



Formulation and *In-Vitro* Characterization of Paliperidone Nanosuspension by using Nanoprecipitation

M. Sreenivasulu Reddy, J. Sreeramulu*, Y. Narendra Reddy,
G. Rammohan.

Department of Chemistry, Sri Krishnadevaraya University, Ananthapuram, Andhra Pradesh, India

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Corresponding Author Email: nivasreddy.msc@gmail.com

Abstract

The main aim of present research is to formulate Nanosuspension of Paliperidone to improve the solubility and bioavailability. Paliperidone nanosuspension was prepared by Nano precipitation method using various stabilizers such as SLS, Tween80, Pluronic F127, PVP K30 and methanol. All the prepared formulations entrapment efficacy was found to be in the range of 83.74%-97.15% respectively. IR spectroscopic studies indicated that there are no drug-excipient interactions. When compared to other all the formulations F9 is the best formulation which showed 97.41% of drug released respectively with in 20 min and follows Zero order release kinetics.

Keywords

Paliperidone, SLS, PVP K30, Pluronic F127, Tween 80.

INTRODUCTION:

One of the main problems responsible for the low turnout in the development of new molecular entities as drug formulations is poor solubility and poor permeability of the lead compounds. The increasing frequency of poorly water soluble new chemical entities exhibiting therapeutic activity is of major concern to the pharmaceutical industry. Various formulation parameters that play a crucial role for successful formulation are aqueous solubility, stability at ambient temperature and humidity, photostability, compatibility with solvents and excipients, etc. Of these, solubility is the most important property for developing formulations. A

major hurdle that has prevented the commercialization of many promising poorly soluble drugs is dissolution rate-limited bioavailability.¹⁻⁴ Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 μm in size. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., oral or

intravenous [IV] administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without blockade of the blood capillaries.

MATERIALS AND METHODS

Paliperidone obtained as a gift sample from Euro Biotech, Tween 80, Pluronic F127, SLS, Methanol, PVP K30 and all other chemicals and solvents used are from Rankem, Mumbai.

Preparation of Paliperidone Nanosuspension by nanoprecipitation method:⁶

Nanosuspension were prepared by the precipitation technique. Paliperidone was dissolved in a methanol at room temperature (organic phase). This was poured into water containing different combinations of Tween 80, SLS, Pluronic F127 and PVP-K30 maintained at room temperature and subsequently stirred on magnetic stirrer which is stirred at rpm 2000-3000 for 15 min to allow the volatile solvent to evaporate. Addition of organic solvents by means of a syringe positioned with the needle directly into stabilizer/surfactant containing water. Organic solvents were left to evaporate off under a slow magnetic stirring of the nanosuspension at room temperature for 1 hour followed by sonication for 1 hour.

Evaluation parameters of Paliperidone

Nanosuspensions:⁷⁻¹⁵

Entrapment efficacy:

The freshly prepared nanosuspension was centrifuged at 20,000 rpm for 20 min at 5°C temperature using cool ultracentrifuge. The amount of unincorporated drug was measured by taking the absorbance of the appropriately diluted 5 ml of supernatant solution at 269 nm using UV spectrophotometer against blank / control nanosuspensions. DEE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken.

The entrapment efficiency (EE %) could be achieved by the following equation:

%Entrapment efficiency= Drug content *100/Drug added in each formulation

Scanning electron microscopy: The morphological features of Paliperidone nanosuspension are observed by scanning electron microscopy at different magnifications.

In vitro drug release study: The dialysis membrane diffusion technique was used. One millilitre of the nanosuspensions was placed in the dialysis membrane (Mw cutoff 12,000–14,000 Hi-media), fixed in a Kiserly apparatus of surface area and receptor volume of 20 ml. A solvent system of pH 6.8 buffer was used as receptor medium. The entire system was kept at 37 °C with continuous magnetic stirring at. Samples (1 ml) were withdrawn from the receptor compartment at predetermined time intervals and replaced by fresh medium. The amount of drug dissolved was determined with UV spectrophotometry at 269 nm.

The results of in vitro release profiles obtained for the NDDS formulations were fitted into

Four models of data treatment as follows:

1. Cumulative percent drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining versus time (first-order kinetic model).

