Evaluation of Drug-Excipient Compatibility for Paroxetine Nanoformulations Using DSC and FTIR Analysis

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ABSTRACT

The drug-excipient compatibility study is a critical component of the preformulation stage in pharmaceutical development. It provides essential insights for selecting suitable excipients to ensure the stability, efficacy, and safety of the final formulation. For the development of Paroxetine nanoparticle formulations, the compatibility of Paroxetine with commonly used pharmaceutical excipients was assessed using Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FTIR). In this study, Paroxetine was evaluated in combination with Poly (lactic-co-glycolic acid) (PLGA), a widely used biodegradable polymer. The drug and excipient were mixed in a 1:1 ratio and subjected to DSC and FTIR analysis to detect any potential chemical interactions or incompatibilities. The DSC thermograms of the drug, excipient, and their mixture were analyzed. Paroxetine exhibited a characteristic endothermic peak corresponding to its melting point, which remained unchanged in the drug-excipient mixture. This result suggests that the physical and thermal properties of the drug and excipient were retained, indicating the absence of any interactions that could lead to incompatibility. FTIR spectroscopy was employed to study the functional group interactions between the drug and the excipient. The spectra revealed no significant shifts or alterations in the characteristic peaks of Paroxetine and PLGA. This absence of new peaks or changes in the existing peaks confirmed that no chemical interaction occurred between the drug and the polymer. The findings from both DSC and FTIR analyses demonstrated that there were no incompatibility issues between Paroxetine and PLGA. The results infer that Paroxetine-loaded nanoparticles can be successfully formulated using PLGA as the polymer, ensuring the stability and integrity of the drug during formulation and storage. The compatibility study data support the development of optimized Paroxetine nanoparticle formulations for potential therapeutic applications, with PLGA serving as a reliable and compatible excipient.

Key words:

Compatibility, Paroxetine, PLGA, Fourier Transform Infrared Spectroscopy and Differential Scanning Colorimetry.

INTRODUCTION

Preformulation characterization is a fundamental and critical step in the development of pharmaceutical dosage forms. It involves evaluating the physicochemical and mechanical properties of a drug substance to ensure its suitability for formulation. Among the various parameters involved in preformulation characterization such as solubility determination, melting point analysis, analytical method development, solid-state stability studies, true density, bulk density, Carr's index, and compressibility index, the compatibility study between the drug and excipients holds particular importance. This study is essential because the interaction between the drug and excipients can significantly impact the stability, efficacy, and safety of the final dosage form. Identifying potential incompatibilities early in the development phase can prevent formulation failures and reduce development time and costs. Together, these parameters provide valuable insights that guide the selection of suitable excipients, optimize manufacturing processes, and ensure the development of a robust and effective dosage form [1,2]. The compatibility studies between drugs and excipients are usually carried out to identify any possible interaction between drugs and different excipients [3,4].

In compatibility studies, the interaction between the drug and various excipients is evaluated under accelerated stability conditions. Samples are exposed to moisture and different temperature settings, such as 4°C, 37°C (room temperature), and 60°C, typically for a period of 45 days or longer. During this period, the exposed samples are analyzed at regular intervals using FTIR (Fourier-Transform Infrared) spectral analysis. FTIR spectral analysis helps assess the presence of functional groups by measuring transmittance versus wavenumber (cm^{-1}) at specified time points. This analysis provides initial insights into possible interactions between the drug and excipients, such as the formation of new bonds or changes in chemical structure. To confirm these interactions and gain a more comprehensive understanding, further detailed studies can be performed. These studies may involve increased quantities of the sample, extended exposure times, and varying solvent conditions to enhance the sensitivity and accuracy of the findings. Such evaluations are crucial to ensure the stability and compatibility of the drug formulation. [5-11].

In current pharmaceutical research, drug-excipient interaction studies are increasingly assessed using advanced thermal methods such as Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). Among these, DSC has emerged as a particularly significant and reliable technique. DSC provides valuable insights into the thermal behaviour of a drug-excipient mixture, such as melting point, crystallinity, and potential interactions. This method is advantageous because it requires only a few hours to evaluate a sample, using a precise temperature programming protocol. The efficiency and reliability of DSC make it an essential tool in preformulation and formulation studies, enabling rapid and accurate characterization of drug-excipient compatibility. [12-14].

