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Solubility Enhancement of Brexpiprazole for Schizophrenia using HPβ Cyclodextrin Ternary Complexation

Mejora de la solubilidad del brexpiprazol para la esquizofrenia mediante complejación ternaria de ciclodextrina HPβ

Chauhan Neha[1] 0000-0002-8097-7289
Patel Amit[2] 0000-0001-8223-9311
Patel Ravish[3] 0000-0002-8442-0349
[1]Charotar University of Science and Technology (CHARUSAT), India
[2]Ramanbhai Patel College of Pharmacy (RPCP), India
[3]At & Post- Changa, Tal- Petlad, Dist- Anand, India

Correspondence
Dr. Patel Amit
amitpatel.ph@charusat.ac.in

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Conflict of interest
The authors declare no conflict of interest.

Resumen

Introducción: El presente estudio se centra en la mejora de la solubilidad y la velocidad de disolución del brexpiprazol con hidroxipropil β-ciclodextrina y ácido succínico como solubilizador para la esquizofrenia.

Método: Brexpiprazol se obtuvo como muestra de regalo de CTX Life sciences, Sachin, Surat. La hidroxipropil beta ciclodextrina fue donada por Good Health Pvt. Limitado. Ltd. Sachin, Surat. Los complejos binarios y ternarios se prepararon utilizando tres métodos diferentes y se caracterizaron mediante espectroscopia infrarroja por transformada de Fourier, calorimetría diferencial de barrido, difracción de rayos X y estudios de disolución in vitro.

Resultados: Se observó que entre las diferentes proporciones de fármaco y polímero utilizadas, la proporción 1:5 de fármaco y polímero para el complejo binario resultó ser la optimizada y el método de evaporación del disolvente dio los mejores resultados. Luego se preparó el complejo ternario usando esta proporción en diferentes concentraciones de ácido succínico (0,25, 0,5 y 1 % p/p) y la concentración óptima de ácido succínico como solubilizador fue del 1 %. Se encontró que la liberación del fármaco era máxima del 92% en comparación con el complejo binario. Los resultados de la espectroscopia infrarroja por transformada de Fourier, la calorimetría diferencial de barrido y la difracción de rayos X confirmaron la formación de un complejo estable.

Conclusiones: Se concluyó que el complejo ternario tuvo una liberación máxima del fármaco del 92 % al final de 60 minutos, lo que resultó en una mejora de la solubilidad y la velocidad de disolución.

Palabras clave: Esquizofrenia; Brexpiprazol; Complejo ternario; solubilidad de fase; tasa de disolución

Abstract

Introduction: The present study focuses on the solubility and dissolution rate enhancement of Brexpiprazole with Hydroxy Propyl β-cyclodextrin and succinic acid as a solubiliser for schizophrenia.

Materials & Method: Brexpiprazole was obtained as a gift sample from CTX Life sciences, Sachin, Surat. Hydroxypropyl beta cyclodextrin was gifted by Good Health Pvt. Ltd Sachin, Surat. Binary and ternary complexes were prepared using three different methods and characterized using the fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction and invitro dissolution studies.

Results: It was observed that among different ratios of drug and polymer used, 1:5 ratio of drug and polymer for binary complex was found to be the optimized and solvent evaporation method gave the best results. The ternary complex was then prepared using this ratio in different concentration of succinic acid (0.25, 0.5 and 1 % w/w) and optimum concentration of succinic acid as a solubiliser was of 1 %. The drug release was found to be maximum 92 % as compared to binary complex. The fourier transform infrared spectroscopy, differential scanning calorimetry and X-ray diffraction results confirmed the formation of stable complex.

Conclusions: It was concluded that ternary complex had maximum drug release of 92% at the end of 60 minutes resulting in solubility and dissolution rate enhancement.

Keywords: Schizophrenia; Brexpiprazole; Ternary complex; Phase solubility; Dissolution rate

Highlights

Solubility enhancement of Biopharmaceutical Classification System (BCS) class II drugs is a need in order to have the maximum drug dissolution and quick onset of action for diseases like schizophrenia where the patients require quick onset of action and faster delivery of drug to brain.

