SUITABILITY ASSESSMENT OF LURASIDONE HYDROCHLORIDE FOR SUSTAINED RELEASE INJECTABLE MICROSPHERE FORMULATION BY PRE-FORMULATION STUDIES

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ABSTRACT

The objective of pre-formulation study is to develop the elegant, stable, effective and safe injectable microsphere dosage form by establishing kinetic profile, compatibility with other formulation excipients and physico-chemical parameters of Lurasidone Hydrochloride (LRH). This could provide important information for formulation design or support the need for molecular modification. So, in the present study pre-formulation studies were performed on LRH to assess its suitability for parenteral formulation. LRH is a potent and benzoisothiazol derivatives used as anti-psychotic. The authenticity of the drug was established by UV maximum wavelength, HPLC retention time, Melting point, DSC and FTIR spectra. Along with this chloride salt form is confirmed by Chloride test. A UV spectrophotometric method and HPLC method were employed for determination of LRH in bulk active pharmaceutical ingredient (API). The UV method was linear in the range of 5-30 µg/ml. The retention time of LRH in HPLC method was found to be 11.6 min. The method was proven robust by obtaining very high regression coefficient value (0.999). Drug compatibility of Drug with Excipient had been proved by DSC and FTIR spectra. The results of the physicochemical study of drug revealed suitability of LRH for parenteral route microsphere in PLGA polymer with use of compatible solvent like Dichloromethane.

KEY-WORDS: Pre-formulation, Lurasidone HCl (LRH), HPLC, UV, Drug polymer compatibility, FT-IR, DSC, Solubility

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INTRODUCTION

Physical and Chemical characteristic of active pharmaceutical ingredient is back born of Drug delivery dosage form selection. After any drug discovery, with a background of physico chemical properties of the drug molecule, the drug need to be formulated in suitable dosage form to be administered. During first phase of Development, physico-chemical data to be analysed from drug substances, evaluating potential salts thereof and excipient suitability to be performed prior to formulation of dosage form, is known as pre-formulation. Pre-formulation is the interface between New drug molecule and New Dosage form development. It provides the road map for formulation development (Gopinath and Naidu 2011). Pre-formulation involves the application of bio pharmaceutical principles to the physico chemical parameters of the drug with the aim of designing an new drug delivery system. Characterization of the Active molecule is the very important step in the pre-formulation phase of product development. Therefore, Pre-formulation studies are important tool early

during development of both Drug substance and drug products. The interaction between the drug substance and the excipient to be used in the formulation are generally included in the study which gives idea of selection of excipients. The preliminary study drug degradation need to study for a stable Drug product Development. This studies aid the development of the monitoring process during the development of formulation (Verma and Mishra 2016).

The objective of pre-formulation study is to develop the stable, efficient and safe dosage form by establishing kinetic profile, compatibility with formulation material attributes and establish physico-chemical parameter of new drug substance.

Schizophrenia is characterized by cycles of psychosis relapse and remission which requires a long-term treatment of antipsychotics for prevention of relapses (Arciniegas 2015). Due to early onset and chronicity in schizophrenia, daily injections/ Administration for months or even lifetime have resulted in poor patient compliance. Currently there are many anti-psychotic drugs with different dosage forms are available in the market, but the prime concern about anti-psychotic drug is repeated administration and dose dependence unwanted side effect (Broome et al. 2005). Alternatively, long-acting drug delivery can result in steady levels that are Maintained above the minimum threshold for therapeutic efficacy but below the toxic threshold, resulting in prolonged drug action (i.e., better pharmacodynamics) without unwanted side effects (David et al. 1992).

