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IP International Journal of Comprehensive and Advanced Pharmacology

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Review Article

# Formulation, optimization and evaluation of self nanoemulsifying drug delivery system of paliperidone

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ARTICLE INFO

*Article history:*
Received 23-03-2022
Accepted 18-04-2022
Available online 23-08-2022

*Keywords:*
Paliperidone
Labrafil
Emulsification time
Formulation

ABSTRACT

Paliperidone is a BCS-II drug. It means paliperidone is poorly water soluble and hence shows problem in absorption as well as permeation through GIT which together contributes for its lower oral bioavailability. Paliperidone as drug, oil oleic acid, surfactant labrasol and co surfactant labrafil m 1944 were taken and formulation were done. From the emulsification time study as the concentration of Smix increases emulsification time decreases. Further emulsification time study I found that F3 has the lowest emulsification time. From the dissolution study it was observed that Q30 is above 85% obtained for formulation F3 and F6 that is 93.75 & 91.25. This can be due to the higher concentration of Smix present in formulation F3 & F6 since mean cumulative % drug release at 30min (Q30) is highest for F3 formulation and it was selected for optimized formulation. As in the DSC study thecrystalline property of Paliperidone is lost and it becomes amorphous. In the FT-IR study there is no significance sifting of characteristic peak. Hence there is no incompatibility between drug and excipient.



## 1. Introduction

Microemulsions are clear, thermodynamically stable, isotropicliquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phasemay contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form uponsimple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The three basic types of microemulsions are direct (oil dispersed in water, o/w), reversed (water dispersed in oil, w/o) and bicontinuous.[1]

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactantmoleculesmay form a monolayerat the interface between the oil and water, with the hydrophobictails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. Various theories concerning microemulsion Formation,[2] stability and phase behavior have been proposed over the years. For example, one explanation for their thermodynamic stability is that the oil/water dispersion is stabilized by the surfactant present and their formation involves the elastic properties of the surfactant film at the oil/water interface, which involves as parameters, the curvature and the rigidity of the film. These parameters may have an assumed or measured pressure and/or temperature dependence (and/or the salinity of the aqueous phase), which may be used

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https://doi.org/10.18231/j.ijcaap.2022.024

to infer the region of stability of the microemulsion,[3] or to delineate the region where three coexisting phases occur, for example. Calculations of the interfacial tension of the microemulsion with a coexisting oil or aqueous phase are also often of special focus and may sometimes be used to guide their formulation. Microemulsions also have industrial applications, one of them being the synthesis of polymers.Microemulsion polymerization[4] is a complex heterogeneous process where transport of monomers, free radicals and other species (such as chain transfer agent, co-surfactant and inhibitors) between the aqueous and organic phases, takes place. Compared with other heterogeneous polymerization processes (suspension or emulsion) microemulsion polymerization is a more complicated system. Polymerization rate is controlled by monomer partitioning between the phases, particle nucleation, and adsorption and desorption of radicals. Particle stability is affected by the amount and type of surfactant and pH of dispersing medium. It is also used in the process of creating nanoparticles. The kinetics of microemulsion polymerization has much in common with emulsion polymerization kinetics, the most characteristic feature of which is the compartmentalization, where the radicals growing inside the particles are separated from each other, thus suppressing termination to a high extent and, as a consequence, providing high rates of polymerization.

## 2. Nanoemulsion

Nanoemulsion has been identified as a promising delivery system for various drugs including biopharmaceuticals. Nanoemulsion is a heterogeneous system composed of one immiscible liquid dispersed as droplets within another liquid. The droplets size of nano emulsion is between 20 to 500 nm. Diameter and surface properties of droplets of nanoemulsion plays an important role in the biological behavior of the formulation. Small droplet sizes lead to transparent emulsions so that product appearance is not altered by the addition of an oil phase. In this paper various aspects of nanoemulsion have been discussed including advantages, disadvantages and methods of preparation. Furthermore new approaches of stability of formulation, effect of types and concentration of surfactant, process variables and method are also discussed to improve the stability of nanoemulsion formulation.[5]

