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Original Article

Pharmacokinetics Studies of Lurasidone Hydrochloride in Nano Structured Lipid Carrier Formulation for Nasal to Brain Delivery

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ABSTRACT

Aim: Lurasidone Hydrochloride (LH) is a benzothiazole derivative used as an antipsychotic drug for the treatment of schizophrenia. Oral administration of Lurasidone hydrochloride, however, results in low bioavailability and inadequate concentration of Lurasidone in the brain tissue. Therefore, to improve the bioavailability and to achieve desired drug concentration at the site of action, intra nasal administration could be a feasible, non-invasive route for targeting the brain. The current study involves development and validation of reverse phase HPLC method for quantitation of Lurasidone from biological matrix and application of the validated HPLC method to compare pharmacokinetic parameters after intranasal administration of the Nano structured Lipid Carrier (NLC) formulation of Lurasidone in a rat model. **Materials and Methods:** Lurasidone hydrochloride were obtained from Micro Laboratories (Batch no: LUR4O15005). A reverse phase HPLC method was developed on a binary Gradient HPLC System from Agilent Tech. (1100) for detecting and quantifying Lurasidone from rat plasma. UV (DAD) G13148 detector and Quaternary Gradient (G130A) S.NO. DE9180834) pump along with Fortis C_{18} column (Particle size: 5 M and dimensions of 4.6 mM×250 mM) was used for chromatographic separation. The chromatographic data was evaluated using the CHEMSTATION 10.1 software. All chemicals used were of analytical grade. The developed method was validated for parameters like linearity, specificity, precision, accuracy, robustness etc., The validated RP-HPLC method was then applied to quantitate LH from plasma of experimental rats. The rats were administered with 0.81 mg/kg per body weight of API of LH and NLC formulation of LH by intra nasal route. Nine blood samples were collected from the retroorbital plexus at 0.00 hr (pre-dose) till 24 hr post dose. After 24 hr, the brain tissue from the treated rats was excised under anesthesia. LH was quantified from the blood plasma and the brain tissue homogenate using the validated RP-HPLC method. **Results:** The results of the method validation experiments indicate that the developed method is specific, accurate and precise. The response of the HPLC system is linear in the range of LH concentration from 10 µg/mL to 50 µg/mL. The LOD and LOQ of the method are 0.527 µg/mL and 1.598 µg/mL respectively. The method is robust with adequate tolerance to changes in analyst, system and mobile phase composition and mobile phase flow rate. After intranasal administration of LH at a dose equivalent to free LH of 0.81 mg/kg, in NLC formulation, the concentration of LH in the brain tissue was 111.465 µ/g while after administration of free form of LH, the concentration was found to be 27.49 µ/g. This indicates better penetration of the Lurasidone across the Blood Brain Barrier (BBB) due to the nano sized drug carrier vehicles in the NLC formulation. **Conclusion:** In the current study, the validated reverse phase HPLC method developed to detect and quantify LH, has good precision and accuracy. The method can be successfully applied to quantify LH from API, NLC formulations and biological matrix. The NLC formulation developed is novel and it effectively delivers LH across the BBB. The NLC formulation is thus a possible alternative to oral administration of LH which provides advantages of convenience of administration, increased patient compliance, faster onset of action, lower dosage, better safety and lesser systemic exposure.

Keywords: Nano Lipid Complex, Lurasidone Hydrochloride, Pharmacokinetics, Bio-distribution, RP-HPLC.

