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Physico-Chemical Characterization of Paliperidone Palmitate and Compatibility Studies with its Pharmaceutical Excipients

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Authors' contributions

This work was carried out in collaboration among all authors. Author RRN designed the study. Author PP performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SPM managed the analyses of the study. Author PA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The main aim of the present study was to characterize and perform the compatibility studies of paliperidone with its excipients.
Study Design: Physico-chemical characterization and compatibility studies.
Place and Duration of the Study: Chalapathi Drug Testing Laboratory, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, Lam, Guntur-522034 between December 2020 and January 2021.
Methodology: Physico-chemical characterization and compatibility studies of paliperidone palmitate with its excipients like HPMC, lactose, magnesium stearate, talc, microcrystalline cellulose was done using the FTIR spectrophotometer, Scanning electron microscopy, X-ray diffraction, Differential scanning calorimeter.
Results: Interaction of the paliperidone palmitate with its excipients were studied by this technique. Paliperidone palmitate showed the transition at 117.92^0C with the specific heat of 101.9J/g. The IR

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spectrum of paliperidone palmitate and excipients mixture has shown a characteristic stronger band of the N-H at 3412.75cm^{-1}, C-H at 2921.98 cm^{-1}, stretching vibrations of C=O at 1737.47 cm^{-1}, C=C at 1651.94 cm^{-1}, N-O at 1541.16 cm^{-1} followed by C-F at 1160.46 cm^{-1}. XRD showed good crystalline properties with relative crystallinity index of 60.01%. The photomicrographs obtained by SEM did not evidence any interaction between paliperidone palmitate and the excipients, providing visual support for the results.

Conclusion: There were no interactions of drug with selected excipients and found to be compatible. Therefore, it is a mandatory clause for the compound compatibility with various excipients in the formulation which affect the stability and efficacy of the formulation.

Keywords: Paliperidone palmitate; DSC; TG; IR; XRD and SEM.

1. INTRODUCTION

Paliperidone palmitate Fig. 1, paliperidone palmitate is a psychotropic agent belongingto the chemical class of benzisoxazole derivatives. The chemical name is (9RS)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidin-1-yl] ethyl] -2-methyl4-oxo-6,7,8,9-tetrahydro- 4H -pyrido [1,2-a] pyrimadin-9-yl hexadecanoate. The molecular formula of paliperidone palmitate is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol and slightly soluble in ethyl acetate [1,2].

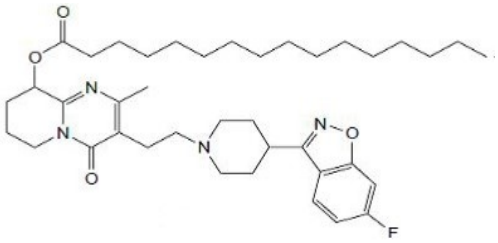

Fig. 1. (±) Paliperidone palmitate

Thermal techniques are used for analysis of pharmaceuticals and excipients. Different techniques include differential scanning calorimetry (DSC), differential thermal analysis (DTA) and crystallographic technique like X-ray diffraction and scanning electron micros copy (SEM) in which substances are analysed based on their physical properties reactions with the temperature and are measured by temperature difference [3-5].

Drug-excipient compatibility studies during the formulation development is a significant process in getting to know about the physical and chemical interaction between the substance and excipients [6-8]. This process of knowing the in compatibility, by comparing the thermal curves of substance with pharmaceutical excipients used in formulation in the ratio of 1:1 for their evaluation. Infrared spectrophotometer is used for the characterization of the compounds and excipients [9-11]. It is done based on the analysis of functional groups present in the compound and in excipients. XRD was used in knowing the crystal structure and properties of the molecule and also lattices in the molecule, whereas SEM was used to identify problems with particle size and shape of the molecule [12,13].

2. MATERIALS AND METHODS

2.1 Materials

Paliperidone palmitate bulk material was procured from Merck. The tested pharmaceutical excipients were procured from local vendor national scientific products.

2.2 Instrument

Differential scanning calorimeter manufactured by TA instruments of Q20 model was used for the studies by using TA instrument explorer and TA universal analysis software's under nitrogen atmosphere with the flow rate of 10 mL/min. Approximately 2 mg of samples were weighed and sealed in the aluminium pans. The temperature program was given from 30 to 300°C at a heating rate of 10°C/min.