Among the various techniques in thermal analysis, Differential Scanning Calorimetry (DSC) is one of the most widely used methods. In DSC analysis, specific properties of a sample, particularly the physical characteristics of materials, are evaluated based on temperature-dependent principles. Thermal analysis, as a group of techniques, involves measuring the physical properties of a drug substance or its reaction products as a function of temperature.

This is achieved while the drug substance, or a mixture of the drug and excipients, is subjected to a controlled temperature program. Thermal methods have found extensive applications in both research and quality control. Currently, they are widely used in areas such as composition analysis, stability studies, environmental monitoring, product reliability, dynamic property evaluation, and chemical reaction analysis. Their versatility and precision make thermal analysis an indispensable tool in pharmaceutical and materials science.[15-20].

Thermal analysis is widely used to estimate the physicochemical properties of polymers (e.g., PLGA) and drug substances in formulation development. Modern instruments based on thermal analysis principles can measure various parameters, including transition temperatures, weight loss, transition energies, viscoelastic properties, dimensional changes, and modulus changes. Additionally, the purity of materials can be evaluated by analyzing the temperatures at which phase changes and reactions occur, as well as by measuring the heats of reaction. These techniques provide valuable insights into the material characteristics, helping to ensure the quality and stability of the formulation.

Paroxetine is one of the most potent clinically available selective serotonin reuptake inhibitors (SSRIs) used as an antidepressant. It works by inhibiting serotonin reuptake; however, its action is less selective at the serotonin site compared to other SSRIs, such as fluvoxamine or sertraline. Paroxetine is clinically available in oral dosage forms, including tablets, capsules, and oral suspensions. It is readily absorbed from the gastrointestinal tract (GIT) and extensively metabolized in the liver. Following an oral dose of 30 mg per day, the half-life of paroxetine can be up to 21 hours [Citation2]. However, its pharmacodynamics make it less suitable for oral administration due to extensive first-pass metabolism, resulting in lower bioavailability.

Paroxetine is commonly used in the treatment of depression, social anxiety disorder, obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder (PTSD). The drug was FDA-approved and introduced to the market in 1992 under the trade name Paxil. Other brand names include Brisdelle, Aropax, Seroxat, Pexeva, and Sereupin. Paroxetine is a white, odorless powder with a molecular weight of 374.8 g/mol and a melting point range of 120-138°C. The structure of paroxetine contains an amine group located in the piperidine ring, which is linked to fluorophenyl and benzodioxol groups. Paroxetine is classified as a highly lipophilic basic amine that exhibits both hydrophilic and hydrophobic properties.

Based on the above literature, the use of synthetic and natural polymers in specific formulations can enhance drug delivery by employing simple formulation techniques, such as the development of nanoparticles with functional activity. With this perspective, the current research focuses on the formulation and evaluation of an oral drug delivery system using paroxetine as the drug candidate in nanoparticle form. Drugs with low solubility in water, such as those classified in BCS Class IV and Class II, present significant challenges in the development of appropriate dosage forms. Dissolution is the rate-limiting step for these drugs due to their poor water solubility. The characteristic of poor solubility in water limits the rate of absorption, and for BCS Class IV drugs, intestinal permeability further complicates drug development. Currently, no nanoparticle formulations of paroxetine have been reported. This study, therefore, aims to evaluate the compatibility of paroxetine, a selective serotonin reuptake inhibitor, with commonly used pharmaceutical excipients, specifically in the context of developing paroxetine-loaded nanoparticles.

Materials and Methods

Paroxetine (99.82%) and PLGA was procured from Sigma Aldrich. All chemicals used in the study were of analytical grade and used without further purification.