Low-aqueous solubility is a significant issue when developing novel dosage form. Antipsychotic drug LRH (LRH), which is used specifically to treat schizophrenia, is a good illustration of the issues brought on by low water solubility. LRH is an atypical antipsychotic and derivative of benzisothiazol. This belongs to BCS class II and the molecular weight is reported to be 529.14 gm/mol. LRH first approved dosage form is tablet with 20 mg strength to 120 mg strength. With initial dose of 40 mg once a day with effective dose range of 40 mg to 120 mg once a day. LRH in tablet reaches peak serum concentration in 1-3 hours but with limited bioavailability (9-19%) and 18 hours half-life (40 mg Dose), drug can be accumulated in body which results in unwanted side effect in body which can not suggest longer use of tablet in clinical circumstances like schizophrenia (Madan et al. 2015). LRH Drug binds to dopamine and serotonin type 2 (5-HT2) receptors (Cruz 2011; Patel et al. 2019). In such cases, Long-acting injectable dosage form like polymeric microsphere can solve problems by increasing bioavailability, minimize dosing frequency and dose dependant side effects.

Polymeric microspheres as a parenteral drug delivery system are primarily developed for sustained release of drugs for prolonged systemic therapeutic effects after subcutaneous (SC) or intramuscular (IM) administration. Polymers used for formulation of microspheres are biodegradable and biocompatible. There are various polymers available in the market for preparing microparticles. Some of them include PVA, PLGA and recently silk fibroin were in use (Rajendra et al. 2022). In the present research PLGA is used as a polymer. This polymer is usually used for biodegradable controlled release microparticles (Mao et al. 2012; Qi et al. 2019). In the present research solvent evaporation method is applied to formulate microparticles for injectable controlled release drug delivery system. Microspheres in the finished product are in a dry powder form (Behera et al. 2008).

So, in the present study focus was given on pre-formulation studies of LRH. The main objective of the study was to assess LRH for its suitability to be formulated as controlled release injectable microspheres.

MATERIALS AND METHODS

MATERIALS:

LRH API was obtained as a gift sample from RAKS pharmaceuticals, Vishakhapatnam, India. Biodegradable polymer, poly(lactide-co-glycolide), RESOMER® RG 502 H (L:D::50:50 with Mw: 15000 Da), RESOMER® RG 503 H (L:D::50:50 with Mw: 35000 Da), RESOMER® RG 504 H (L:D::50:50 with Mw: 50000 Da), RESOMER® RG 750 S (L:D::75:25 with Mw: 1.25K Da) were obtained as a gift sample from Evonik. Methanol, Ethanol, Acetonitrile, Dichloromethane (DCM) were obtained as a gift sample from Finar Limited, India. Dibasic sodium phosphate, citric acid anhydrous, Hydrochloric acid was purchased from Avantor. Sodium lauryl sulfate (SLS) was purchased from Sigma-Aldrich. Chemicals and solvents used were of high-performance liquid chromatography (HPLC)

grade. Purified water was used throughout the study.

METHODS:

IDENTIFICATION OF LRH:

Identification of LRH was performed by organoleptic properties, melting point, UV, HPLC, FTIR, XRD and DSC and Chloride test.

Identification by Organoleptic property:

Transfer approx. 2 gm LRH in to petridish and observe against white background.

Identification by Melting point:

Pour few samples in capillary tube and check for melting point in melting point apparatus.

***Identification by UV spectrophotometry method** (Joshi et al. 2012):*

Standard stock solutions of LRH were prepared in solvent and scanned spectrophotometrically over the range of 200–400nm with double beam spectrophotometer (Shimadzu UV spectrophotometer, 240 j/PC, Japan), against the respective blank, to determine wave length of maximum absorbance (λmax).

***Identification by HPLC** (Suneetha et al. 2015):*

LRH was quantified using a Shimadzu prominence-iLC2010 high performance liquid chromatography (HPLC) system equipped with isocratic pump, auto sampler, and photodiode array detector against Standard LRH.

***Identification by FT-IR** (Heng et al. 2019):*

Weight 300 mg Potassium bromide in fine powder form in which 3 mg of LRH was added, mixed well, grinded and make pellet and record IR spectrum between 4000 cm^{-1} to 400 cm^{-1}.