Various polymers and techniques can be used as solubility enhancing agents among which cyclodextrin complexation is one of the highly recommended techniques. Using cyclodextrins in combination with solubilizers like succinic acid are more effective as they give a synergistic effect to solubility enhancement.

The result obtained can be used for practically water insoluble drug's solubility enhancement and can be used to enhance the dissolution rate which can be used to make fast dissolving dosage forms.

Introduction

People with schizophrenia experience a serious mental disease in which they interpret reality in an unusual way. Childhood schizophrenia is an uncommon but dangerous mental disorder. Children with the disease show poor emotional regulation and reasoning skills, which causes them to lose interest in reality. Delusions include things like hearing or seeing things that aren't there, hallucinations, and false beliefs[1]. Delusions, or irrational, incorrect beliefs, or hallucinations, or misleading sensations involving any sensory modality, are the most typical characteristics of psychotic conditions[1]. The development of new neurotherapeutics is limited by the challenges associated with translocating molecules across the blood-brain barrier (BBB) and the low water solubility of most of the new medication candidates. Because non-target regions, particularly those outside the central nervous system, are exposed to larger drug concentrations, poor solubility increases systemic exposure. This raises the possibility of adverse outcomes[2-3]. Solubility can be enhanced by using various techniques like co-solvency, complexation, hydrotropy, cryogenic method, liquisolid compact, high pressure homogenization, manipulation of solid state, micellar solubilisation, microemulsion & self-emulsifying system, micronization, nano crystallization, nanosuspension, neutralization, cosolvency, particle size reduction, pH adjustment, solid dispersion, solubilisation, precipitation, salt formation, solvent deposition, sonocrystallization, spray drying, supercritical fluid process[4-6].Cyclodextrins (CDs) have received increasing attention in pharmaceutical field because of their ability to enhance solubility, stability, and bioavailability through the formation of inclusion complexes[7-10]. However, it is imperative that pharmaceutical dosage form should contain appropriate and approved concentration of CDs, because use of excess amounts of CDs may lead to potential toxicity and other related side effects, which may impede its use in drug development. Hence, optimization of complexation process and possibility to explore multicomponent systems to gauge the cyclodextrin concentration within permissible limits and further improve efficiency in terms of dissolution and bioavailability were mandated. In this context, the influence of additional (ternary) components in enhancing cyclodextrin solubilization of poorly water-soluble drug has received research focus and momentum over the years[11].

The current study attempts to improve brexpiprazole's solubility and dissolution. Atypical antipsychotics like brexpiprazole are prescribed to treat schizophrenia and depression in addition to depression. It's practically water-insoluble nature leads to an extended half-life of 91 hours and a protein binding percentage of >99%. Brexpiprazole was found to be 0.0063 mg/ml soluble in water at pH 7.0. Drug dissolving rate is slowed down by low water solubility. In this investigation, hydroxypropyl β cyclodextrin and a solubilizer succinic acid were used to produce a ternary complex, which improved the solubility and dissolution of brexpiprazole[12,13].

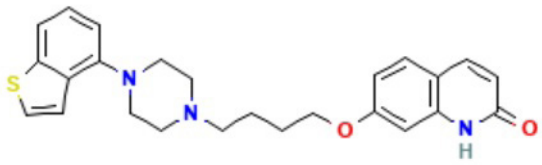

Figure 1. Structure of brexpiprazole

Material and Methods

Materials

Brexpiprazole was obtained as a gift sample from CTX Lifesciences Pvt. Ltd. located in Sachin, Surat, Gujarat, India. A gift sample of hydroxypropyl β cyclodextrin was also provided from Good Health Pvt. Ltd. in Sachin, Surat, Gujarat, India. All other ingredients were of analytical grade.

Methods

Phase solubility studies

Phase solubility studies were conducted to examine the drug's solubility in HPβCD solutions at several concentrations (4–20 mM/L). A saturated solution was generated in a vial by gradually adding excess medication to each of the various solutions. After being screwed shut and sealed, the vials were agitated at room temperature for a full day. The samples were taken out and filtered using a 0.22 µm nylon filter after a 24-hour period. After that, these saturated systems were examined using a UV spectrophotometer set at 214.5 nm[14,15].