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INTRODUCTION

Lurasidone Hydrochloride (LH) is a benzisothiazol derivative used as an antipsychotic drug. It was approved in US (2010) and Canada (2012) for the treatment of schizophrenia.[1] Its bioavailability is between 9 and 19% by oral route and its solubility in water is also very less. Its therapeutic effect is by antagonism of

central dopamine D2 and serotonin Type 2 (5HT2A) receptors.[2] Latuda® is the brand name of the Reference Listed Drug (RLD) available as oral tablets with strengths of 20 mg, 40 mg, 60 mg, 80 mg and 120 mg of Lurasidone hydrochloride.[3] Reported studies indicate that, after an oral administration of Lurasidone hydrochloride as a 40 mg tablet, a C_{max} of 53 ng/mL is attained in 2 hr. Thus, with a low bioavailability, the conventional drug delivery system fails to deliver effective concentration of Lurasidone to brain and is therefore less effective in treating schizophrenia. Since Lurasidone hydrochloride, in its currently available form has very low bioavailability and therefore higher doses are administered to patients. This increases the incidences of adverse events and results in inadequate patient compliance to treatment regimen. Hence, it is necessary to enhance the bioavailability of LH by circumventing the BBB and targeting the receptor site for better therapeutic effect. By inhibiting first-pass metabolism, intranasal administration to the brain decreases adverse effects and accelerates the onset of action. Additionally, by avoiding the BBB, intranasal administration could deliver the substance more precisely to the brain.

An alternative method, which is patient compliant, is therefore needed, to deliver Lurasidone more effectively to the tissues of brain. BBB acts as the most efficient regulator to the entry of drugs to the brain, especially to those drug molecules that are hydrophilic and with large molecular weight. Due to the lack of paracellular opening in the BBB, the absence of pinocytosis and the protein mediated efflux, the uptake of drug molecules by brain is significantly reduced.[4] Therefore, to improve the bioavailability and to achieve desired drug concentration at the site of action, the receptor sites must be targeted by circumventing the BBB.[5] Intra nasal administration could be a feasible, non-invasive route for targeting the brain. The nasal cavity, as a site for systemic absorption of drug, has advantages like large surface area, porous endothelium basement membrane, highly vascularized epithelial layer, high total blood flow per cm^3, avoidance of first pass metabolism and easier access to Central Nervous System (CNS).[6-8] Thus, intra nasal route becomes the easiest alternative and non-invasive route to deliver Lurasidone molecules to the brain and to increase the bioavailability of Lurasidone. Due to easier accessibility, intranasal delivery can result in faster onset of action and enable the use of lower dosage regimen. Additionally, conversion of drug molecules to nano size can enable penetration of BBB and prevent loss of drug by nasal drainage.[9] Better targeting of drug molecules to brain, reduces chances of drug molecules reaching non-target sites thereby, minimizing side effects. There are several reports on the potential use of various colloidal drug carriers such as polymeric nanoparticles, liposomes, nanoemulsions, Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLC) for delivery through intranasal route.[9-13] Of these, NLC has the distinct advantage of being made using lipids that are biodegradable and biocompatible. This helps not only to have higher payload of drug but also the possibility of being used for both hydrophilic and lipophilic drugs. NLC, being a water-based formulation, avoids organic solvents, reduces toxicity and improves stability of drug molecule. NLCs can be produced at lower costs as compared to polymeric or surfactant-based carriers. Their production systems are easier to scale up, sterilize, validate and therefore easier to obtain regulatory approval.[14]

NLCs are modified SLN and are the second-generation innovative lipid nanoparticles used as a bioactive carrier system.[15] The current study involves evaluation of a NLC formulation of Lurasidone for nose to brain delivery. The study involves 2 parts; (i) Development and validation of reverse phase HPLC method for quantitation of Lurasidone from biological samples. (ii) Application of the validated HPLC method to the comparative pharmacokinetic study of Lurasidone in Albino Wistar rats. The effectiveness of the NLC formulation of Lurasidone is evaluated by studying its pharmacokinetic parameters after intranasal administration in a rat model. The bioavailability of Lurasidone after intranasal administration has been estimated using a validated reverse phase HPLC method that has been developed to estimate the Lurasidone concentration in plasma of treated rats. The pharmacokinetic parameters for the NLC loaded Lurasidone formulations have been compared with that of the API of Lurasidone. The study has also estimated the LH concentrations achieved in the plasma and brain after intranasal administration. The pharmacokinetic parameters have been estimated to evaluate comparative bioavailability of LH loaded in NLCs and the pure unprocessed Lurasidone using the estimated drug half-life. The study results will ultimately help in optimizing the therapeutic use of LH loaded NLCs in the management of schizophrenia.