Identification by DSC:

The thermal analysis of LRH was performed by using 3-5 mg of samples in a standard thermal aluminum pan with a comparable lid. Close it properly using closure machine till “click noise” achieved while rotating closing rotter. Then puncture lid with sharp needle and put it in detectable PAN to heat from 0 to 300°C at a 10°C/min heating rate in METTLER TOLEDO DSC (METTLER TOLEDO, Switzerland).

Identification by X-Ray Diffraction (XRD):

Take sufficient sample into sample holder and Spread in all directions. Tap to get compactness and press it gently for uniform and dense surface. Excess sample from sample holder should be scrapped out by knife. Place the bottom plate on the sample holder ring, press gently to clamp. Invert the sample preparation table so that sample holder should face the floor, rotate the sample holder slowly to avoid rough surface and press the spring-loaded knob to detach it. (Make: PANalytical, Model: Empyrean at spinning mode and 1.0000 spinner revolution time)

Identification by Chloride test:

Weigh 100 mg of LRH and transfer into Nessler's tube. Add 15 mL of methanol from measuring cylinder into Nessler's tube and sonicate to dissolve. Add 10 mL of water and shake well. Add 2-3 drops of concentrated nitric acid and 1 mL of 0.1N Silver nitrate solution and shake well.

DETERMINATION OF THERMODYNAMIC SOLUBILITY

Solubility study of drug was performed using different solvents such as water, methanol and Dichloromethane. Weight accurately 1 gm LRH and add 30 mL Dichloromethane in one tube, Weight accurately 1 gm LRH and add 30 mL Dichloromethane in second tube weight 0.5 gm LRH and add 50 mL methanol in third tube and weight 10 mg LRH and add 100 mL water in fourth tube. Shake well and physically check solubility of LRH in different solvents.

Apart from physical evaluation solubility studies were performed in Purified water, 0.1N HCl, 3.8 pH Mcclvaine, 4.5pH Acetate buffer, 6.8 pH phosphate buffer, 7.0 pH phosphate buffer and 7.0 pH phosphate buffer with 1%SLS as a part of Dissolution media selection. 100 mg LRH was taken and add 10 mL of above-mentioned media were taken in different tubes and shaken on a rotary shaker for 24 hours at Human body temperature that is 37°C. Filter all above media using 0.1-micron Nylon filter and Amount of solute in filtrate was determined using UV spectrophotometric analysis at 232 nm wavelength (λmax) for each media.

ANALYTICAL PRE-FORMULATION

Analysis of LRH by UV spectrophotometry method:

Standard stock solutions of LRH was prepared in acetonitrile (For Assay Analysis) and Acetonitrile + Phosphate buffer 7.0 with 1% SLS (For Dissolution Analysis) and observe absorbance at 232 nm wave length of maximum absorbance (λmax) in double beam spectrophotometer (Shimadzu UV spectrophotometer, 240 j/PC, Japan), against the respective blank, to determine

Preparation of stock solution in Acetonitrile:

A stock solution containing 100 µg/ml LRH was prepared by dissolving 10 mg LRH in 100 ml of acetonitrile in a 100 ml of volumetric flask and volume was made up to 100 ml with the acetonitrile. From these stock solutions, 0.5ml, 1ml, 1.5ml, 2ml, 2.5ml and 3.0ml were taken and each made up to 10ml with acetonitrile in suitable volumetric flasks to obtain 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml and 30 µg/ml solutions. Shake flask to dissolve and properly mix.

Preparation of stock solution in Acetonitrile and 7.0 pH phosphate buffer with 1% SLS:

A stock solution containing 100 µg/ml LRH was prepared by dissolving 10 mg LRH in 100 ml of acetonitrile in a 100 ml of volumetric flask and volume was made up to 100 ml with the acetonitrile. From these stock solutions, 0.5ml, 1ml, 1.5ml, 2.0ml, 2.5ml and 3.0ml were taken and each made up to 10ml using 7.0 pH phosphate buffe with 1% SLS in suitable volumetric flasks to obtain 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml and 30 µg/ml solutions.