Buffer solubility studies of the brexpiprazole:

Solutions of various pH values were generated in order to determine the drug's saturation solubility at various pH values (pH 2, 3, 5, 6, 8, and 9). The drug was gradually added to each vial of buffer solution until a saturated solution was achieved. Each buffer solution was taken in its own vial. After that, all of the solutions were left to agitate for a full day. The samples were taken out and filtered using a 0.22 µm nylon filter after a 24-hour period. After the filtrate was diluted, a UV spectrophotometer was used to measure the absorbance[14,15].

Preparation of Binary Complex of Drug and Hydroxy propyl beta cyclodextrin

The inclusion complex of drug and HPβCD was prepared by three different methods including physical mixture, kneading method and solvent evaporation method by taking three different ratios of drug: HPβCD 1:1, 1:3 & 1:5[16-20].

Physical mixture

The drug powder that had been milled was combined with HP-β-CD in several drug to CD ratios, such as 1:1, 1:3, and 1:5, to create the physical combinations. After going through sieve mesh #60, the mixes were kept in a desiccator until more testing was completed.

Kneading method

With precision, various ratios of Brexpiprazole: HP-β-CD were weighed. In order to get a slurry-like consistency, a tiny amount of ethanol: water (1:1 v/v) was added to the mortar along with HP-β-CD. After that, the medication was gradually added to the slurry, and trituration was carried out for an additional forty-five minutes. After a 24-hour drying period at 45°C, the slurry was grinded, put through a no. 60# filter, and kept in desiccators until needed again.

Solvent Evaporation Method

After dissolving the medication in 20–25 ml of ethanol, the mixture was stirred magnetically until a transparent solution was created. The necessary quantity of cyclodextrin was added to the clear solution to make it clear, and the mixture was heated intermittently to produce the dry residue. After being scraped from the beaker, the dried residue was ground into a fine powder and put through a sieve with a 60# mesh.

Preparation of ternary complex and its characterization

According to the research, the solvent evaporation approach yielded an 80 % drug release in salivary medium at the conclusion of a 60-minute duration. One to five was the ideal ratio. Thus, the ternary

complex was prepared using this optimized ratio (1:5) and solvent evaporation method. The medication was dissolved in the least amount of solvent possible and stirred with a magnetic stirrer until a transparent solution formed. To create a clear solution, cyclodextrin was combined with the necessary amount of succinic acid as solubiliser at varied concentrations (0.25 %, 0.5 %, and 1 % w/w) separately. After that, the mixture were heated sporadically on the magnetic stirrer until the solvent had completely evaporated. After being scraped from the beaker, the dried residue was ground into a fine powder and put through a 60# sieve[19,21-22].

In vitro dissolution studies

Through the dissolution of the complexes formed in water and salivary buffer, the inclusion complex was optimized. Using the United States Pharmacopoeia (USP) dissolution tester Lab India Disso Smart 8S, in vitro dissolution tests were carried out under sink conditions for medication cyclodextrin complexes. 900 mL of distilled water kept at 37.0±0.5 °C and rotating at 100 rpm made up the dissolving media. Weighing precisely, 10 mg of the drug's equivalent of powder complex was placed into each vessel. At predetermined intervals of 15, 30, 45, and 60 minutes, 5 mL samples were manually removed and filtered using a 0.22 µm nylon filter. Using a UV spectrophotometer, the drug concentration in the sample was determined.

Fourier transform infrared spectroscopy

Infrared spectra were recorded on FTIR (Nexus FTIR, J Thermo Nicolet, and USA). In order to create the sample disk, 1–2 mg of a solid sample was grinded in the mortar and was quickly triturated with 0.10–0.20 g of potassium bromide for infrared spectrophotometry. Care was taken to prevent moisture absorption. The pellet was then placed in the sample holder of the FTIR spectrometer. And the IR spectrum was recorded in the desired range (usually 4000–400 cm^{-1}).

Differential scanning calorimetry

The differential scanning calorimetry measurement was performed using a DSC. A sample of 3 – 10 mg was weighed in aluminium pans and crimped. The samples were heated over a temperature range of 0 – 350 °C at a constant rate of 10 °C/min under nitrogen flow of 20 mL/min. An empty aluminium pan was used as a reference.