RESULTS AND DISCUSSION

Paliperidone is a BCS class-II drug having low solubility and high permeability. Thus, it is challenging to enhance the solubility of Paliperidone particles in an aqueous solution. Nano precipitation method has been employed to produce nanosuspension of Paliperidone. The different formulative variables (1) amount of Pluronic F127 or PVP K30 (2) amount of Tween 80 or sodium lauryl sulphate and organic to aqueous solvent ratio were contributed much towards the change in particle size in nanosuspension preparation. Determination of Paliperidone λ -max was done in pH 6.8 phosphate buffer medium for accurate quantitative assessment of drug dissolution rate. The λ -max was found to be 269 nm, i.e., at its absorption maxima. Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The entrapment efficacy of the formulated Nanosuspension was found to be in the range of 83.74%-97.15% respectively.

Average particle size of nanosuspension of optimized formulations (F9) was found to be 130nm The in vitro drug release studies were compared for F1 to F9 formulations. Among all the three stabilizers we have used F9 containing Pluronic F127 at 0.75% concentration releases maximum drug release at the end of 20 mins, when compared to the formulations prepared by using SLS and PVP K30.

Increase in the stabilizer concentration of Pluronic F127 shows 97% of drug release as Pluronic F127 is a hydrophilic polymer, so the formulations prepared

by using Pluronic F127 releases more drug release at the end of 20mins than the other stabilizers.

Table-1: Composition of Nanosuspension of Paliperidone

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Paliperidone	120	120	120	120	120	120	120	120	120
SLS (%)	0.25	0.5	0.75	--	---	--	--	--	--
PVP K30(%)	--	--	--	0.25	0.5	0.75	--	--	--
Pluronic F127(%)	--	--	--	--	--	--	0.25	0.5	0.75
Tween-80	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Methanol (ml)	10	10	10	10	10	10	10	10	10
Water (ml)	100	100	100	100	100	100	100	100	100

Table 2: Entrapment efficiency of formulated Nanosuspensions:

Formulation code	Mean % entrapment efficiency
F1	83.74±0.15
F2	85.16±1.26
F3	89.02±0.44
F4	90.10±0.26
F5	93.32±0.02
F6	92.52±0.14
F7	91.14±0.19
F8	95.26±0.54
F9	97.15±0.04