Infrared spectrophotometer manufactured by Bruker of Alpha model was used for the characterization of compounds using OPUS software.

2.3 Preparation of Physical Mixtures

The study for the interactions was performed by using a physical mixture of paliperidone palmitate and excipients of equal proportions (1:1 W/W). The mixtures were prepared in the way of simple

mixing using the motor and pestle, weighed of required quantity and were sealed in the aluminium pans for the analysis.

3. RESULTS AND DISCUSSION

3.1 Characterization and Compatibility Studies

The DSC curve obtained for paliperidone palmitate are shown in Fig. 2. The DSC curve has shown a sharp endothermic curve at (T_{Peak}=117^{0}C; T_{Onset}=116^{0}C; DH_{Fusion}=101.9Jg^{-1}), corresponding to melting point followed by decomposition. The DSC data allow evidencing a thermal stability upto 180°C. Also small broad exothermic peak was seen from 210-260^{0}C which indicates the oxidation and followed by decomposition from 260°C.

The IR spectrum of paliperidone palmitate has shown in Fig. 3, a characteristic stronger band of the N-H at 3412.75 cm^{-1}, C-H at 2921.98 cm^{-1}, stretching vibrations of C=O at 1737.47 cm^{-1}, C=C at 1651.94 cm^{-1}, N-O at 1541.16 cm^{-1} followed by C-F at 1160.46 cm^{-1}.

In fact, DSC has been proposed to be a rapid method for evaluating physic chemical interactions between components of the formulation through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 physical mixture and therefore select adequate excipients with suitable compatibility.

DSC curve of paliperidone palmitate / HPMC / lactose / magnesium stearate / talc/ microcrystalline cellulose has shown in Fig. 4 as an endothermic event of melting point of paliperidone palmitate in the range of 147-151^{0}C, followed by melting point at 116.40°C. Finally, the result showed that the absence of movement of the melting drug transition suggests there were no covalent or other strong interactions with that of its excipients. Hence it is was compatible with that of its excipients.

IR spectroscopic studies has been applied as a supplementary technique to investigate drug excipient interaction and to conform the results obtained from the thermal analysis [14,15]. It is the most suitable technique of nondestructive spectroscopic methods and has become an attractive method in the analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample preparation, therefore preventing solid state transformations [11,3]. The appearance of new absorption bands, broadening of bands and alteration in intensity is the main characteristics to evidence interactions between drug and excipients.

The spectra of the drug and all excipients used in this study were obtained for pure compounds as well as binary mixtures (1:1 mass/mass) in order to identify a possible chemical interaction between them.

The IR spectrum of paliperidone palmitate and excipients mixture was shown in Fig. 5 with a characteristic stronger band of the N-H at 3392.85cm^{-1}, stretching vibrations of C-H at 2920.31 cm^{-1}, C=O at 1737.37 cm^{-1}, C=C at 1652.18cm^{-1}, and C-F at 1021.37 cm^{-1}. Moreover, the spectra of binary mixtures can be considered as the superposition of the individual ones without absence, shift or broadening in the vibration bands of paliperidone palmitate.