X-Ray Diffraction (XRD) studies

This study was performed at PW1710 X-ray diffractometer with Cu as anode material and graphite monochromator, operated at a voltage of 35 kV, current 40 mA in the 2θ angle range of 10-70 °C with scan time of 0.5 s. The X-ray diffractogram showed narrow and broad peaks reflecting the nature of drugs, excipients and complexes.

Results

Results & Discussion

Phase solubility determination:

Phase solubility tests show that when the molar concentration of hydroxy propyl beta cyclodextrin increases, the drug's concentration climbs linearly. The stability constant's value was ascertained by applying the Higuchi & Conors method. Based on the Kc value, it was also thought that the medication and polymer showed a 1:1 stoichiometric ratio. With a stoichiometric ratio of 1:1 between the drug and polymer, and a better complex formation, the values of Kc were found to be 176 and 133 cm^{-1} in water and buffer, respectively. An A_L-type graph was also anticipated because the medication concentration increased linearly with the HPβCD concentration. (Table 1).

Table 1. Phase solubility of drug in water and buffer

Medium	mM/L conc.	R^2	Kc (M^{-1})	Graph type
Water	4-20mM/L	0.98	133	A_L type
Buffer	4-20mM/L	0.97	176	A_L type

pH solubility studies of brexpiprazole

pH solubility studies are critical in evaluating how a drug's solubility changes across different pH levels, which reflect the physiological conditions of the human body, particularly in the gastrointestinal tract. These studies are especially important for weakly acidic or basic drugs, as their ionization state—and therefore solubility—can vary significantly with pH. The ionization of a compound affects its dissolution and absorption in the body, impacting its bioavailability. Understanding solubility at various pH levels can guide the design of formulations to improve drug solubility and absorption. pH-dependent solubility profiles can assist in predicting drug absorption and identifying potential challenges in drug delivery systems, aiding in the development of more effective pharmaceutical formulations. It was found that the drug has maximum solubility at acidic pH 4. Amongst different pH range it could be predicted that as it was maximum soluble at 4 pH it would be weakly basic in nature[23] (Table 2).

Table 2. pH solubility profile of Brexpiprazole

S. No.	pH	Conc of drug (mg/ml)	Drug conc(mg/ml)
1	2	0.0063	0.0063±0.0001
2	3	0.0208	0.0208±0.0001
3	4	0.0346	0.0345±0.0001
4	5	0.0297	0.0297±0.0003
5	6	0.0064	0.0064±0.0001
6	8	0.0060	0.0060±0.0001
7	9	0.0055	0.0055±0.0001

In vitro drug release

Using a USP type II equipment dissolution device, the drug dissolving tests were conducted in vitro at 37 ±0.5 °C. Three distinct approaches were used to conduct drug dissolving tests in water and salivary buffer pH 6.8 for various drugs and the HPβCD binary complex. The solvent evaporation method was discovered to be the optimal approach, and the optimized ratio was found to be 1:5. The highest drug release in the binary complex was discovered to be 86.10 % after 60 minutes. In order to create the ternary complex, this optimized batch of complex was utilized together with varying concentrations of succinic acid as a solubilizer (0.25, 0.5, and 1 % w/w). At the end of the 60-minute period, 92 % of the ternary complex's medication was released. Therefore, it can be inferred that the addition of a co-solubiliser, succinic acid at a concentration of 1 % w/w resulted in maximal drug release. Additionally, hydroxypropyl beta cyclodextrin and succinic acid demonstrated a synergistic effect that improved drug release and sped up the beginning of action. (Table 3 and 4).

Table 3. Drug release profile of binary complex

Method	Drug:HPBCD Ratios	Maximum percent cumulative drug release
Physical mixture	1:1	20.56±1.78
	1:3	34.33±2.0
	1:5	35.50±2.45
Kneading method	1:1	39.24±1.54
	1:3	56.56±1.45
	1:5	61.60±2.04
Solvent evaporation method	1:1	53.14±1.65
	1:3	67.09±2.31
	1:5	86.10±2.11

