schizophrenia. SLNs use solid lipids such as glyceryl tristearate, tripalmitin, and glyceryl stearate citrate, followed by hot homogenization and ultrasonication. Particle size (P.S.), zeta-potential (Z.P.), polydispersity index (PDI), entrapment efficiency (E.E.), drug content, and *in vitro* release studies were conducted on all produced formulations. The optimized formulation (PDP 4) containing tripalmitin has been observed. In this instance, low lipid concentration has been associated with higher drug release percentages (86.51%), lower P.S. (210.68 nm), higher E.E. (74.65%), low PDI (0.208), and good Z.P. (-28.97), all of which point to a stable formulation. Pharmacokinetic studies show that the formulation (PDP 4) has an improved relative bioavailability that is 2.26 times higher than the coarse suspension of pure drug. It was concluded that the tripalmitin-containing formulation SLN-PDP (4) exhibits significant results.

KEYWORDS: Solid lipid nanoparticles, Paliperidone, Hot homogenization & ultrasonication, and Pharmacokinetic studies.

1. INTRODUCTION

Solid lipid nanoparticles (SLNs) are essentially solid lipids, representing a stabilizer when diffused in water at the sight of a surfactant.[1] SLNs are about their nano size, higher surface area and extensive drug loading proportions. Similarly, it promotes drug consistency and can potentially enhance the oral bioavailability of water-insoluble drugs.[2]

The therapeutic efficacy of a drug depends on drug concentration. The drug shows low concentration, which leads to therapeutic failure of a drug due to first-pass effect, poor solubility, low bioavailability and high fluctuation of plasma. A pioneering assuring design to defeat these distinguished difficulties by advancing appropriate colloidal carrier approaches. Encompassed by the carrier methods, they have a lot of benefits and limited obstacles of solid lipid nanoparticles as correlated to variant carrier methods.[3]

Paliperidone (PPD), an atypical (second-generation) antipsychotic recommended for managing schizophrenia, presents biopharmaceutical challenges and pharmacological constraints which dissuade it from crossing the brain barrier. It is the primary active metabolite of risperidone and acts as a dopamine receptor D2 and 5-hydroxy tryptamine. It has an oral bioavailability of about 28% as it is poorly soluble in water and undergoes hepatic first-pass metabolism.[4]

The present research work was conducted to develop the formulations of paliperidone-loaded solid lipid nanoparticles (PPD-SLNs) for treating schizophrenia. The controlled and targeted drug delivery systems are needed for the effective treatment of schizophrenia. Most drugs cannot cross the blood-brain barrier (BBB) for effective treatment. The PP-SLNs could be promising for the delivery of the drug in a controlled release manner, and the permeability of BBB can be solved by using permeation enhancers as a surfactant in SLN formulation development.

2. MATERIALS AND METHODS

2.1. Materials

Paliperidone was acquired as a gift sample from A.R Life Sciences Ltd, India. Glyceryl stearate citrate, tripalmitin and Glyceryl tristearate were procured from Hi Media Labs, Mumbai. Stearic acid and GMS were obtained from Sigma Aldrich, Hyderabad. Egg lecithin was procured from Lipoid, Germany, respectively. Polysorbate 80 was obtained from Rankem, Chennai. Methanol and chloroform were of HPLC grade Merck, Mumbai.

2.2. Methods

2.2.1. Preparation of paliperidone-loaded solid lipid nanoparticles

The paliperidone solid lipid nanoparticles (PDP-SLNs) were produced through ultrasonication-based homogenization. A mixture of 10 mL of chloroform and methanol (1:1) was used to dissolve the drug, solid lipid, and egg lecithin. The organic solvents were isolated using a rota evaporator (Heidolph, Germany). The heating system was set at 5°C higher than the melting point of the lipid utilized in the formulation, melting the drug-encapsulated lipid covering layer. The surfactant polysorbate 80 was used to develop the water phase. This surfactant dissolves in double distilled water before being heated to the same temperature as the oil phase. After adding the heated water phase to the oil phase, the mixture was homogenized for 5 min at 12,000 rpm in a homogenizer. The resultant oil-in-water (O/W) emulsion was ultrasonicated for 10 min to make it coarser. The SLNs were produced by letting the nanoemulsion drop to ambient temperature after it was heated.[5] The various constituents of the formulation are listed in Table 1.