Calibration curves were constructed at concentrations range 5-30 µg/ml. Absorbance of each solution was measured at the wavelength of 232 nm. Calibration curves was constructed for LRH by plotting absorbance versus concentration at 232 nm wavelength.

Analysis of LRH by HPLC method

LRH was quantified using a Shimadzu prominence-iLC2010 high performance liquid chromatography (HPLC) system equipped with isocratic pump, auto sampler, and photodiode array detector. The mobile phase A was 2000 mL water + 10 mL Triethyl amine – pH adjusted 3.5 with Ortho phosphoric acid and Mobile phase B was Methanol: Acetonitrile (60:40). The system was equipped with an all-time Zorbax SB. Phenyl (250 X 4.6) mm, temperature of column was 40°C and the flow rate was set to 1.5 mL/min. The injection volume for drug loading samples was 10 µl. The chromatographs were analyzed with empower software at 232 nm. Linearity of the method was proved for concentration range of 200 µg/ml to 1000 µg/ml.

DRUG-POLYMER COMPATIBILITY STUDY

As sustained release formulation contains drug polymer matrix in finish product, physical stability of LRH with polymer need to check. SO, Drug polymer compatibility was evaluated by mixing of LRH and mixture of Poly lactic co-glycolic acid (PLGA;50:50) grade at 25°C for 1 month and 40°C for 1 month. The samples were removed after 30 days. Initial result of mixture is analysed compare against 25°C/1 month sample and 40°C/1 month sample.

Fourier transform-infrared (FTIR) study

The FTIR analysis was used for qualitative estimation and identification of functional group present in the compound. LRH was mixed with polymer components at worst ratio that can be used in formulation process. Mixture was stored in USP type-1 glass vial at 25°C±5°C/ 60±5% RH (relative humidity) for one month and 40°C±5°C/75±5% RH for one month. FTIR spectroscopy, Shimadzu, Model 8400, Japan, was used to study the compatibility of pure LRH drug and other preparation composites, by KBr pellet method and scanned from 4000 to 400 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC is the thermal analysis method by which we can measure the interaction of drug with polymer. The thermal analysis above mentioned samples was performed by using 3-5 mg of samples in a standard thermal aluminum pan with a comparable lid and heated from 0 to 300°C at a 10°C/min heating rate in Mettler toledo DSC (METTLER TOLEDO, Switzerland).

RESULTS AND DISCUSSION

DRUG IDENTIFICATION

Organoleptic properties and Melting Point:

LRH is odourless and almost white powder which is slightly sticky in nature. The melting point of drug was in the range **270–272°C**.

Drug identification by UV:

The maximum absorbance of LRH was found to be 232 nm and other peak was found at 316 nm as depicted in figure 1.

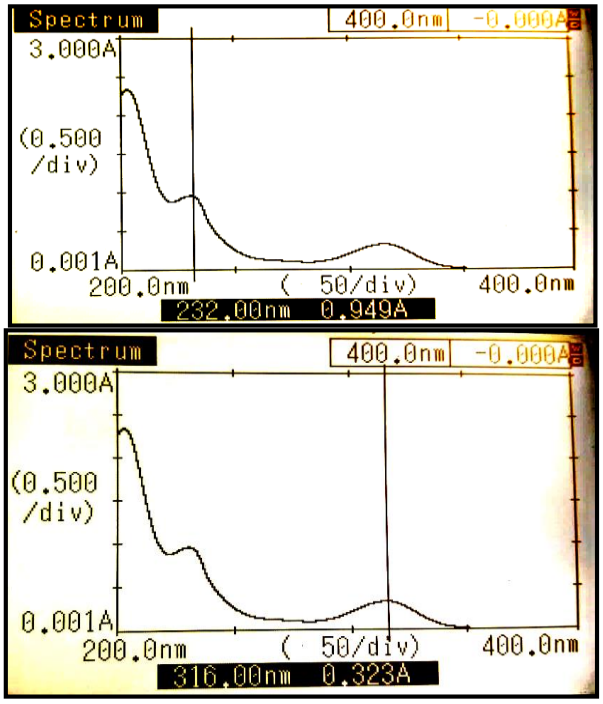

Figure 1: UV spectra of LRH.