Table 4. Drug release profile of ternary complex

Time (min)	%Drug Release		
	Ternary Complex 0.25 %(w/w)	Ternary Complex 0.5 % (w/w)	Ternary Complex TC 1 %(w/w)
0	0	0	0
15	54.90±1.11	59.48±2.01	57.00±1.44
30	55.28±1.43	61.50±1.67	59.55±1.23
45	57.75±1.78	62.10±2.61	89.63±1.99
60	63.68±1.23	70.13±2.22	91.95±1.56

FTIR Studies

Standard FTIR of the drug shows characteristic peaks of -C-O stretching at 1219.06 cm^{-1}, -C=O ketone at 1653.73, CH alkane stretch at 2815.89 and secondary NH amine group at 3429.90 cm^{-1}(Illustrated in figure 1). In case of binary inclusion complex the physical mixture did not show any change in shift in peaks as compared to standard drug indicating no complex formation. Comparatively, in case of inclusion complex the characteristic peaks shifted to 1250, 1600, 2900 and 3300-3400 cm^{-1} of the respective functional groups in the pure drug. This shift in peaks and also the decrease in peak sharpness or broadening of peak indicate the formation of complex. When a ternary complex is prepared using succinic acid it was found that the characteristic drug peaks of -C-O stretching at 1219.06 cm^{-1}, -C=O ketone at 1653.73, CH alkane stretch at 2815.89 and secondary NH amine group at 3429.90 cm^{-1} shifted to 1153, 1650.17, 2901.06 and 3047.77 cm^{-1} of the respective functional groups. These shifts of peaks confirmed the formation of ternary complex. The FTIR graph of binary and ternary complex is illustrated in figure 2 and 3.