### *2.1. Self -nanoemulsifying drug delivery system (SNEDDS)*

Self-emulsifying drug delivery systems (SEDDS) are regarded as a potential implement for oral delivery of water insoluble APIs to overcome their poor and irregular bioavailability. The correlation between the physicochemical parameters and the behavior of self-emulsifying drug delivery systems was established. The objective of this study was to summarize these physicochemical factors characterized SEDDS. Determination of self-emulsifification process and ternary phase diagram are the basis of preparations. The position of APIs in SEDDS inclusion can be determined by dye solubilisation test. The end point of self-emulsifification was controlled by turbimetric evaluation. Optimisation of droplet size and zeta potential are crucial parameters because they can inflfluence i.e. the dissolution rate of APIs and the stability of SEDDS. Besides the basic methods in the characterization of SEDDS such as dispersibility tests, turbidimetric evaluation, viscosity tests, determinations with complex instruments such as photon correlation spectroscopy or dynamic light-scattering, electro kinetic potential measurement, non-destructive spectroscopic techniques (LFDS, FTIR, RS) and various microscopic techniques (SEM, PLM, EDS) has also been described**.**[6]

1. Self-emulsifying drug delivery system (SEDDS): Droplets size is more than 600 nm**.**
2. Self-microemulsifying drug delivery system (SMEDDS): Droplets sizes lies between 100- 150 nm.
3. Self-nanoemulsifying drug delivery system (SNEDDS): Droplets of nanosized i.e. lies between 10-100 nm.

### *2.2. Advantages of self-nanoemulsion as a delivery system*

1. When compared with emulsions, which are sensitiveand metastable dispersed forms, SNEDDS are physically stable formulations.[7]
2. They are characterized by excellent stability, circumventing the stability problem of solid lipid nano-particles and liposomes.
3. Bioavailability from SNEDDS was higher than oils and surfactant dispersions.[8]

### *2.3. Disadvantages of nanoemulsion as a delivery system*

1. Limitation of the lipid excipients
2. Stability solely dependent on the lipid stability
3. For the formulation stability, one should have to select only synthetic oils
4. Delivery system needs large amount of surfactants,[9,10] which ultimately leads to toxic effect on the GI mucosa
5. It faces the dispensing problems

## 3. Drug Profile

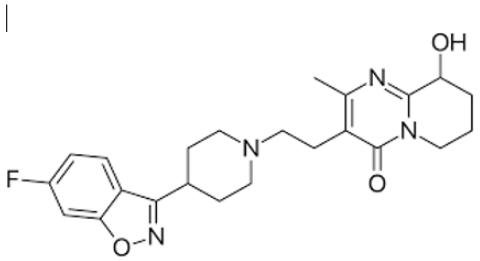
### *3.1. Paliperidone*

#### *3.1.1. Description*

Paliperidone is the primary active metabolite of risperidone. The mechanism of action is unknown but it is likely to act

via a similar pathway to risperidone. It has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism. Paliperidone is also active as an antagonist at alpha 1 and alpha 2 adrenergic receptors and H1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone was approved by the FDA for treatment of schizophrenia on December 20, 2006.

*3.1.2. Structure*



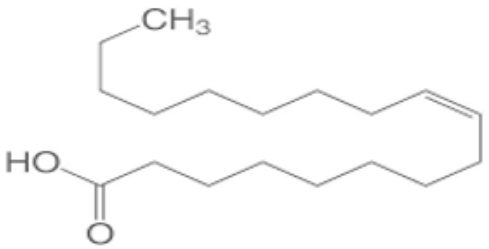

**Chemical formula** C23H27FN4O3
**Weight:** 426.4839
**Indication:** For the treatment of schizophrenia.
**Pharmacology:** Paliperidone is an atypical antipsychotic developed by Janssen Pharmaceutica. Chemically, paliperidone is primary active metabolite of the older antipsychotic risperidone(paliperidone is 9-hydroxyrisperidone). The mechanism of action is unknown but it is likely to act via a similar pathway to risperidone.

## 4. Excipient Profile

### *4.1. Labrafil m 1944 cs*

*4.1.1. Description*

A nonionic water-dispersible surfactant for lipid-based formulations to solubilize and increase oral bioavailability of poorly water-soluble APIs. Self-emulsifies in aqueous media forming a coarse dispersion, i.e., emulsion (SEDDS). Co-emulsifier in topical formulations to improve stability of emulsions.