Drug identification by HPLC

The peak retention time of LRH was found to be about 11.8 min as observed from figure 2 which is exactly matching with Standard LRH at 11.8 min.

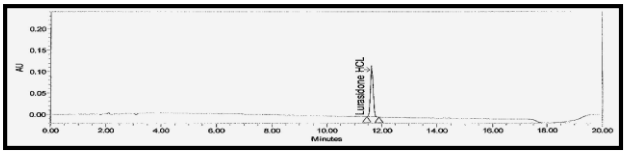

Figure 2: Peak of LRH by HPLC

Drug identification by FTIR

The characteristic absorption peaks of LRH in FT-IR spectra as shown in Figure 3 and the functional groups responsible for characteristic peaks of LRH are mentioned in Table 1.

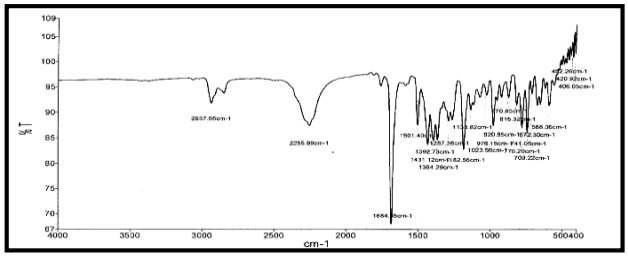

Figure 3: Fourier transform-infrared spectrum of LRH

Table 1. Functional groups, experimental and reported frequencies of LRH

Functional group	Frequency (cm^{-1})	
	Experimental	Specified in literature
C-H stretch (Alkane)	2937.55 cm^{-1}	3000-2850 cm^{-1}
C-N -stretch(nitrile)	2255.99 cm^{-1}	226-2100 cm^{-1}
C=O stretch (amide)	1684.05 cm^{-1}	1820-1670 cm^{-1}
C=C -stretch (Aromatic)	1501.4 cm^{-1}	1600-1400cm^{-1}
C-N -stretch(amine)	1182.56 cm^{-1}	1360-1080cm^{-1}
C-H-bending(alkene)	920.85cm^{-1}	1000-675 cm^{-1}
C-Cl – stretch (Alkyl Halide)	709.22 cm^{-1}	800-600 cm^{-1}

Drug identification by DSC:

DSC thermogram of LRH is shown in Figure 4. Reported melting point value was found 273.44°C and practically melting point value were found 270-272°C by DSC and capillary method respectively.

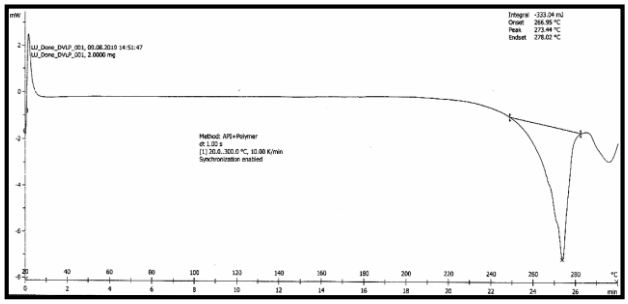

Figure 4: Differential Scanning Calorimetry (DSC) of LRH

Drug identification by XRD:

During XRD analysis of Drug sharp peak observed at below table 2.

Table 2. Reference and measured 2 θ value of LRH

Sr no	Reference 2 θ value	Measured 2 θ value
1	15.1 ± 0.2	15.1
2	15.5 ± 0.2	15.5
3	17.2 ± 0.2	17.2
4	19.5 ± 0.2	19.5
5	21.9 ± 0.2	21.9

Drug identification by chloride test:

A white precipitate observed after addition of nitric acid and silver nitrate solution which meets chloride test requirement as per USP<191>.