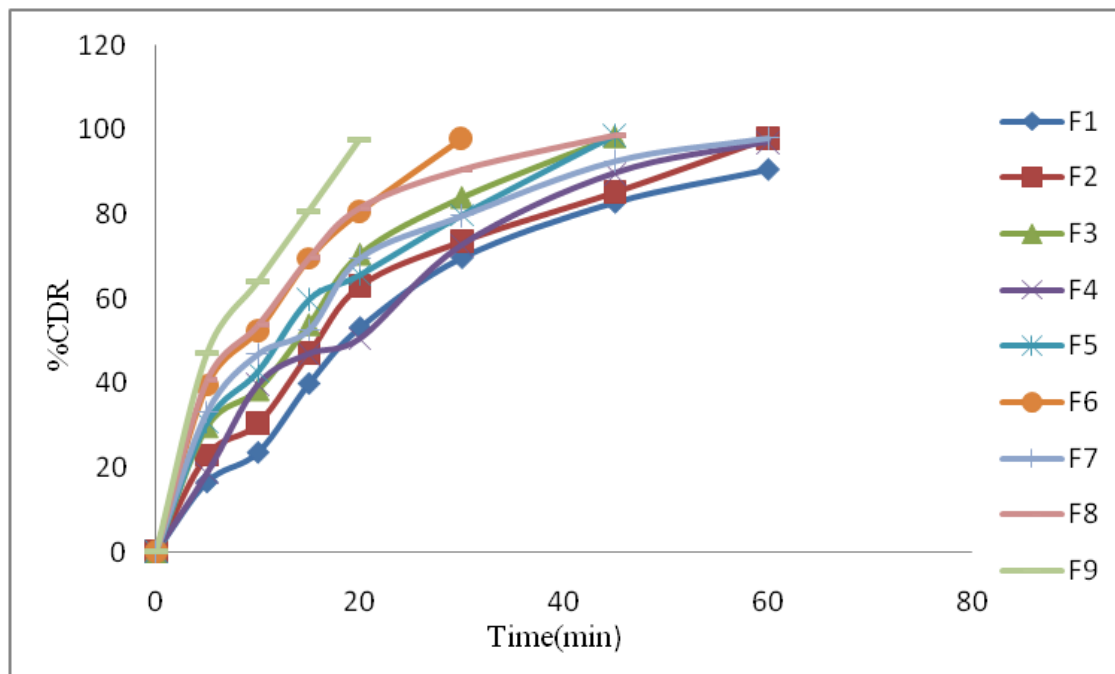


Fig 1: In vitro dissolution profiles of Paliperidone Nanosuspensions

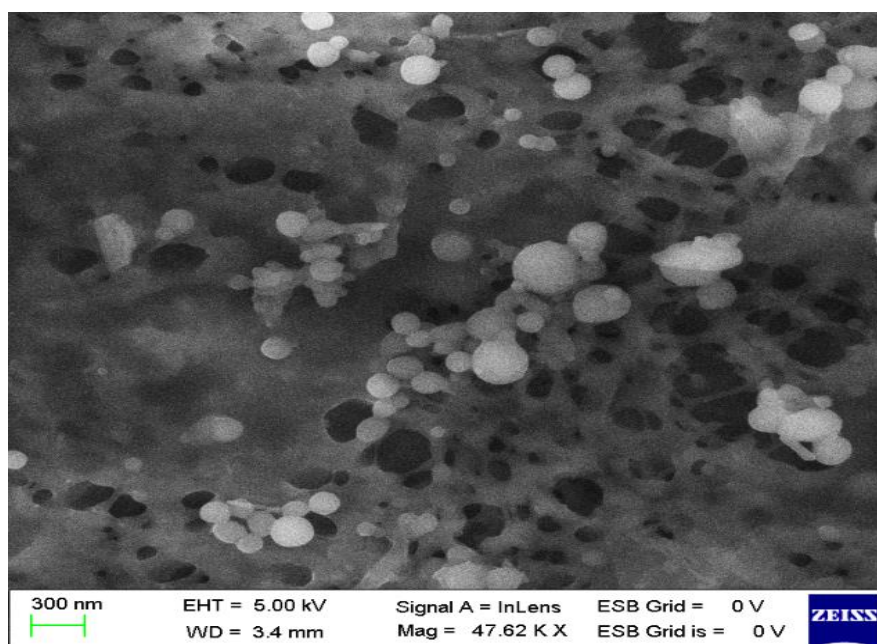


Fig 2: SEM analysis of Optimized formulation

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-15.8 mV	-0.000122 cm ² /Vs
2	--- mV	--- cm ² /Vs
3	--- mV	--- cm ² /Vs

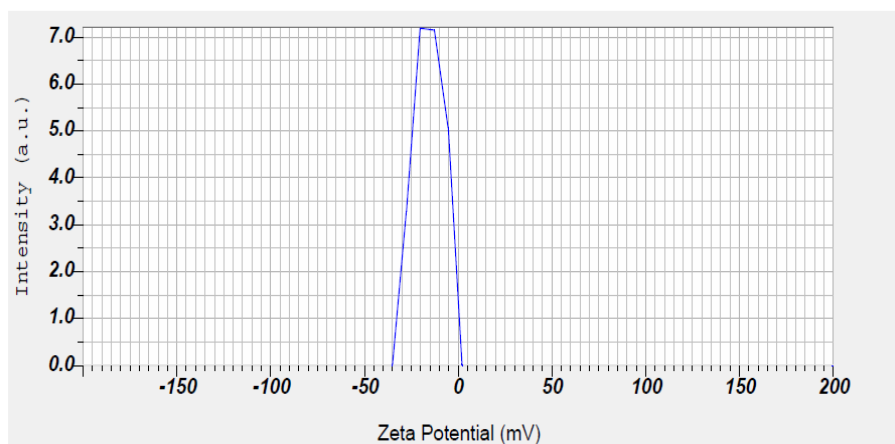


Fig.3: Zeta potential of Optimized formulation

CONCLUSION:

Oral Nanosuspension of Paliperidone by Solvent evaporation method using various polymers such as SLS, Tween-80, PVP K30, Pluronic F127 and methanol. All the prepared formulations were found to be having entrapment efficiency within acceptable limits in the range of 83.74%-97.15% respectively. As the stabilizer concentration increases, the drug release time decreases, whereas Nanosuspension strength increases. Optimized formulations of Nanosuspension displayed zero order release

kinetics and drug release. IR spectroscopic studies indicated that there are no drug-exipient interactions. When compared to other all the formulations F9 is the best formulation which showed 97.41% of drug released respectively with in 20 min and follows Zero order release kinetics and zeta potential value shows -15.8mv.

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