Table 1: Formulations of PDP-SLNs.

Ingredients (mg)	Developed Formulations								
	PPD 1	PPD 2	PPD 3	PPD 4	PPD 5	PPD 6	PPD 7	PPD 8	PPD9
Paliperidone	3	3	3	3	3	3	3	3	3
Glyceryl stearate citrate	30	60	90	--	--	--	--	--	
Tripalmitin	--	--	--	30	60	90	--	--	--
Glyceryl Tristearate	--	--	--	--	--	--	30	60	90
Egg lecithin	85	85	85	85	85	85	85	85	85
Solvent ratio (1:1) ml	10	10	10	10	10	10	10	10	10
Polysorbate 80 (w/v)	100	100	100	100	100	100	100	100	100
Double dist water (mL)	10	10	10	10	10	10	10	10	10

2.3. Evaluation studies of PDP-SLNs

2.3.1. Measurement of particle size, zeta potential and polydispersity index

A Zetasizer (Malvern Instruments, UK, Nano ZS90) was used to measure the zeta potential (Z.P.), polydispersity index (PDI) and particle size of PDP-SLNs. The prepared PDP-SLNs were diluted from 100µl to 5mL using double-distilled water. The Zeta potential (Z.P.) of SLNs was measured using a Zetasizer at 25 °C.[6]

2.3.2. Assessment of entrapment efficiency

The entrapment efficiency (E.E.) was determined by measuring the concentration of free drug (unentrapped) in aqueous medium. The aqueous medium was separated by ultrafiltration using centrisart tubes (Sartorius, USA), which consisted of a filter membrane (M.Wt. cut-off 20k Da) at the base of the sample recovery chamber. About 2 mL of the formulation was kept in the outer chamber, and a sample recovery chamber was placed over the sample and centrifuged at 2500 rpm for 30 min. The SLN and the encapsulated drug remained in the outer chamber, and the aqueous phase moved into the sample recovery chamber through the filter membrane. The amount of drug in the aqueous phase was estimated by HPLC.[7] The entrapment efficiency of SLNs was calculated as follows;

Entrapment efficiency (EE) = (Wa-Ws/Wa) x 100

Where, Wa stands for the mass of paliperdone, and Ws is the analyzed weight of drug supernatant.

2.3.3. *In vitro* drug release studies

The release studies were executed using a dialysis membrane with an adequate pore size of 2.4nm, and it was immersed overnight in double distilled water. The drug release of formulations was carried out successively in 0.1N HCl, subsequently by using pH 6.8 in phosphate buffer by open tube approach. In which dialysis membrane was fixed to an open tube (SLNs dispersion) as the donor compartment and buffer (100mL) containing 200mL beaker as receptor compartment, and the temperature was maintained at 37±0.5°C, 2mL sample was withdrawn at the different time interval sampling points up to 24 hrs and replaced with an equal proportion of fresh buffer. The samples were collected and examined by UV-visible spectrophotometer at λmax 280 nm to determine the extent of the drug released.[8]

2.3.4. Stability studies

The paliperidone-loaded solid lipid nanoparticles (optimized formulation PDP 4) were stored at room temperature (25°C/60 ± 5% R.H.) and refrigerated temperature (4°C) for 90 days, and average size, zeta potential, polydispersity index and entrapment efficiency were determined.[9]

2.4. Pharmacokinetic studies

2.4.1. Animals

Healthy Wistar rats (weighing 200-220gm) were exploited for the pharmacokinetic study of the developed formulation. The animals were starved overnight and had available access to water. The animal studies were carried out with earlier acceptance by the Institutional Animal Ethical Committee (IAEC).