DETERMINATION OF THERMODYNAMIC SOLUBILITY

Based on Physical evaluation of LRH in solvent; clear solution is found for Dichloromethane (1 gm in 30 mL DCM), Acetonitrile (1 gm in 30 mL Acetonitrile) and Methanol (0.5 gm in 50 mL Methanol), but insoluble particles were found in water (10 mg in 100 mL water).

LRH solubility is evaluated in purified water, 0.1N HCl, 3.8 pH Mcclvaine, 4.5 pH acetate buffer, 6.8 pH phosphate buffer and 7.0 pH phosphate buffer, 7.0 pH phosphate buffer with 1% SLS. The solubility of LRH in various solvents is shown in Table 2.

Table 3. Solubility parameters of different solvents

Solvents	Solubility (mg/mL)
Purified water	0.286
0.1N HCl	0.1861
3.8pH Mcclvaine	0.1518
4.5pH acetate buffer	0.0222
6.8 pH phosphate buffer	0.0004
7.0 pH phosphate buffer	0.0008
7.0 pH phosphate buffer +1% SLS	3.452

ANALYTICAL PRE-FORMULATION

Analysis of LRH by UV spectrophotometry method

Absorbance of LRH is tabulated in below Table III and Table IV and Based on the experimental data the standard calibration curves were plotted. The regression analysis showed very good correlation (r^2=0.9999) in acetonitrile and (r^2=0.9903) in acetonitrile and 7.0 pH phosphate buffer with 1% SLS. These solutions obeyed Beer-Lambert's law and the linearity was found in concentration range of 5-30 µg/ml. The standard curves of LRH is shown in Figure 5 and Figure 6. Table 4 and 5 shows the concentration and absorbance values of drug in acetonitrile and acetonitrile+ 7.0 pH phosphate buffer with 1% SLS.

Table 4. Concentrations and absorbance of LRH in Acetonitrile by UV

Calibration curve In Acetonitrile at 232 nm	
Concentration (µg/mL)	**Absorbance ± SD (Average of 3)**
0	0.000 ± 0.000
5	0.163 ± 0.002
10	0.315 ± 0.003
15	0.474 ± 0.005
20	0.638 ± 0.008
25	0.800 ± 0.002
30	0.950 ± 0.006

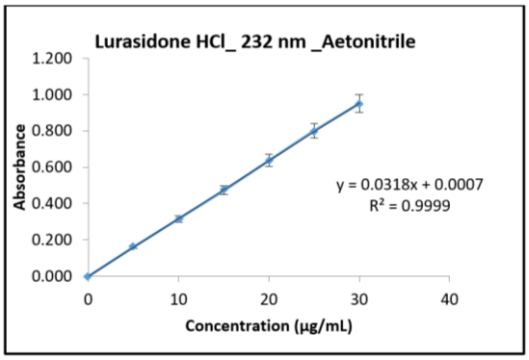

Figure 5: Standard curve of LRH in acetonitrile.

Table 5. Concentrations and absorbance values of LRH in Acetonitrile and 7.4 pH phosphate buffer by UV

Calibration curve In Acetonitrile + Phosphate buffer pH 7.0 with 1%SLS at 232 nm	
Concentration (µg/mL)	**Absorbance ± SD (Average of 3)**
0	0.000 ± 0.000
5	0.185 ± 0.004
10	0.369 ± 0.004
15	0.463 ± 0.004
20	0.585 ± 0.006
25	0.715 ± 0.004
30	0.848 ± 0.007

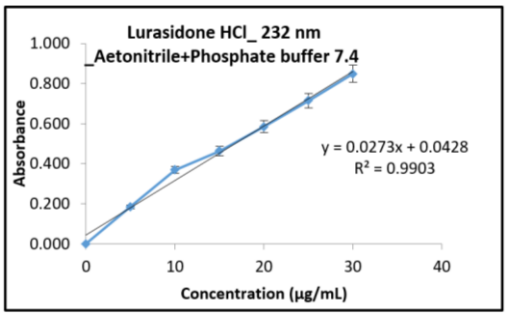

Figure 6: Standard curve of LRH in acetonitrile and 7.4 pH phosphate buffer.