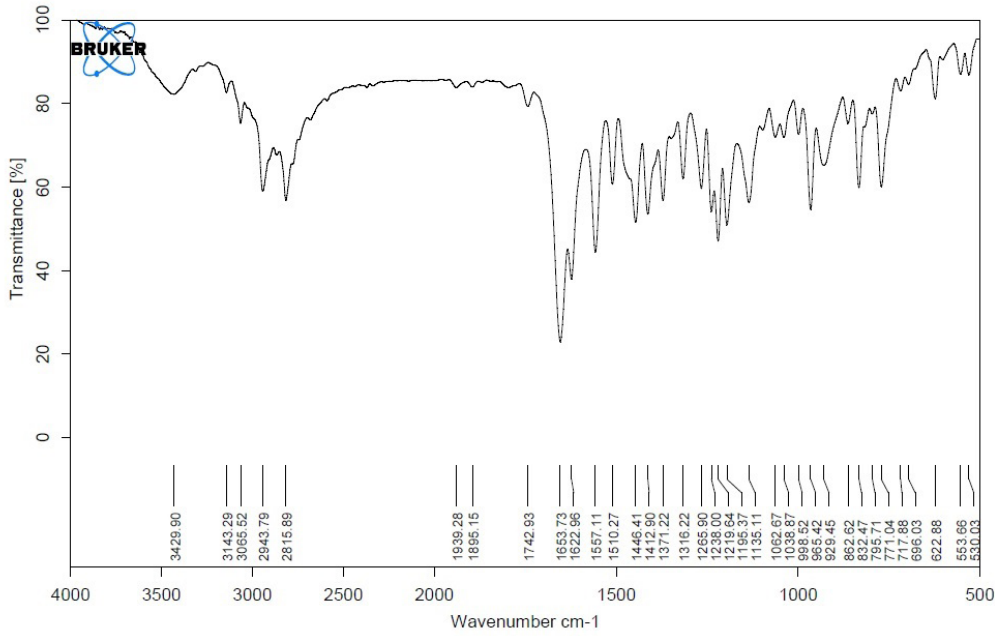

Figure 1. FTIR of Brexpiprazole

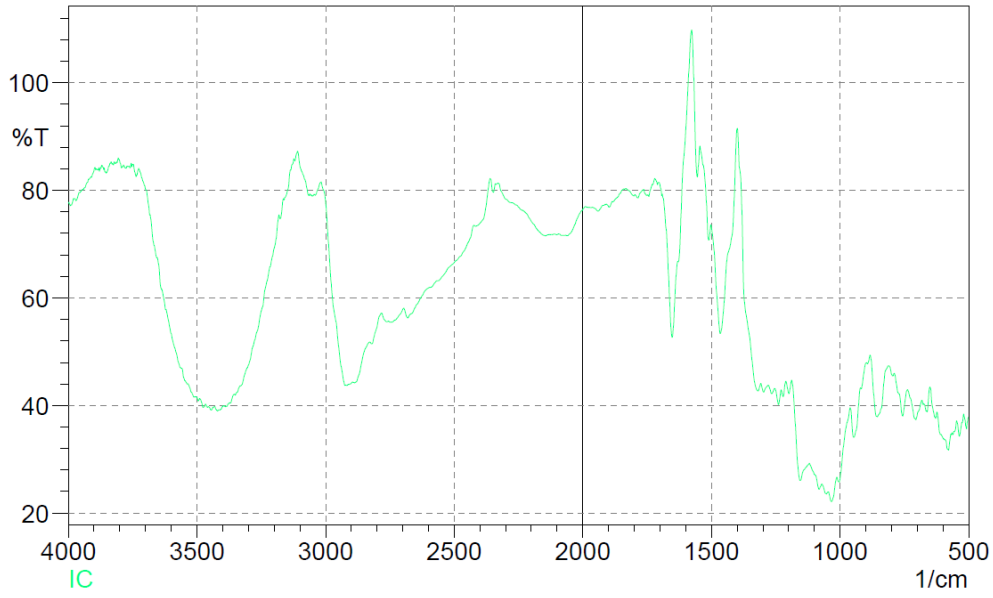

Figure 2. FTIR of binary complex

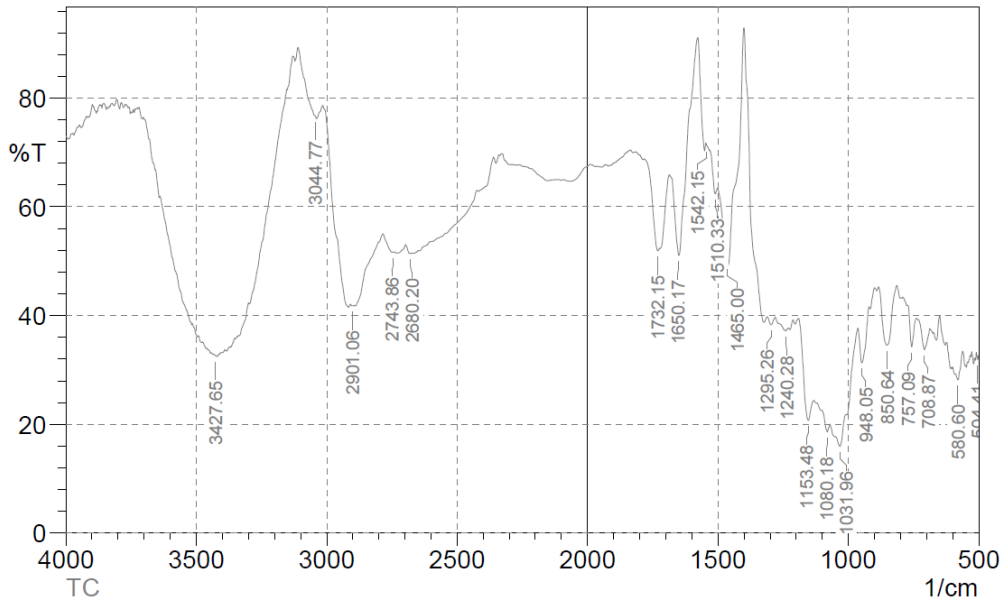

Figure 3. FTIR of ternary complex

Differential Scanning Calorimeter

Differential Scanning Calorimetry (DSC) is a thermal analysis technique used to measure the heat flow associated with material transitions as a function of temperature or time. This method provides critical insights into the thermal properties of substances, such as melting point, crystallization, glass transition, and thermal stability, which are crucial for material characterization in fields like pharmaceuticals, polymers, and food science. DSC is particularly valuable in the pharmaceutical industry for studying drug-excipient compatibility, polymorphism, and the solid-state stability of active pharmaceutical ingredients (APIs). DSC can effectively identify phase transitions in drug substances, which helps optimize formulation processes by ensuring the stability and efficacy of the final product. To create the medication, solubilizer, and cyclodextrin complex, the solvent evaporation method was employed. The medication cyclodextrin and solubilizer complex's DSC data verified the complex's formation. The pure drug DSC exhibited a prominent endothermic peak in the binary complex, close to its melting point of 184.4 ^{0}C. The physical mixing of the binary complex likewise showed no alterations in minor peak as compared to pure drug. However, at 86.68 °C, the complicated endothermic peak was observed. Along with the peak›s decrease in length, the peak was also seen to be broad in nature. This suggested the formation of an inclusion complex. When the DSC of the ternary complex was compared to the standard drug, the ternary complex›s endothermic peak was observed at 87.39 ^{0}C, nearly parallel to the base line, suggesting the formation of a more stable complex. Additionally, the ternary complex was significantly more stable than the binary complex since it had a greater drop in peak area and enthalpy value[24]. The DSC curve of pure drug is shown in (figure 4) while the overlay graph of DSC of binary and ternary complex is shown in (figure 5).