**Full Name:** Oleoyl polyoxyl-6 glycerides
**Composition:** Consists of mono-, di- and triglycerides and PEG- 6 (MW 300) mono- and diesters of oleic (C18:1) acid
**Product Form:** liquid
**Viscocity (mPa s):** 75 – 95 (20°C)
HLB: 9

## 5. Main Functionalities

Solubilizer for poorly-soluble API and bioavailability enhancer Single excipient formulation system: self-emulsifies in aqueous fluid into emulsion – LFCS type II (SNEDDS) Combine with Labrasol®ALF or Gelucire® 44/14 for LFCS Type III (SNEDDS) Co-emulsifier in topical formulations often associated with Tefose® 63 in antifungal cream Safety of use is supported by substantial toxicological data and precedence of use in approved pharmaceutical products.

## 6. Experiment

### *6.1. Physical properties **of** drug*

The gifted pure drug sample of Paliperidone was initially characterized for its color, order, melting point, solubility in different solvents.

### *6.2. Standard graph of Paliperidone in 0.1N HCl*

Paliperidone stock solution (1000 $\mu$g/ml) was prepared by dissolving accurately weighed 100 mg of drug in 100 ml 0.1N HCl. 5 mL of this stock solution was taken out into a 50 mL volumetric flask and volume was made up to the mark with 0.1N HCl in order to get working standard solution having concentration 100 $\mu$g/ ml. From the above working standard solution (100 $\mu$g/mL), aliquots of sample ranging from 0.5 to 2.5 ml were transferred into a series of 10 mL volumetric flasks and volumes were adjusted up to the mark by the diluents (0.1N HCl) to get the optimum concentrations of 5 to 25 $\mu$g/ml.

### *6.3. Solubility*

The solubility of Paliperidone was determined in distilled water, Phosphate buffer solution of pH 6.8, Methanol, Ethanol, 0.1N NaOH and 0.1N HCl. An excess amount of drug was added to 10 mL of different solvents. The contents were shaken continuously for 24 h at $37^0$C and allowed to equilibrate [Sachan et al., 2016]. After 24 h, the sample were withdrawn and filtered through membrane filter and the filtrate were suitably diluted with an appropriate solvent and analyzed spectrophotometrically at 271 nm with reference to a corresponding calibration curve. Each experiment was done in triplicate and the equilibrium solubility was recorded.

The solubility of Paliperidone in various oil, surfactants and co-surfactant was determined by adding excess amounts of drug in 1 ml of oils/surfactants in small micro centrifuge tube. The tubes were closed and were continuously shaken

to reach equilibrium for 48 h at $25^0$C in a water bath shaker. After that, the mixtures were centrifuged using High Speed cooling Centrifuge at 6000 rpm for 20 min at $4^0$C. The supernatant was separated, diluted with 0.1N HCl and solubility was quantified by UV Spectrophotometer at 271 nm

**Table 1:** List of liquid lipids and surfactants used in experiments

| Surfactant | Co- surfactant | Oil |
|---|---|---|
| Tween 80 | Labrafil m 1944 | Oleic acid |
| Labrasol | Peg 200 | |

The self-emulsifying formulations consisting of oil, surfactants, co-surfactants, and drug to produce a clear and monophasic liquidat ambient temperature when introduced to aqueous phase and have good solvent properties to allow presentation of the drug in solution (Kommuru et al., 2001). Screening of excipients can be done by determining the saturation solubility of vardenafil in different oils, surfactants and co surfactants. An excess quantity of drug was added to the 2.0 ml of excipients in 5 ml vial. Both the components were mixed in a vial for 5min using CM101, Cyclomixer (Remi, Mumbai, India). The mixtures in vials were shaken for 48h using RS 12 R Rotary shaker (Remi, Mumbai, India). After solubilization some extra amount of drug was added to drug-excipient mixture. The process repeat till saturation solubility of vardenafil reached, which was indicated by presence of undissolved drug at the bottom of vial. The mixtures were kept at room temperature for 24h and centrifuged using RM-12C B2 Bench top-centrifuge (Remi motors, Mumbai, India) at 2800 rpm. The supernatant was separated and paliperidone was extracted in 100ml 0.1N HCL. The drug content was analyzed using Shimadzu-1800 UV visible spectrophotometer at 271 nm.