Analysis of LRH by HPLC method

The method was developed to quantify LRH for assay method and the concentration vs absorbance gives the linearity of the same is depicted in figure 6. Table V shows the absorbance and concentration values of LRH.

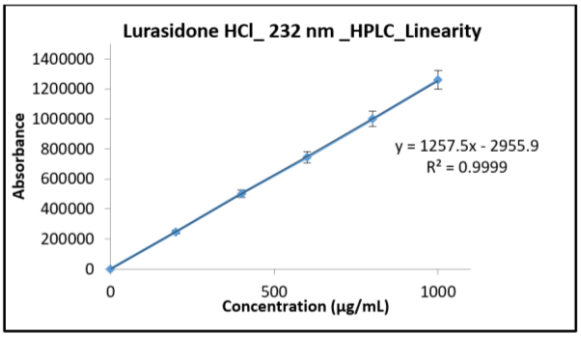

Figure 7: Linearity of LRH by HPLC

Concentration (µg/mL)	Area
0	0
200	247115
400	502252
600	744928
800	1000441
1000	1259917

Table 6. Concentrations and areas of LRH in HPLC

DRUG-POLYMER COMPATIBILITY STUDY

Fourier transform-infrared (FTIR) study

The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug LRH and in the physical mixture with polymer which confirms the absence of chemical interaction between drug and polymers. The FT-IR spectra of initial drug alone and physical mixture is shown in the figure 8. Each peak Available in LRH drug remains same in Physical mixture with polymer.

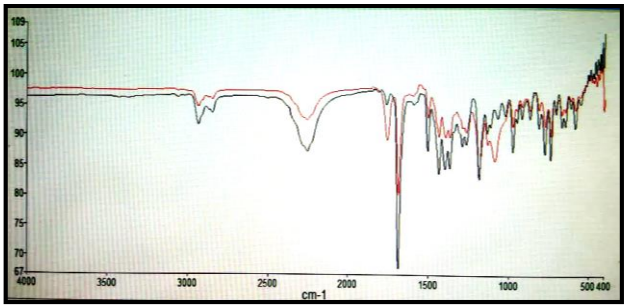

Figure 8: FT-IR spectrum of LRH Vs physical mixture with Drug.

Where,

---------- **LRH _ Initial**

---------- **LRH with polymer_ Initial**

The FT-IR spectra of physical mixture at 25°C and 40°C shown in figure 9 and 10 respectively.

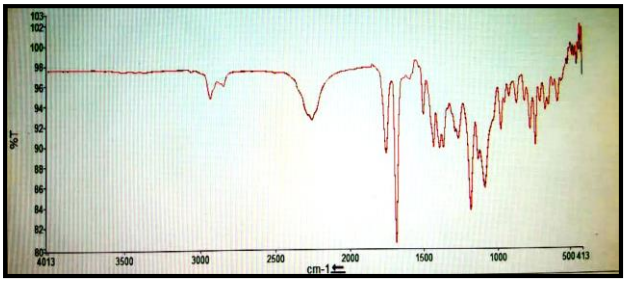

Figure 9: FT-IR spectrum of LRH -Polymer mixture after 1 month at 25°C

Where,

---------- **LRH+Polymer_1M, 25°C**

---------- **LRH+Polymer_Initial**

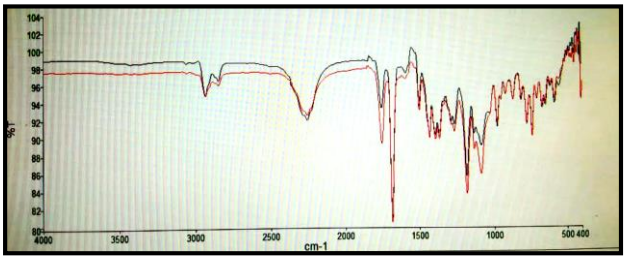

Figure 10: FT-IR spectrum of LRH -Polymer mixture after 1 month at 40°C

Where,

---------- **LRH+Polymer_1M, 40°C**

---------- **LRH+Polymer_Initial**

Almost, all the functional groups of drug with physical mixture remains same at 25°C with >99% similarity factor showing good compatibility between polymer and drug at 25°C but drug with physical mixture shows some intensity change at 40°C.