MATERIALS AND METHODS

Chemicals and reagents

Lurasidone hydrochlorides were obtained from Micro Laboratories (Batch no: LUR4O15005). Methanol, acetonitrile n-hexane and 2% isopropyl alcohol were purchased from Merck Chemicals (Mumbai). Filters of 0.45 and 0.22 µM were purchased from Axiva Sichem Biotech (New Delhi, India).

Instruments

Wenser High Precision Balance (Model: PGB 100; 0.001-100 g) was used for weighing of chemicals and reagents. Wenser Ultra Sonicator (Model and capacity: WUC-4L) was used in preparation of formulation. A binary Gradient HPLC System from Agilent Tech. (1100) was used for detecting and quantifying Lurasidone from plasma. It was equipped with UV (DAD) G13148 detector and Quaternary Gradient (G130A) S.NO.DE9180834) pump. Fortis C18 (Particle size: 5 M and dimensions of 4.6 mM×250 mM) column was used for chromatographic separation. The detector signals of eluents from the column were evaluated using the CHEMSTATION 10.1 software.

Preparation and characterization of NLC formulation

The Quality by Design (QbD) approach was used for the development of NLC of Lurasidone hydrochloride for intranasal delivery. The process was optimized using a three-factor, three-level Box Behnken experimental Design (BBD). Several trials were conducted with the percentages of solid lipid, surfactant and sonication time as independent variables and entrapment efficiency (%) and particle size nm) as dependent variables. The characterisation of NLC and three months accelerated stability are as in Table 1.

Bioanalytical Method Development and Its Validation

Reverse Phase HPLC

LH was quantified in plasma using a validated isocratic reverse phase HPLC technique. The method was validated before using it. Separation using reverse phase HPLC was achieved using a mobile phase containing 65 parts of methanol and 35 parts of Orthophosphoric Acid (OPA-0.05% in water) in a v/v ratio. The separation was obtained using a C_{18} column of particle size: 5 M, diameter of 4.6 mM and length of 250 mM. A guard column (Javelian, 5 µ particle size and dimension of 4.6 mM×10 mM) was attached. The mobile phase was pumped at the rate of 0.8 mL/min and Lurasidone was detected at the wavelength of 230 nm.

Linearity of response and preparation of standards

A standard solution of Lurasidone hydrochloride (1000 mg/mL) was prepared as stock. For this, 10mg of Lurasidone hydrochloride was transferred to a volumetric flask of volume 10 mL. Mobile phase (1 mL) was added so that the analyte would be dissolved and then distilled water was added to make up the volume.

Method validation

The validation experiments were conducted as per reported literature and USFDA guidelines,[16,17] for the following parameters:

Specificity

Evaluation of specificity of the method was done by separately injecting 20 µg/uL of stock solution of LH in mobile phase and plain mobile phase. The chromatograms of LH stock solution were compared with blank mobile phase chromatogram for appearance of co-eluting peaks.[18]

LOD (Limit of Detection) and LOQ (Limit of Quantification)

The minimum concentration of analyte that can be estimated by the method is the LOD while, the minimum concentration that can be quantified is the LOQ. The LOD and LOQ for Lurasidone hydrochloride were estimated for the current HPLC method. They were calculated using standard formula:

$$LOD=3.3\sigma/S \text{ and } LOQ=10\sigma/S$$

Where σ is the standard deviation of the response and S is the slope of the calibration curve.[19]

Linearity and sensitivity

Replicate injections of five different concentrations of Lurasidone hydrochloride (in the range of 10 µg/mL to 50 µg/mL) in mobile phase was made to evaluate the linearity of the response of the HPLC system to the analyte concentrations. The data was analyzed using least square regression to evaluate the correlation.