Experimental Studies:

The DSC thermal traces of the drug and excipient mixture were evaluated using a differential calorimeter (Shimadzu DSC 60). Mixtures of paroxetine and PLGA were weighed and placed in a standard aluminum pan. Dry nitrogen, at a flow rate of 20 mL/min, was used as the carrier gas in the instrument. Thermal scanning was performed up to 250°C with a scan speed of 10°C/min. Instrument calibration was done using indium as the standard reference. Each sample weighed between 5 and 10 mg. The onset temperature of the highest peak corresponds to the main transition temperature (Tc). Based on the area under the main transition peak, the enthalpy change (ΔHm) was automatically calculated. The heat flow for all samples was measured to evaluate any thermal events and transitions. [21-25].

FT-IR (Fourier transform infrared) spectroscopy

The FT-IR spectra was generated for Paroxetine drug substance as well as for drug substance sample along with mixture of selected PLGA of the optimized formula in 4000–500 cm_1 range. In FT IR spectrophotometer (Cary 630, Agilent Technologies, Danbury, USA), the samples were placed in light path of sample cell and the spectrum of samples were generated.

RESULTS AND DISCUSSION

In the pharmaceutical industry, Differential Scanning Calorimetry (DSC) is commonly used to evaluate drug-excipient interactions or incompatibilities between different components blended in a formulation. This is done by observing the corresponding enthalpy peaks, which may shift to a different temperature or disappear, indicating potential interactions or incompatibilities. The DSC curves (presented in Figures 1-3) were evaluated to assess the interaction or compatibility of paroxetine with various excipients.

DSC analysis measures the gain or loss of heat due to changes in the physical or chemical nature of a sample or a mixture of samples as a function of temperature. The relative purity of a sample is indicated by a sharp, symmetric melting endotherm, whereas the presence of impurities or multiple thermal processes is identified by a broad, asymmetric curve. Endothermic peaks observed in DSC below 120°C typically indicate moisture loss from the compound. In this study, DSC analysis was performed to investigate the physical behavior of paroxetine as a drug substance and to confirm that there was no interaction between paroxetine and PLGA. The thermograms of the drug substance, polymer, and their physical mixture were evaluated. The DSC thermograms are shown below in Figures 1 and 2. The DSC thermogram of the physical mixture of paroxetine with PLGA exhibited the characteristic peak of the drug substance at its melting point of 118°C. This confirms that there is no interaction between the drug and the polymer.