Differential Scanning Calorimetry (DSC)

DSC thermogram of LRH and polymer mixture showed that there is no change observed in the endothermic peak of drug and polymer in physical mixture at initial condition and after 1 month 25°C, which confirms the absence of chemical interaction between drug and polymers as shown in figure 11 and 12 respectively.

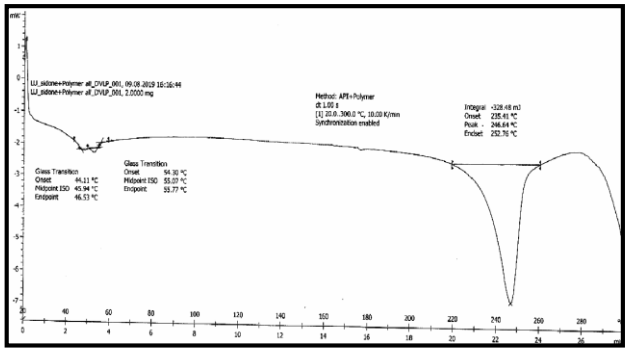

Figure 11: DSC spectra of LRH -Polymer mixture (Initial)

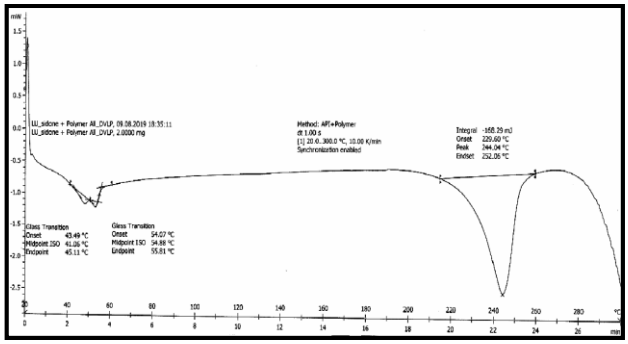

Figure 12: DSc spectra of LRH -Polymer mixture at 1Month, 25□/60%RH)

CONCLUSION

From result of Identification tests (Organoleptic property, melting point, UV, FT-IR, HPLC, XRD and DSC), we can conclude available drug is Lurasidone and Positive result of chloride test (As per USP<191>) concludes hydrochloride salt of Lurasidone. LRH were found soluble in dichloromethane and Acetonitrile, sparingly soluble in methanol and practically insoluble in water. Based on this we can select Dichloromethane and methanol to soluble LRH from which Dichloromethane is also used for solubilization of PLGA polymer during microsphere preparation. Due to freely solubility of LRH in acetonitrile, acetonitrile is used for calibration curve preparation in UV method. Based on UV analyzed result of Solubility of LRH in Different media; 7.0 pH phosphate buffer with 1% SLS can be used as dissolution media in bottle rotating apparatus with 90 mL media volume capacity. The UV method and HPLC method showed good correlation indicating they can be used for quantification of drug in Bulk and *in vitro* studies. Drug Compatibility Study with DSC and FT-IR suggest that there no incompatibility of Drug polymer mixture at 25°C (>97% similarity indicates, there is no incompatibility) and

expected no physical and chemical interaction (negative) on finish product stability analysis but FT-IR Spectrum comparison with initial and 1M/40°C indicates that might be some physical interaction possible at 40°C which suggest finish product storage condition should be 2°C-8°C considering 25°C as accelerated condition. The solubility study of LRH in organic solvent allowed us to use listed solvent in our formulation as processing aid to assist sustained release microsphere finish formulation. From the results of the above pre-formulation studies, we can conclude that LRH is suitable for sustained release injectable formulation.

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