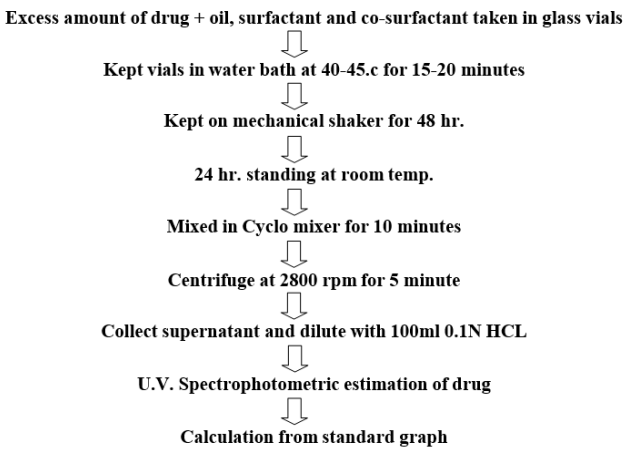



**Fig. 1:** Schematic presentation of the process of solubility study

### *6.4. Formulation of Paliperidone S-SNEDDS*

SEDDS formulations were prepared using oleic acid, labrasol, labrafil m 1944 as oil, surfactant and cosurfactant (smix), respectively. The composition of the formulations is represented in Table 1. Accurately weighed amount of paliperidone (3 mg) was placed in a centrifuge tube containing oil, surfactant and co-surfactant mixture. The obtained SEDDS formulations were stored at room temperature until used.

**Table 2:** Composition of various SEDDS formulation containing paliperidone

| Components (% w=w) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Oleic Acid | 10mg | 10mg | 10mg | 20 mg | 20mg | 20mg |
| Labrasol | 10mg | 15mg | 20mg | 10 mg | 15mg | 20mg |
| Labrafil m 1944 | 10mg | 15mg | 20mg | 10 mg | 15mg | 20mg |
| Neusilin | 30mg | 40mg | 50mg | 40 mg | 50mg | 60mg |

All the formulations contain 3 mg of paliperidone.

### *6.5. Preparation of Solid SEDDS*

Optimized SEDDS formulation containing oleic acid, labrasol and labrfi m 1944 was adsorbed onto neusilin to produce solid SEDDS (SEDDS-N). Neusilin was placed in a small bowl and blended with SEDDS formulation and mixed vigorously to get the granular mass. Further the resultant free flowing powder was passed through sieve no. 120 to get uniform particle size and was stored in a desiccator until further evaluation.

## 7. Evaluation

### *7.1. Emulsification time (ET)*

All the formulations were taken in USP dissolution apparatus II using in 900ml of 0.1N HCl at $37^0$ C with 50 rpm rotation speed.The emulsification time was measured by visual inspection andwas recorded.

### *7.2. Cumulative % Drug release at 30 min (Q30)*

All the formulations were taken in USP dissolution apparatus II. The dissolution study was performed in 900ml of 0.1N HCL at $37^0$ C with 50 rpm. Then the sampling is been taken in 15min, 30min, 45min,60min, 90min, 120min. After the completion of the dissolution the sample were taken to the UV spectroscopy to record the absorbance at 271 nm. From the dissolution profile Q30 of each of the formulation were determined.

### 7.3. Solid state characterization

#### 7.3.1. Differential scanning calorimetry (DSC) study

The DSC measurements were performed on a DSC-60 (Shimadzu, Japan) with a thermal analyzer. All samples (about 2 mg) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of $10^0$C/min from 25 to $250^0$C. An empty aluminum pan was used as reference. DSC study of drug alone as well as its physical mixtures with carriers was carried out.