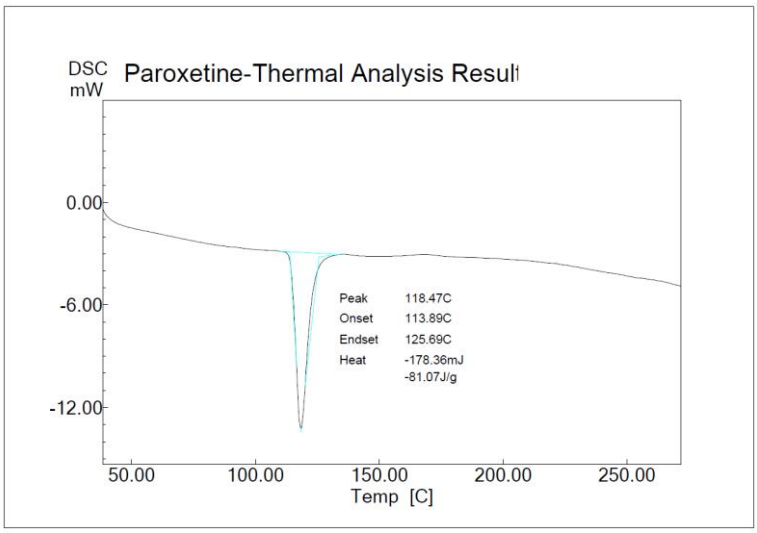

Figure 1 DSC thermogram of Paroxetine

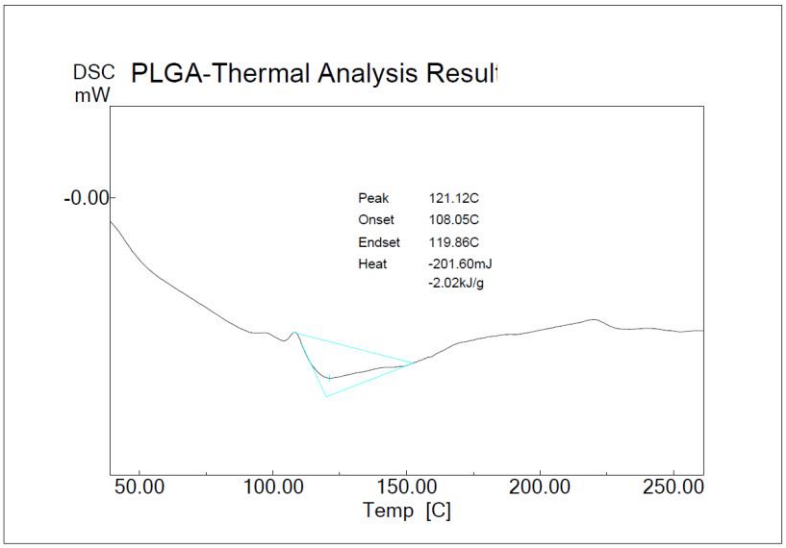

Figure 2 DSC thermogram of PLGA

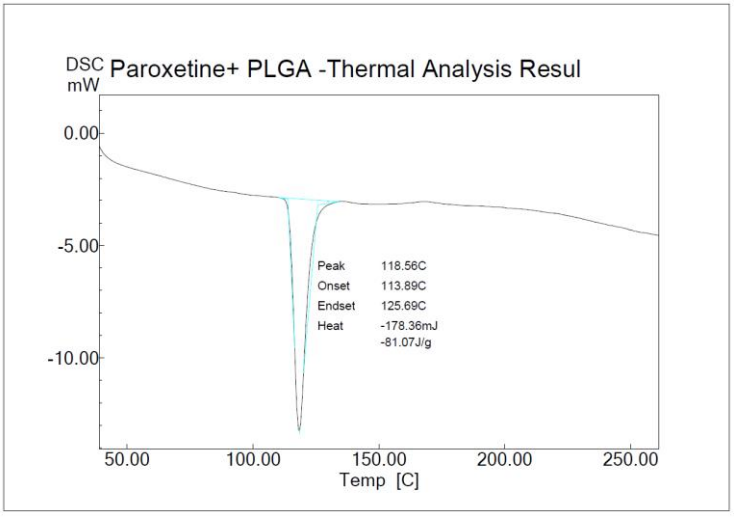

Figure 3 DSC thermogram of Paroxetine with PLGA physical mixture

Additionally, FT-IR spectra of the samples are presented in Figures 4 and 5. A comparative assessment of the FT-IR spectra of the drug substance alone and the drug substance mixed with excipients showed no significant differences in the spectra, further supporting the lack of interaction between the drug and excipients.