2.4.2. Study design and sampling schedule

The animals were divided into two groups (n=6) and administered orally with a fabricated formulation of PDP-SLNs (PDP 4) and coarse suspension of a pure drug at a dose level of 10mg/kg body weight. All the formulations were administered orally with the rat oral feeding tube. At suitable specified time intervals after

oral administration, blood samples were collected at different time interval points by retro-orbital venous plexus puncture method. The blood samples were permitted to clot and centrifuged for 10 min at 12000 rpm. The serum was isolated, conveyed into clean microcentrifuge tubes, and stored at -20°C until HPLC studies.[10]

2.4.3. Calculation of pharmacokinetic parameters

The concentration of PDP-SLNs in rat serum samples was attained from the calibration curve prepared. The pharmacokinetic parameters like C_{max}, T_{max}, AUC and $t_{1/2}$ were measured by Kinetica (2000) software.[11] The following equation determined the relative bioavailability: % Relative BA= (AUC_{SLN} X Dose control/AUC control X Dose ^{SLN}) X100.

3. RESULTS AND DISCUSSION

The present inquiry into the possibility included the Preparation of paliperidone-loaded solid lipid nanoparticles (PDP-SLNs) employing a hot homogenization followed by ultrasonication. Three different lipids were used, each at three distinct doses. The choice and use of lipids and the production method were determined based on previous research findings.

3.1. Particle size, Zeta Potential and Polydispersity index of PDP-SLNs

The particle size measured using the Malvern zeta sizer varied between 210.68 and 296.51 nm in the produced formulations. The PDP 4 formulation, which has a lower size of 210.68 nm, suggests improved stability. The particle sizes of the formulations increased steadily as the lipid content increased. In addition, the Z.P. acts as a reliable measure of SLN formulation stability by evaluating the surface charge and tendency to aggregate. All the formulations are within the range of -26.56 to -32.79 mV, respectively. The presence of the drug leads to a reduction in the surface charge of all the samples being examined, most likely because a portion of the drug is situated on the surface of the lipid nanoparticles. The polydispersity index (PDI) measures particle size homogeneity and varies from 0.0 to 1.0. It indicates the uniformity of particle size within the formulation. The higher the PDI value, the lower the uniformity of the particle size in the formulation. Based on the acquired findings, formulations containing tripalmitin exhibited considerably smaller particle sizes. At the same time, the PDI and Z.P. were favourable compared to the other formulations generated with glyceryl stearate citrate and glyceryl tristearate.[12]

3.2. Entrapment efficiency and assay of PDP-SLNs

In line with the data obtained, all formulations exhibited significant entrapment efficiency, ranging from 68.36% to 79.47%. To attain maximum entrapment efficiency, many variables are altered, such as the lipid type, stirring speed, and duration of stirring.[13] The optimized formulation (PDP 4) showed 74.65%. All the formulations showed assay results ranging from 90.32 mg to 95.47%. The expected results are listed in Table 2.

The optimized formulations (PDP 4) were selected based on obtaining the lowest particle size, the low PDI and good Z.P., the highest entrapment efficiency, and the maximum drug content.

Table 2: Size, Z.P., PDI, E.E. and assay of PDP-SLNs.