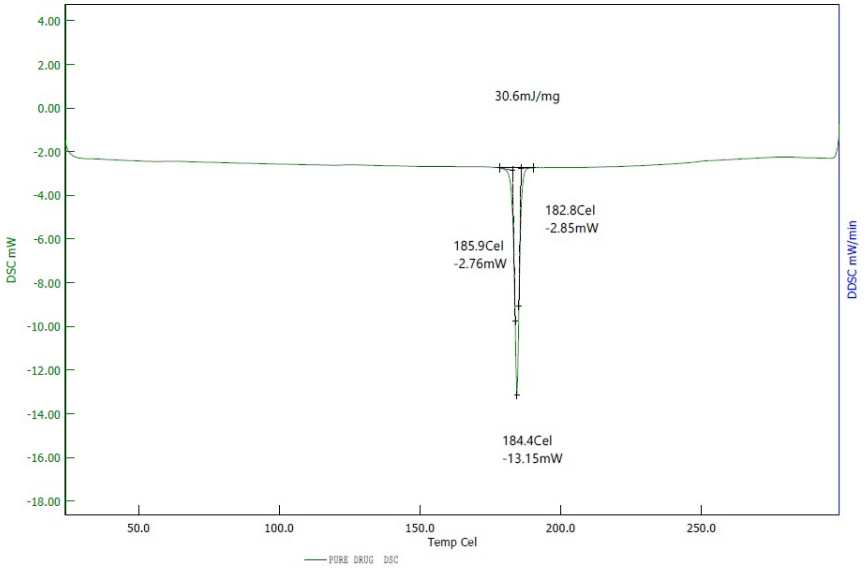

Figure 4. DSC of Brexpiprazole

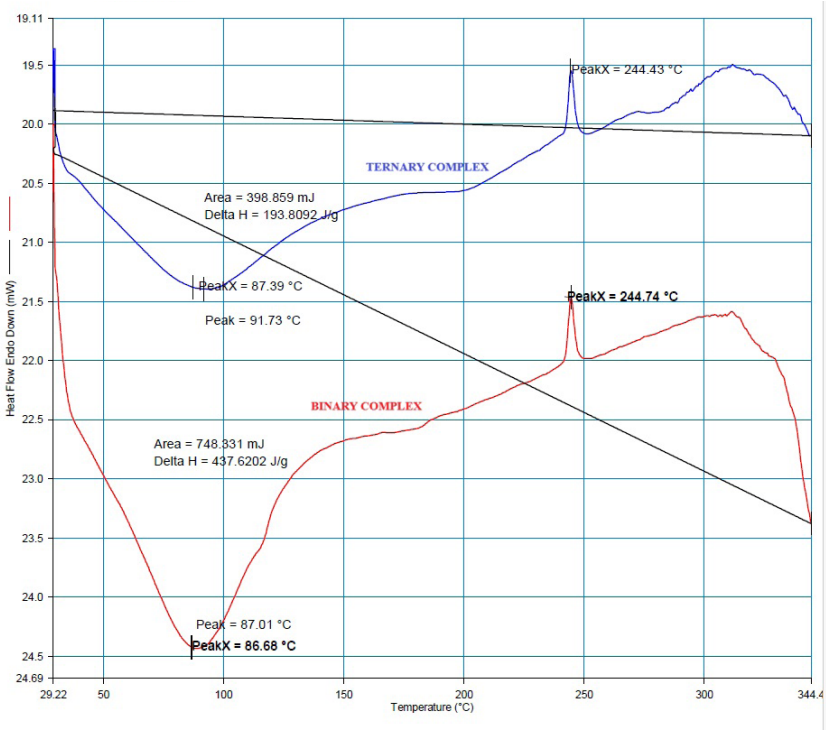

Figure 5. DSC curve of binary and ternary complex

XRD Studies

The ternary complex, binary complex, and pure drug were all studied using XRD. The pure drug's diffractograms showed a number of strong peaks, indicating that they were crystalline in nature. On the other hand, the diffractograms of the binary complexes showed a notable reduction in peak intensity (amorphization), and the ternary complex showed an even greater reduction in peak intensity when compared to the binary complex. This suggested that the drug's crystalline to amorphous state shifted, increasing its solubility and dissolution. X-ray Diffraction (XRD) studies are widely employed to analyze the crystalline structure of materials, providing essential information about the phase composition, crystallinity, and molecular arrangement within a product. This technique is particularly important in the pharmaceutical field, where it is used to differentiate between polymorphic forms of a drug, assess the degree of crystallinity, and ensure batch-to-batch consistency of solid-state products. XRD can also be used to detect amorphous content, which is critical for understanding solubility and bioavailability. XRD analysis plays a vital role in pharmaceutical development by helping identify different solid forms of a drug substance, which can significantly impact its therapeutic performance and stability. The results of XRD of pure drug, binary complex and ternary complex are illustrated in an overlay form in (figure 6).

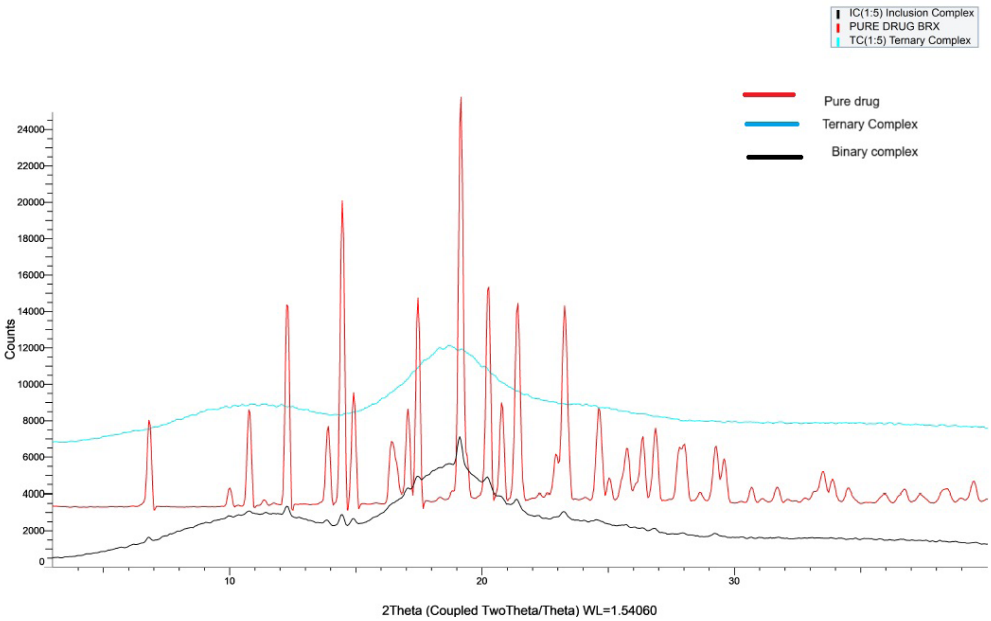

Figure 6. XRD graph of pure drug, binary and ternary complex

Conclusion

The studies mentioned above indicated that the ternary complex enhanced the solubility of brexpiprazole, resulting in a higher rate of dissolution and quicker onset of action. One of the preferred complexation methods was presumed to be solvent evaporation, and succinic acid was thought to be a promising solubilizer for developing a ternary complex.

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