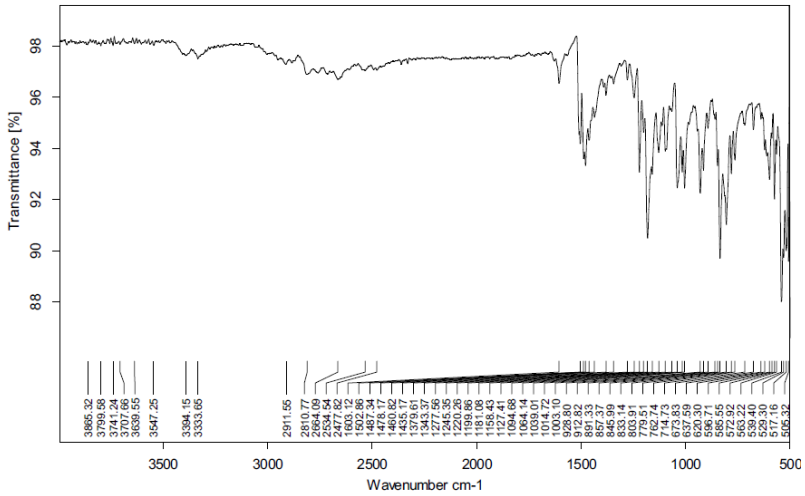

Figure 4 FTIR Spectra of Paroxetine

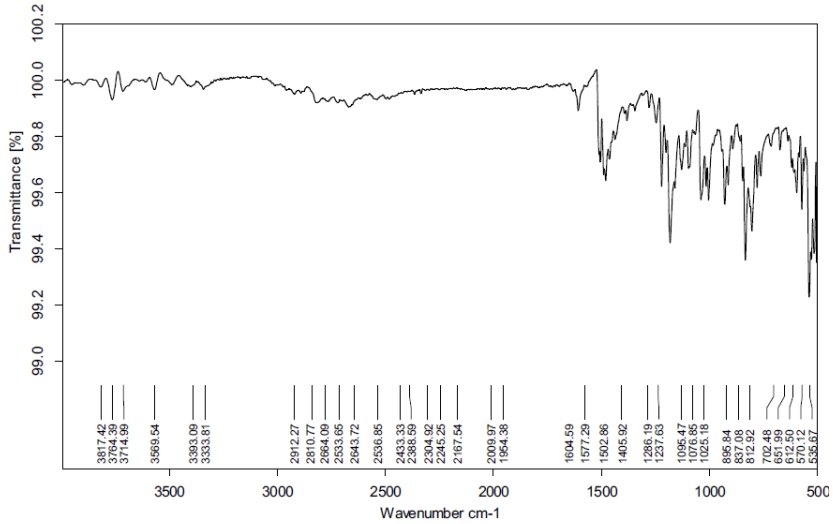

Figure 5 FTIR Spectra of Paroxetine with PLGA physical mixture

CONCLUSION

The compatibility of Paroxetine with Poly (lactic-co-glycolic acid) (PLGA) was evaluated using Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FTIR) to ensure the polymer is stable and does not react with the drug. The FTIR analysis showed no significant changes in the chemical structure, indicating there were no chemical interactions between Paroxetine and PLGA. Similarly, the DSC analysis confirmed that the heat-related properties of both the drug and the polymer remained unchanged when combined, further supporting the absence of any incompatibility. These results confirm that PLGA is chemically inert and does not interfere with Paroxetine. Therefore, PLGA is a suitable and safe polymer for the development of Paroxetine-loaded nanoparticles, ensuring the stability and effectiveness of the final formulation.

REFERENCES

1. Martin. A, Bustamante. P. and Chun. A.H.C. Physical Pharmacy, 4th Ed., Indian Reprint, B.I.Waverly Pvt. Ltd., New Delhi, 1994; 444.
2. P. Venkatesan, V. Sree Janardhanan, R. Manavalan, K. Valliappan. Preformulation Parameters Characterization to Design, Development and Formulation of Loxoprofen Loaded Microspheres, International Journal on Pharmaceutical and Biomedical Research, 2011; 2(3): 107- 117.
3. Vijay J, Sahadevan JT, Prabhakaran R, Mehra Gilhotra R. Formulation and Evaluation of Cephalexin Extended-release Matrix Tablets Using Hydroxy Propyl Methyl Cellulose as Rate-controlling Polymer, Journal of Young Pharmacists, 2012; 4: 3-12.
4. Venkatesan. P, Manavalan. R and Valliappan. K. Preparation and evaluation of sustained release loxoprofen loaded microspheres, Journal of Basic and Clinical Pharmacy, 2011; 2(3): 159-162.
5. M.M. Gupta, T.R. Saini. Preformulation parameters characterization to design, development and formulation of vancomycin hydrochloride tablets for Psudomembranous colitis, IJPRD, 2009; 1: 1-7.
6. P. Venkatesan, V. SreeJanardhanan, C. Muralidharan, and K.Valliappan. Improved HPLC Method with the Aid of Chemometric Strategy: Determination of Loxoprofen in Pharmaceutical Formulation, Acta Chim. Slov., 2012; 59: 242– 248.
7. Lachman,L., Liberman, H.A., and Kanig, J.L., The Theory and Practice of Industrial Pharmacy, Lea & Febiger, Philadelphia, 1986,171-195.
8. Shengjum C, Jiabi Z, Fengquin M, Qun F. preparation and characterization of solid dispersion of dipyridamole with a carrier copolyvidonum plasdone S 360. Drug Dev Ind Pharmacy 2007; 33.:888-9
9. Ohwoavworhua FO, AdelakumTA. Some physical characteristics of microcrystalline cellulose obtained from raw cotton of cochlospermum planchonil. Trop J pharm Res 2005;4:1-7.
10. Carstensen, J.T., Pharmaceutical Preformulation, 1998, Technomic Publishing Company, Inc., New Holland Avenue, Lancaster, Pennysylvania, USA, 13 –24, 41 – 48, 259 – 274.
11. P.Venkatesan, R.Manavalan and K.Valliappan Microencapsulation: A Vital Technique In Novel Drug Delivery System. J. Pharm. Sci. & Res. Vol.1(4), 2009, 26-35.
12. Ghosh A, Nayak UK and Roy P. Development, Evaluation and Method selection for the Preparation of lamivudine microspheres. The International. J. Pharmacy June 2007;9:67-71.
13. M. M. Gupta*, T.R. Saini . Preformulation parameters characterization to design, development And formulation of vancomycin hydrochloride tablets for Psudomembranous colitis. IJPRD, 2009;1:1-7.
14. C.Karuppusamy, and P. Venkatesan. Role of Nanoparticles in Drug Delivery System: A Comprehensive review, J. Pharm. Sci. & Res. Vol. 9(3), 2017, 318-325
15. Backett, A.H., and Stenlake, J.B., Practical Pharmaceutical Chemistry, First Edition, Reprint, 2004, CBS Publishers and Distributors, New Delhi, 275 – 325.