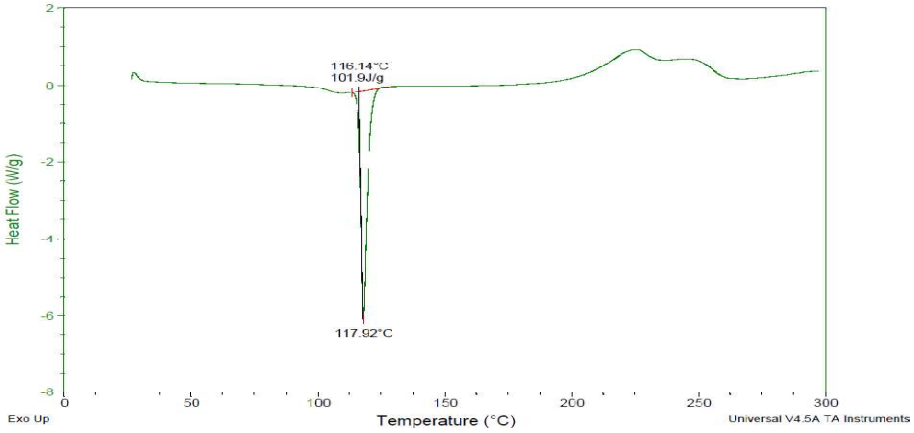

Fig. 2. DSC of paliperidone palmitate

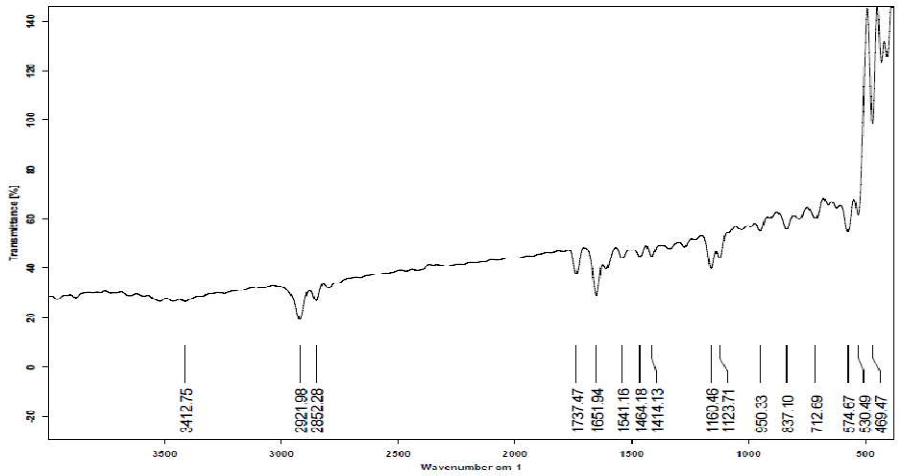

Fig. 3. IR spectrum of paliperidone palmitate

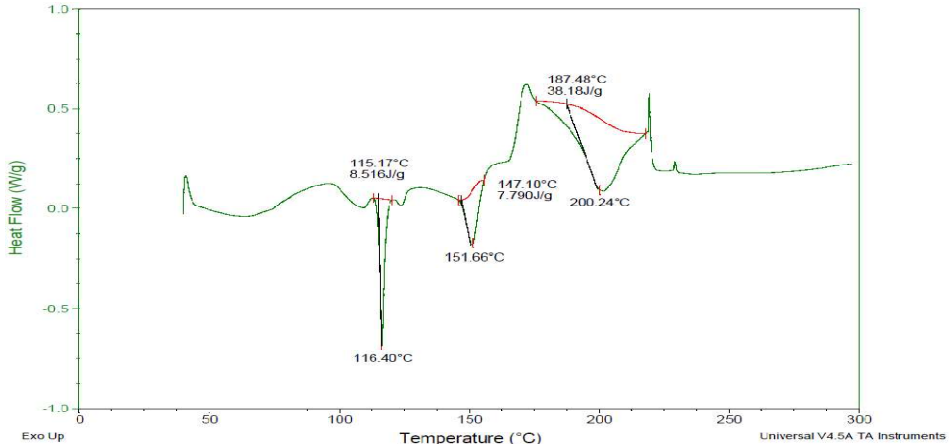

Fig. 4. DSC of paliperidone mixture with excipients (HPMC/lactose/magnesium stearate/talc/ microcrystalline cellulose)

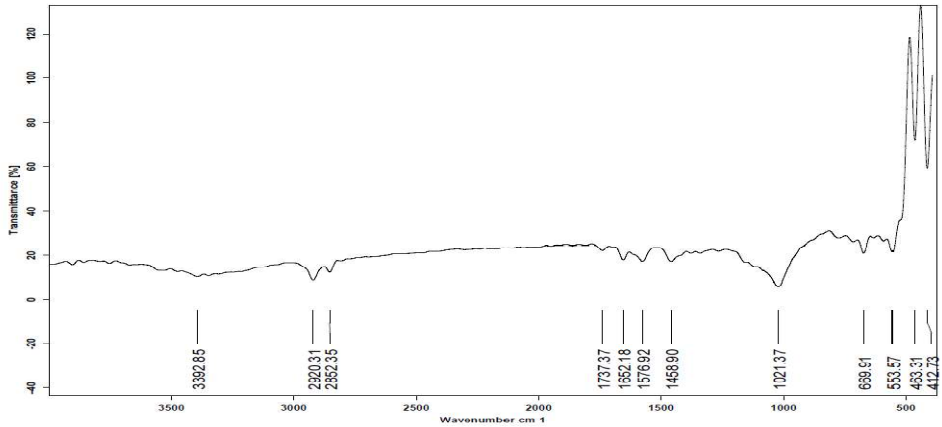

Fig. 5. IR spectrum of paliperidone mixture with excipients (HPMC/lactose/magnesium stearate/talc/ microcrystalline cellulose)

X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity. The XRPD patterns of paliperidone palmitate revealed several diffraction peaks which indicate its crystalline character was shown in Fig. 6. The relative crystallinity of paliperidone palmitate was calculated based on the Ruland method, in which the area of the crystalline diffraction relative to the total area of the diffractogram is taken as a measure of crystallinity. The relative crystallinity index calculated for paliperidone palmitate was 60.01%.