#### 7.3.2. FT-IR spectroscopy study

Interactions of drug with other polymers were assessed by FT-IR spectroscopy. FT-IR spectra of Paliperidone and its physical mixtures (PM) were recorded on IRAffinity-1, (Shimadzu, Japan) using KBr discs. The instrument was operated under dry air purge and the scans were collected at a scanning speed of 2 mm/s with resolution of 4 $cm^{-1}$ over the region 4000–400 $cm^{-1}$. FT-IR study of drug alone, its physical mixture and freeze dried optimized formulation was carried out.

## 8. Results and Discussion

### 8.1. Physicochemical characterisation of Drug

Colour – White
Order – Order less

Solubility - Slightly soluble in dimethylformide; sparingly soluble in 0.1 N HCl, Methylene chloride; practically insoluble in water,hexane,0.1 N NaOH.

### 8.2. Standard curve of Paliperidone in different media

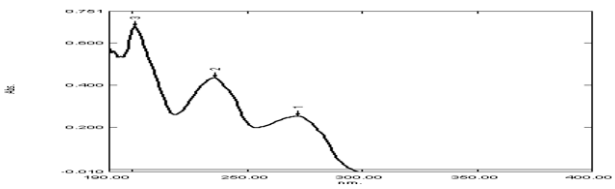


**Fig. 2:** Absorption spectrum of Paliperidone (10$\mu$g/mL) in 0.1N HCl

**Table 3:** Calibration curve data of Paliperidone in 0.1N HCl at 271 nm

| Concentration ($\mu$g/mL) | Absorbance |
|---|---|
| 2 | 0.108 |
| 5 | 0.221 |
| 10 | 0.536 |
| 15 | 0.768 |
| 20 | 0.956 |

**Table 4:** Results of calibration curve of Paliperidone in different medium

| Solvent medium | $\lambda$max (nm) | Equation | $R^2$ value |
|---|---|---|---|
| 0.1 N HCl | 271 | y = 0.0048x - 0.0010 | 0.992 |

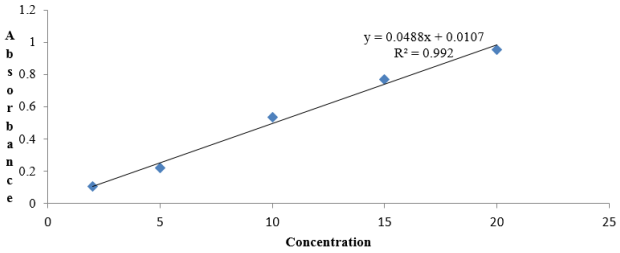



**Fig. 3:** Standard graph of Paliperidone in 0.1N HCl

### 8.3. Solubility study

**Table 5:** Solubility (mg/ml) of paliperidone in different solvents

| S.No. | Solvent | Solubility (Mg/Ml) |
|---|---|---|
| 1 | PB(pH- 6.8) | 0.124 |
| 2 | Ethanol | 0.561 |
| 3 | 0.1N HCl | 4.711 |
| 4 | Methanol | 1.545 |
| 5 | 0.1N NaOH | 1.136 |
| 6 | Water | 0.196 |

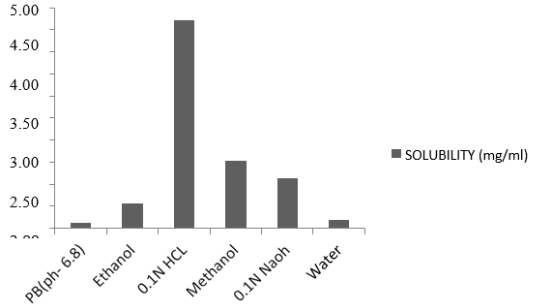



**Fig. 4:** Graphical representation of solubility (mg/ml) of paliperidone in different solvents

**Table 6:** Solubility (mg/ml) of paliperidone in different medium (oil, surfactant and co- surfactant)

| S.No. | Solvent | Solubility(mg/ml) |
|---|---|---|
| 1 | Tween 80 | 1.086 |
| 2 | Peg 200 | 0.561 |
| 3 | Labrafil m 1944 | 4.00 |
| 4 | Oleic acid | 8.00 |
| 5 | Labrasol | 2.00 |

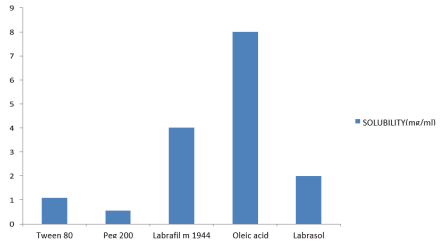



**Fig. 5:** Graphical representation of solubility (mg/ml) of paliperidone in different medium

## *8.4. Evalution*

### *8.4.1. Emulsification time (ET)*

If the value of F2, F3, F6 has emulsification time less than 1min where as other formulations having emulsification time more than 1min. As the concentration of Smix increases emulsification time decreases. Further emulsification time study I found that F3 has the lowest emulsification time.