Formulation codes	Results of PDP-SLNs (Mean ± SD; n=3)				
	Size (nm)	Z.P. (mV)	PDI	EE (%)	Assay (%)
PDP 1	216.72 ± 3.17	-29.18 ± 1.97	0.214 ± 0.02	69.37 ± 2.13	90.32 ± 2.56
PDP 2	229.41 ± 2.85	-26.56 ± 1.89	0.223 ± 0.04	74.29 ± 2.58	94.61 ± 1.95
PDP 3	241.85 ± 3.02	-27.21 ± 2.13	0.235 ± 0.07	76.04 ± 2.05	91.58 ± 2.48
PDP 4	210.68 ± 2.74	-28.97 ± 2.58	0.208 ± 0.03	74.65 ± 1.97	95.47 ± 1.79
PDP 5	228.54 ± 2.58	-30.14 ± 2.15	0.216 ± 0.09	75.81 ± 2.29	96.83 ± 2.19
PDP 6	245.95 ± 3.29	-31.93 ± 2.71	0.212 ± 0.05	79.47 ± 2.45	93.72 ± 2.84
PDP 7	264.19 ± 3.73	-29.41 ± 2.69	0.217 ± 0.09	68.36 ± 1.84	90.81 ± 2.42
PDP 8	279.82 ± 2.94	-30.52 ± 2.13	0.215 ± 0.06	70.51 ± 2.61	93.69 ± 1.92
PDP 9	296.51 ± 3.01	-32.79 ± 2.02	0.213 ± 0.07	73.18 ± 2.14	94.51 ± 2.05

3.3. *In vitro* drug release of PDP-SLNs

The formulations containing glyceryl stearate citrate, tripalmitin, and glyceryl tristearate exhibited drug release extending from 71.960 to 81.42%, 75.34 to 86.51%, and 67.19 to 79.53%, respectively, for 24 hrs. The fabricated formulation PDP 4 showed higher drug release was found to be 86.51% and release of drug in a sustained manner. Lipid content reduces release by increasing the packing density of lipid molecules within a specific area.[14] The HLB value of polysorbate 80 is 15, which acts as a stabilizer. The optimal 100 mg of polysorbate concentration showed increased drug release from SLNs. The release pattern of all formulations presented a conventional biphasic arrangement with a primary expeditive phase accompanied by a slow phase release pattern observed in phosphate buffer. The primary rapid phase can be because of the burst release of a drug.[15] The release profile of all the formulations is shown in Fig 1.

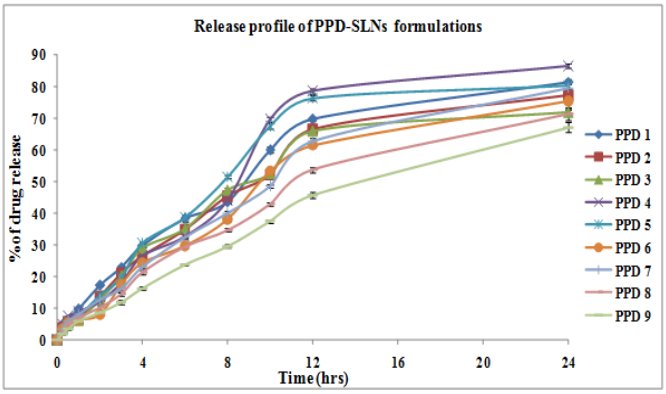

Fig. 1: Release profile of PDP-SLNs formulations (n=3).

3.4. Stability studies

The PDP-SLNs were preserved in a room and refrigerated for 90 days. The characteristics of particle size, Z.P., and PDI were studied, and the results are shown in Table 3. The findings of SLNs (PDP 4) particle size, zeta potential, polydispersity index, and physical appearance of the formulations were nearly identical to the original data, despite minor variations, indicating that they exhibit appropriate stability during storage.[16]

Table 3: Stability studies of formulation PDP-SLNs (PDP 4).