The SEM photomicrographs taken at magnification 500 and 7000 are given in Fig. 7. It was observed that paliperidone palmitate is characterized by regular shaped crystals. The photomicrographs obtained by SEM did not evidence any interaction between paliperidone palmitate and the excipients, providing visual support for the results. The SEM images have shown that both paliperidone palmitate and excipients particles maintained their morphology and the drug crystals appeared dispersed on the surface of excipient particles.

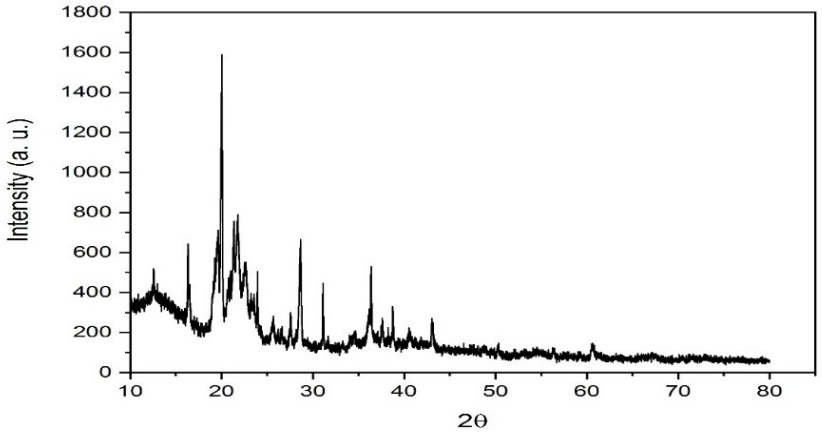

Fig. 6. XRD of paliperidone mixture with excipients (HPMC/lactose/magnesium stearate/talc/ microcrystalline cellulose)

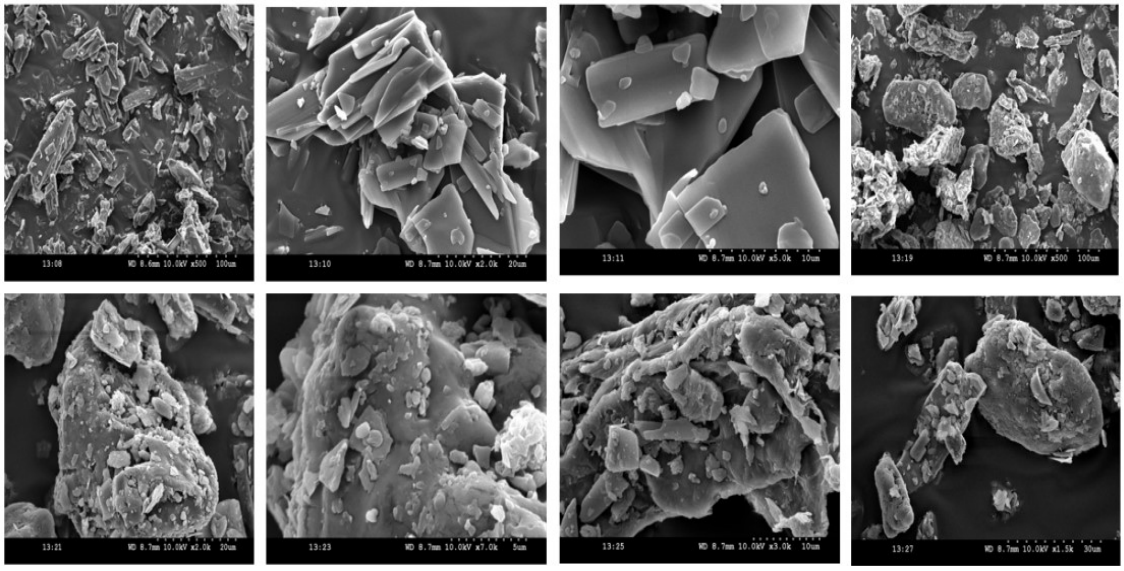

Fig. 7. SEM analysis of paliperidone palmitate with excipients (HPMC/lactose/magnesium stearate/talc/ microcrystalline cellulose)