Precision and Accuracy

Various experiments were conducted to determine the precision of the method by conducting the HPLC analysis using different analysts, different instruments, repeated analysis on the same day and on different days. The variabilities in quantitation during the same day (intraday) and on 2 different days (interday) was evaluated by analyzing three different concentrations of Lurasidone hydrochloride at 20 µg/mL, 30 µg/mL and 40 µg/mL in triplicate injections (n=18). The % RSD between each of the analysis results was calculated by regression analysis to determine the precision. Triplicate injections of known quantity of Lurasidone hydrochloride (20 µg/mL) was made to evaluate the repeatability of the method. The percentage Relative Standard Deviation (% RSD) between each of the replicate injection was calculated by regression analysis to determine the repeatability of the method.[20]

The accuracy of the developed method depends on the closeness of values obtained by the method to the actual values. The accuracy was evaluated by recovery method. In this, percentage recoveries of Lurasidone hydrochloride from the aqueous matrix and plasma were determined. Different concentrations of Lurasidone hydrochloride (8 µg/mL, 10 µg/mL, 12 µg/mL) were spiked in plasma in triplicates using independent stock solutions of Lurasidone hydrochloride (10 µg/mL, n=9). The recovery was accessed by calculating % RSD and mean % recovery.[21] The percentage recovery of Lurasidone hydrochloride from the spiked samples were determined by the following formula:

$$\%\ Recovery = \frac{(Av - Ao)}{Aa} \times 100$$

Table 1: Characterisation and stability of LH-NLC.

Parameters	Initial	3 months 40°C/75%RH
Particle size (nm)	99.58±1.2	128.3±1.4
Poly dispersibility index	0.355±0.2	0.506 ±0.1
Zeta potential (mv)	+18.8±0.2	+19.5±0.3
Entrapment efficiency (%)	96.7±2.2	93.4±2.3
Assay (%)	103.8±0.7	96.2±0.2

Where, Av is the total Lurasidone hydrochloride concentration measured after standard addition.

Ao is the original concentration of Lurasidone hydrochloride.

Aa is the Lurasidone hydrochloride concentration added.

Robustness

The method developed is robust when the results obtained by carrying out the analysis under deliberately altered conditions are within the prescribed acceptable limits for each of the changes made. Injections of known quantity of Lurasidone hydrochloride (20 µg/mL) were made in triplicates (n=18), in deliberately varied conditions of wavelength (229 nm, 231 nm), flow rate (0.7 min/mL, 0.9 min/mL) and mobile phase composition [Methanol (64%)+water with 0.05% OPA (36%) and Methanol (66%)+water with 0.05% OPA (34%)]. The % RSD between each of the area values were calculated by regression analysis to establish the robustness.[22]

Experimental animals

The pharmacokinetic parameters for Lurasidone were estimated in the albino Wistar rat. The animals were housed in a well-ventilated room at the animal house facility under standard experimental conditions with ambient temperature (20±3°C) and, relative humidity (60±5%). The experimental animals were separately housed in cages of polypropylene with sterilized bedding of rice husk. A light/dark cycle of 12 hr light and 12 hr darkness was maintained in the animal house. The animals were provided unhindered access to food and drinking water.

Pharmacokinetic study

The pharmacokinetics of LH was studied in rats (albino Wistar) with body weights in the range of 200 and 250 g. The food for the animals were withdrawn in evening before the dosing but were given free access to water, so that dosing could be done in fasting condition. The Institutional Animal Ethics Committee reviewed and approved the protocol (Protocol No. PES's RTBCOP/IAEC; Clear 2021 R 99). API and NLC formulation of Lurasidone were administered at identical dose (0.81 mg/kg per body weight) in the Wister male rats (n=10) by intranasal route. Blood sampling was done at 0.00hr (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0 and 24 hr post dose. 0.25 mL of the retro-orbital plexus blood was withdrawn at each sampling timepoint, under mild anesthesia with isoflurane. The blood was prevented from coagulation by transferring the blood into micro-centrifuge tubes with 10 µL of EDTA. To separate the plasma, the blood was centrifuged (4000 rpm, 10 min) at 4°C to separate plasma. The plasma samples (200 µL) were stored at -20°C till the further analysis by HPLC.[23,24]