**Table 7:** Table showing emulsification time

| Formulation | Emulsification time (s) |
|---|---|
| F1 | 85 |
| F2 | 54 |
| F3 | 22 |
| F4 | 125 |
| F5 | 65 |
| F6 | 35 |

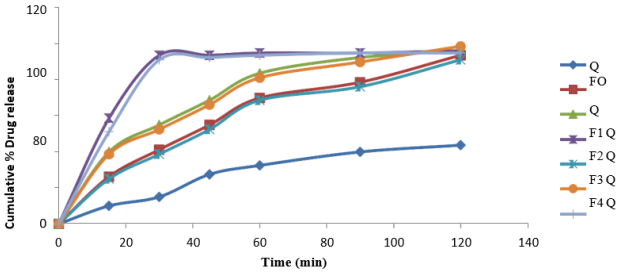



**Fig. 6:** The dissolution study

It was observed that Q30 is above 85% obtained for formulation F3 and F6 that is 93.75 & 91.25. This can be due to the higher concentration of Smix present in formulation F3 & F6 since mean cumulative % drug release at 30min (Q30) is highest for F3 formulation and it was selected for optimized formulation.

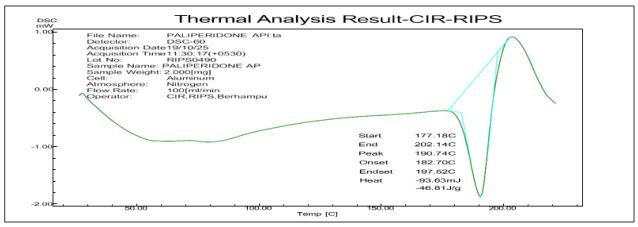



**Fig. 7:** DSC thermogram of pure Paliperidone drug

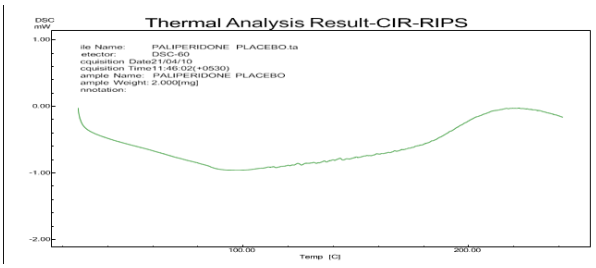



**Fig. 8:** DSC thermogram of Placebo

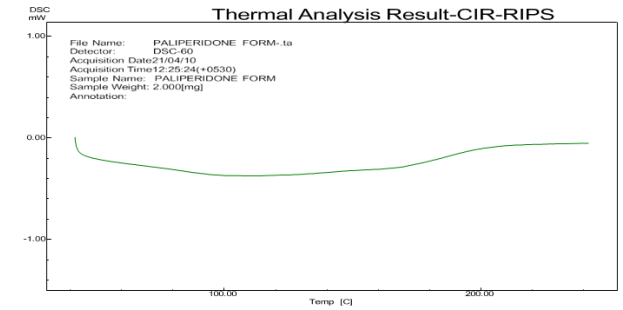



**Fig. 9:** DSC thermogram of Formulation

## *8.5. Solid state characterization*

### *8.5.1. Differential scanning calorimetry (DSC) study (Figures 7, 8 and 9)*

## *8.6. FT-IR spectroscopy study(Figures 10, 11 and 12)*

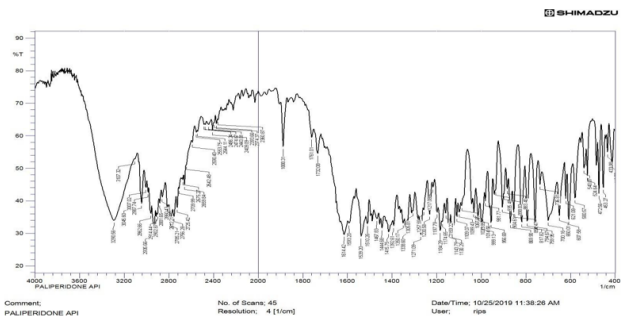



**Fig. 10:** FT-IR spectra of pure paliperidone drug

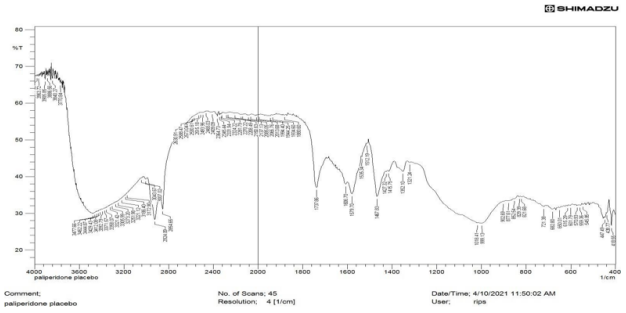



**Fig. 11:** FT-IR spectra of placebo

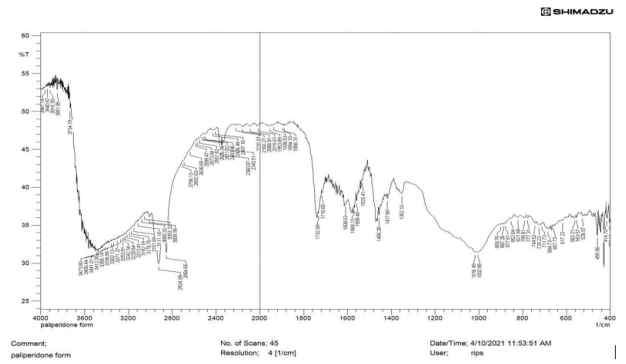



**Fig. 12:** FT-IR spectra of Formulation

## 9. Conclusion

As per Bio-pharmaceutical classification system, Paliperidone is a BCS-II drug. It means paliperidone is poorly water soluble and hence shows problem in absorption as well as permeation through GIT which together contributes for its lower oral bioavailability. To solve this problem, The Self Emulsifying Formulation (SEFs) is a promising method to solve that problem. In this formulation different combination of oil, surfactant, co surfactants are taken in different proportion having