4. CONCLUSION

The thermal analysis provided information about the thermal stability and decomposition of pure paliperidone palmitate and the binary mixtures which can be used in the quality control. The characterization was obtained by IR and DSC, which, in turn, demonstrated paliperidone palmitate physicochemical properties including the crystallinity. In the compatibility studies, the modifications found in the DSC curves suggested that there was no possible physical interaction of paliperidone palmitate with magnesium stearate, starch and micro crystalline cellulose. Additional IR analysis were carried out and no evidence of solid-state interaction or incompatibility was observed. XRD of paliperidone palmitate indicated that the compound is crystalline in nature with good diffraction properties. SEM was carried out with paliperidone palmitate with its excipients and results showed that there were no interactions with good crystal properties from SEM photomicrographs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Emsley R, Kilian S. Efficacy and safety profile of paliperidone palmitate injections in the management of patients with schizophrenia: an evidence-based review. Neuropsychiatr Dis Treat. 2018;14:205-23.
2. Lopez A, Rey J. Role of paliperidone palmitate 3-monthly in the management of schizophrenia: Insights from clinical practice. Neuropsychiatr Dis Treat. 2019; 15:449-56.
3. Zhang H, Turkoz I, Zhuo J, Mathews M, Tan W, Feng Y. Paliperidone Palmitate Improves and Maintains Functioning in Asia–Pacific Patients with Schizophrenia. Advances in Therapy. 2017;34(11):2503-17.
4. Pappa S, Mason K. Partial compliance with long-acting paliperidone palmitate and impact on hospitalization: a 6-year mirror-image study. Therapeutic Advances in Psychopharmacology. 2020;10: 2045125320924789.
5. Emsley R, Kilian S. Efficacy and safety profile of paliperidone palmitate injections in the management of patients with schizophrenia: An evidence-based review. Neuropsychiatr Dis Treat. 2018;14.
6. Bernardo M, Bioque M. Three-month paliperidone palmitate - a new treatment option for schizophrenia. Expert Review of Clinical Pharmacology. 2016;9(7):899-904.
7. Ojimba C, Oyelakin A, Khandaker T. Accidental Overdose of Paliperidone Palmitate. Case Reports in Psychiatry. 2019:7406298.
8. Yılmaz ED, Motor S, Sefil F, Pınar N, Kokacya H, Kisa M, et al. Effects of Paliperidone Palmitate on Coagulation: An Experimental Study. The Scientific World Journal. 2014:964380.
9. Naguy A, Adel T, Almazeedi I. Paliperidone Use in Child Psychiatry: Evidence or Diffidence? Pharmacology. 2019;104(1-2):67-70.
10. Alphs L, Bossie CA, Sliwa JK, Ma Y-W, Turner N. Onset of efficacy with acute long-acting injectable paliperidone palmitate treatment in markedly to severely ill patients with schizophrenia: post hoc analysis of a randomized, double-blind clinical trial. Annals of General Psychiatry. 2011;10(1):12.
11. Schreiner A, Aadamsoo K, Altamura AC, Franco M, Gorwood P, Neznanov NG, et al. Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. Schizophrenia Research. 2015;169(1):393-9.
12. Devrimci-Ozguven H, Atmaca M, Baran Z, Cengisiz C, Çinar C, Erol A, et al. Efficacy and Safety of Paliperidone Palmitate Treatment in Patients with Schizophrenia: A Real-World Multicenter, Retrospective, Mirror-Image Study. Journal of Clinical Psychopharmacology. 2019;39(6).
13. Kramer M, Litman R, Hough D, Lane R, Lim P, Liu Y, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. International Journal of Neuropsychopharmacology. 2010;13(5): 635-47.

14. Funk K, Bostwick J. Paliperidone Palmitate Injection Site. Issues in mental health nursing. 2013;34:779-82.
15. Morris MT, Tarpada SP. Long-Acting Injectable Paliperidone Palmitate: A Review of Efficacy and Safety. Psychopharmacol Bull. 2017; 47(2):42-52.

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