Bio-distribution of Lurasidone

The distribution of Lurasidone as free API and from the NLC formulation were studied in excised tissue samples of rats. Two groups of six male rats (Albino Wistar, 200 g body weight) were randomly selected. Lurasidone as free API and in NLC formulation were administered through the nasal route at a dose of 0.81 mg/kg body weight. After 24 hr following the drug administration, the treated rats were euthanized by excess anaesthesia. The quickly excised brain was weighed. 5 mL of methanol was used to homogenise 200 mg of brain tissue. The homogenate was centrifuged (20,000 rpm, for 20 min) at 4°C. The supernatant was filtered and injected into the HPLC system to determine the Lurasidone concentration.[25,26]

Statistical analysis for pharmacokinetic study

For estimating pharmacokinetic parameters, a non-compartmental model was used in an add-in program of PK Solver software. All values (Mean±SD) were analyzed for significance of differences at 95% confidence and p<0.05.

RESULTS

The results of validation carried out on the RP-HPLC method for quantitation of Lurasidone is as follows:

Specificity: In HPLC analysis, there were no co-eluting peaks observed at the retention time of LH. Similarly, the blank plasma also showed no peaks at the at the retention time of LH. Bothe the standard solution of LH and blank plasma were injected separately.

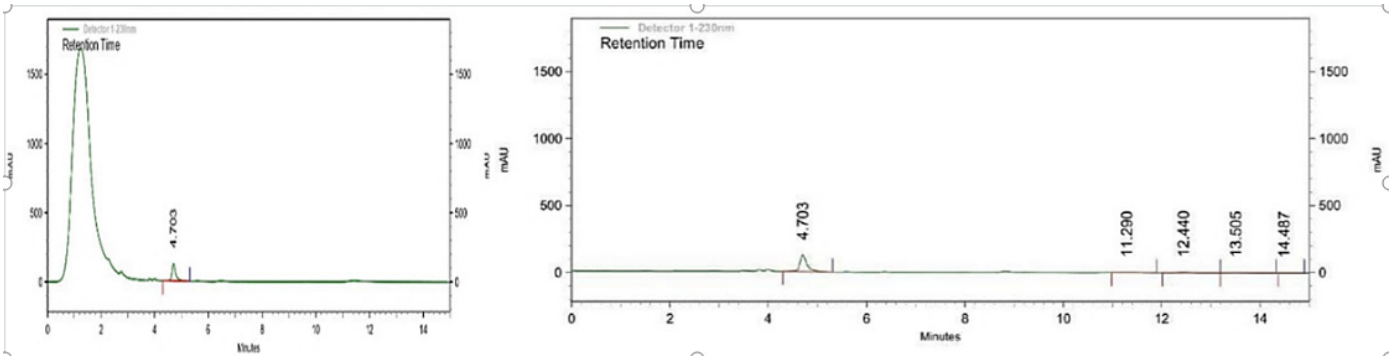

Figure 1: HPLC chromatograms: (A) 3 hr plasma showing Lurasidone hydrochloride from free API; (B) 3 hr plasma showing Lurasidone hydrochloride from NLC formulation.