different HLB value to prepare a stable and effective formulation of nano sized globule. In the above topic "Formulation Optimization and evaluation of Self Nano Emulsifying Drug Delivery System of Paliperidone" as drug, oil (oleic acid), surfactant (Labrasol) and co surfactant (Labrafil M 1944) were taken and formulation were done. From the emulsification time study as the concentration of Smix increases emulsification time decreases. Further emulsification time study I found that F3 has the lowest emulsification time. From the dissolution study it was observed that Q30 is above 85% obtained for formulation F3 and F6 that is 93.75 & 91.25. This can be due to the higher concentration of Smix present in formulation F3 & F6 since mean cumulative % drug release at 30min (Q30) is highest for F3 formulation and it was selected for optimized formulation. As in the DSC study thecrystalline property of paliperidone is lost and it becomes amorphous. In th FR-IR study there is no significance sifting of characteristic peak Hence there is no incompatibility between drug and excipient.

Paliperidone loaded snedds formulations could be a potential oral pharmaceutical product with high drug-loading capacity, improved drug dissolution, increased gut permeation and enhanced oral bioavailability.

## 10. Acknowledgement

Sincerely thank the SIMS College of Pharmacy and Management for providing me the requirements.

## 11. Source of Funding

None.

## 12. Conflicts of Interest

No conflicts of interest.

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**Cite this article:** Lakshmi V, Sunitha N, Babu SM. Formulation, optimization and evaluation of self nanoemulsifying drug delivery system of paliperidone. *IP Int J Comprehensive Adv Pharmacol* 2022;7(3):115-122.