Days	Results of PDP-SLNs (PDP 4) (Mean ± S.D.; n=3)					
	At room temperature (25°C)			At refrigerated temperature (4°C)		
	Size (nm)	PDI	ZP (mV)	Size (nm)	PDI	ZP (mV)
1	210.68±2.74	0.208±0.03	-28.97±2.58	211.46±2.31	0.209±0.04	-29.04±2.11
30	214.51±2.05	0.214±0.05	-30.16±2.14	215.39±2.64	0.215±0.07	-31.49±2.05
60	217.16±2.81	0.219±0.09	-32.82±2.65	218.71±3.02	0.220±0.05	-33.17±1.64
90	219.29±3.46	0.224±0.06	-34.07±2.91	219.87±2.84	0.226±0.02	-35.85±2.83

3.5. *In vivo* pharmacokinetic studies

The pharmacokinetic parameters were determined using non-compartmental methods and Kinetica 2000 software. The optimized PDP-SLNs (PDP 4) were assessed for characteristics such as AUC, C_{max}, T_{max}, MRT, and $t_{½}$ and compared to the coarse suspension. The pharmacokinetic parameters are calculated and shown in Table 4 and Fig 2. The findings indicated that the optimized formulation (PDP 4) had greater C_{max} and $AUC_{0\text{-}24}$ than the pure drug's coarse suspension (PDP). There were notable disparities in the maximum concentration (C_{max}), the area under the curve (AUC), and half-life ($t_{1/2}$) values between PDP 4 and the coarse suspension of PDP. PDP-SLNs (PDP 4) bioavailability is higher than the coarse suspension. The drug's surface area may be increased to boost its solubility and improve its release due to the formulation encased with solid lipid nanoparticles, which facilitate the lymphatic transport of the drug and help prevent its first-pass metabolism.[17] When comparing the delivery of PDP-SLNs (PDP 4) and a coarse suspension, there was a 2.26-fold improvement in relative bioavailability compared to the coarse suspension.

Table 4: Pharmacokinetic studies of paliperidone in Wistar rats.

Parameters	Optimized PDP-SLNs (PDP 4)	Coarse suspension (PDP)
C_{max} (µg/mL)	168.57±4.39***	121.84±4.91
T_{max} (hr)	2	2
AUC(µg/mL).h	2372.38±12.49**	1049.73±9.53
$T_{1/2}$(hr)	15.17±3.72**	6.29±1.85
MRT	19.06±3.41**	7.78±2.48

***significance, **less significance

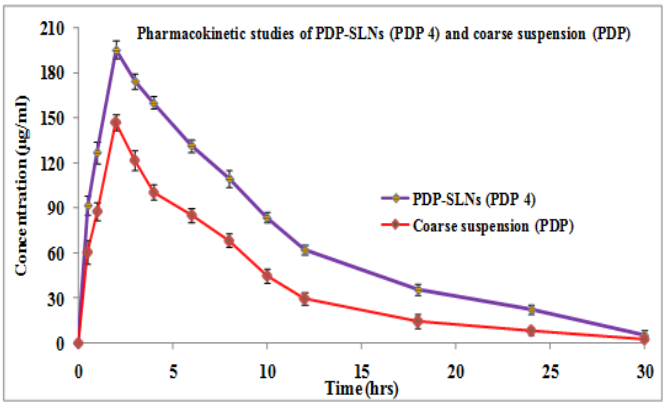

Fig. 2: Pharmacokinetic profile of PDP-SLNs (PDP 4) and coarse suspension (PDP).

4. CONCLUSION

The SLNs play a significant role in the therapeutic area due to their multiple benefits. PDP-encapsulated SLNs were prepared by high-pressure homogenization and ultrasonication, with solid lipids in various quantities. This study used solid lipids to increase PDP solubility by forming them into PDP-loaded SLNs. The optimized formulation of PDP-SLNs (PDP 4) had particle sizes of 210.68 nm, a Z.P. of -28.97 mV, a reduced PDI of 0.208, and a higher E.E. of 74.64%, and it exhibited a higher percentage of drug release, notably 86.51% in 24 hours. In pharmacokinetic investigations, the optimized formulation (PDP 4) showed a 2.26-fold improvement in relative bioavailability compared to the pure drug (PDP) in coarse suspension.

Conflict of Interests

The authors declare that they have no conflict of interest.

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