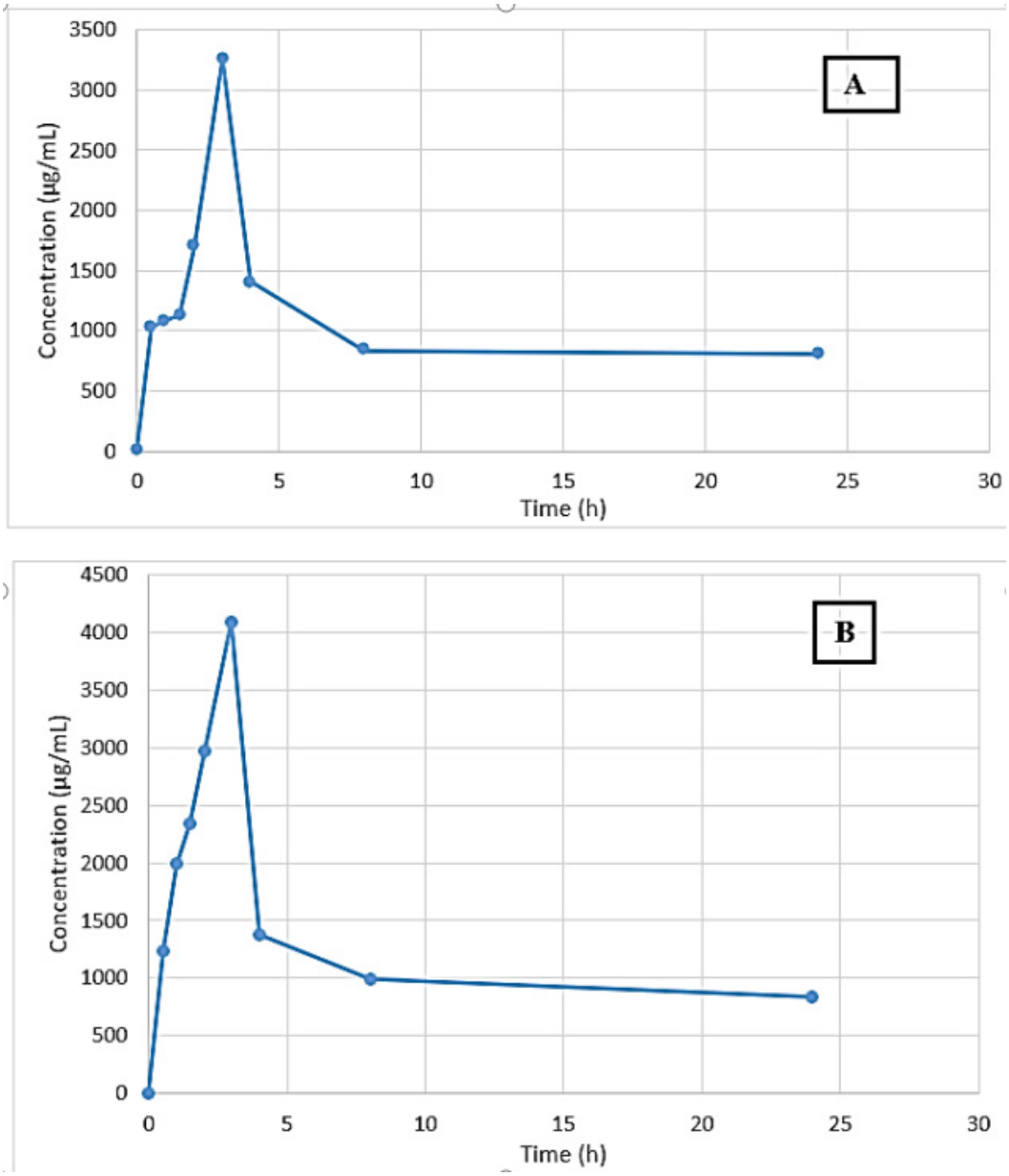

Figure 2: Mean plasma drug concentration-time profile curve showing absorption elimination pattern of Lurasidone hydrochloride in rat plasma after nasal route administration of (A) API and (B) NLC formulation.

LOD and LOQ: The LOD (0.527 µg/mL) and LOQ (1.598 µg/mL) obtained are summarized in Table 2.

Linearity: The response obtained in RP-HPLC for Lurasidone hydrochloride from plasma, was linear in the range from 10 µg/mL to 50 µg/mL. The coefficient of correlation was 0.999 (Table 2).

Precision: Precision was estimated using three different concentrations of Lurasidone hydrochloride (20 µg/mL, 30 µg/mL, 40 µg/mL). Interday and Intraday results showed percent RSD to be less than 2% (Table 2).