16. Gohel MC, Parik RK, Amin AF and Surati AK. Preparation and formulation optimization of sugar cross linking gelatin microspheres of diclofenac sodium. Indian J. Pharm Sci. 2005;67(8):575-81.
17. T.Sudhamani, K. Noveenkumar reddy, V.R. Ravi Kumar, R.Revathi, V.Ganesan, preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery, Int.J.Pharma Research and Development. 2010, 119-125.
18. Saravanan.M., Dhanaraju.D, Sridhar.S.K, Ramachandran.S, kishore Gran sam.S, Anand.P, Bhaskar.K & Srinivasarao.G ,Preparation, Characterization and invitro release kinetics of ibuprofen polystyrene microspheres, Ind.J.Pharm.Sci, 66(3), 2004,287-292.
19. Velavan. P and Venkatesan. P: Evaluation of compatibility of formulation excipients with Pregabalin Using DSC, J. Pharm. Res., 2016; 5(3): 49-51.
20. Sengel CT, Hascicek C, Gonul N, Development and In-vitro evaluation of modified release tablets enclosing ethyl cellulose microspheres loaded with diltiazem hydrochloride, Microencapsule, 2005, 23(2), 135-152.
21. Das MK and Rao K.R., Evaluation ofZidovudine encapsulated ethyl cellulose microspheres prepared by water in oil in oil (w/o/o) double emulsion solvent diffusion technique. Acta Pol Pharm 2006 Mar- Apr, 63(2) , 141-148.
22. Zinutti C, Kedzierewicz F, Hoffman M, Maincent P preparation and Characterisation of ethyl cellulose microspheres containing 5- fluorouracil Microencapsule, 1994 Sep- Oct, 11 (5), 555- 563.
23. R.Sathiya Sundar, A.Murugesan, P.Venkatesan, and R.Manavalan, Formulation Development and Evaluation of Carprofen Microspheres. Int.J. Pharm Tech Research. 2010 Vol.2, No.3, 1674- 1676.
24. Karuppusamy.C and Venkatesan. P. Preformulation Parameters Characterization to Design, Development and Formulation of Miglitol Loaded Nanoparticles. J. Pharm. Sci. & Res. Vol. 9(3), 2017, 326-331
25. Velavan. P and Venkatesan. P: Preparation and evaluation of pregabalin loaded nanoparticles for sustained drug delivery, J. Sci. Res. Phar., 2016; 5(3): 29-32.