Accuracy: The current method could recover drug analyte in the range of 80% to 120% form spiked plasma. The mean percentage recovery values between 97.70% and 98.52%. Standard deviation values were <2.0% and percent RSD was <2% as summarized in Table 2.

Robustness: The HPLC evaluation was performed with varying flow rate, wavelength and mobile phase composition. The validation parameters and results are summarized in Table 2.

Pharmacokinetic Study

LH as free drug (API) and in the form of NLC formulation (0.81 mg/kg as equivalent to free LH) was administered by internasal route in the rats. The blood was collected at pre-determined time points from the retro-orbital plexus. The HPLC method which was developed and validated was applied to estimate the

concentration of LH in the blood plasma. The concentration versus time curve was generated to estimate the pharmacokinetic profile for Lurasidone from free API and from the NLC formulation. The maximum Concentration (C_{max}) of Lurasidone that was obtained in plasma was noted at 3 hr (T_{max}) for both the samples (Figure 1). The C_{max} in plasma was found to be 4085.11 µg/mL for Lurasidone administered in the form of NLC and 3260.98 µg/mL for Lurasidone from the API as depicted in Figure 2. The comparative pharmacokinetic parameters for Lurasidone hydrochloride from NLC as compared to the API are summarized in Table 3.

Bio-distribution study

After administration of LH in the rat, at a dose equivalent to free LH of 0.81 mg/kg, in NLC formulation, the concentration of LH in the brain tissue was estimated. In this study, after the administration of LH through the nasal mucosa, the average concentration of Lurasidone in the brain tissue was found to be 111.465 µ/g. On the other hand, after administration of free form of LH, the concentration of LH in brain tissue was found to be 27.49 µ/g. The results are represented in Figure 3.

DISCUSSION

The specify results indicate that the method was specific to LH and there was no interference observed from the components of the matrix. The linearity results show a high degree of coefficient. The precision results are all within the prescribed acceptable limits. This indicates that the developed method has good precision. The accuracy of the method was within the prescribed acceptable limits of RSD <2%. The method is robust with relative standard deviation <2% which is within the acceptable limits. Pharmacokinetics study showed that optimized NLC formulation showed significant increase in C_{max} indicating improved bioavailability as compared to the Lurasidone as its API. Biodistribution study clearly indicates that the NLC formulation showed better targeting of the LH molecule to the brain as compared to free form of LH. Higher concentration achieved in the brain tissue, in this study indicates better penetration of the Lurasidone across the blood-brain-barrier. This can be attributed to the NLC formulation with the nano sized drug carrier vehicles. There is an improved bioavailability of lurasidone through the formulated NLC when administered intranasal route since, nano formulations increase nose-to brain drug delivery as compared to drug solution of equivalent dose.[27] The efflux of lurasidone back into the intra nasal cavity is prevented by the NLC complex and therefore, nanoparticles as solutions are rapidly cleared from the nasal cavity. The efficacy of nano formulation is maintained till 24 hr was due to the sustained drug release seen in the pharmacokinetic profile.

The current study presents a validated reverse phase HPLC method to detect and quantify LH, with good precision and accuracy, from API, NLC formulations and biological matrix too. The method is thus, unlike earlier reported methods, a single HPLC method for quantitating LH from formulations and biological matric. The NLC formulation developed is novel

Table 2: Summary of validation parameters and results.

Parameters	Results
Wavelength	230 nm
Linearity range (µgm/mL)	10-50
Regression equation (y=mx+c)	45.609x+39.434
Correlation coefficient (r^2)	0.999
LOD (µgm/mL)	0.527
LOQ (µgm/mL)	1.598
Accuracy (%Recovery) (*n*=3) at level 3.	80-120%
Precision (%RSD)	
Repeatability of sample application (*n*=3).	0.32%
Interday (*n*=3) at level 3.	0.08-0.56%
Intraday (*n*=3) at level 3.	0.05-0.34%
Robustness (%RSD)	
Variation in wavelength at 229 nm (*n*=3).	0.23%
Variation in wavelength at 231 nm (*n*=3).	0.05%
Variation in flow rate at 0.7 mL/min (*n*=3).	0.05%
Variation in flow rate at 0.9 mL/min (*n*=3).	0.57%
Variation in mobile phase [64% Methanol+36% (0.05% OPA) water] (*n*=3).	0.34%
Variation in mobile phase [66% Methanol+34% (0.05% OPA) water] (*n*=3).	0.10%

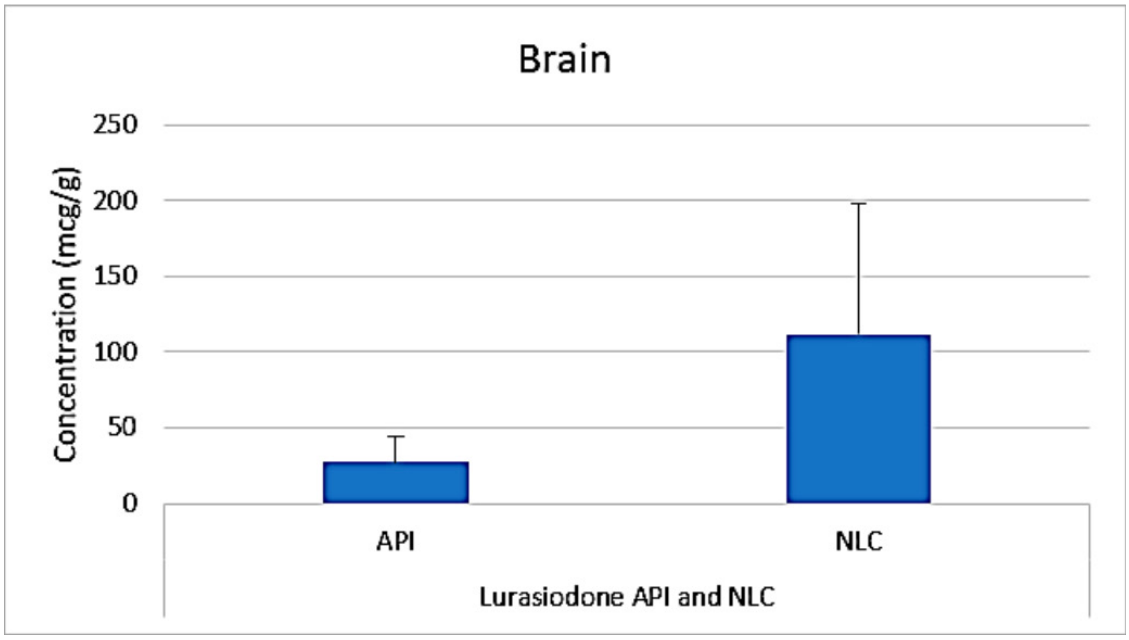

Figure 3: Brain tissue distribution study of Lurasidone hydrochloride.

Table 3: Consolidated pharmacokinetic parameters for Lurasidone hydrochloride.

Parameter	Unit	Value	
		Free drug	NLC
Lambda_z	1/hr	0.044584392	0.020273405
$t_{1/2}$	hr	15.54685733	34.18997288
T_{max}	hr	3	3
C_{max}	µg/mL	3260.983674	4085.111052
Tlag	hr	0	0
$Clast\_{obs}/C_{max}$		0.247158607	0.206496647
AUC_{0-t}	µg/mL*hr	24483.83422	29187.07255
$AUC_{0-\infty\_obs}$	µg/mL*hr	42561.46511	70796.34929
$AUC_{0-t/0-\infty\_obs}$		0.575258257	0.412268045
$AUMC_{0-\infty\_obs}$	µg/mL*hr^2	1089073.03	3325757.672
$MRT_{0-\infty\_obs}$	hr	25.58824108	46.97640069
Vz/F_{obs}	(mg)/(µg/mL)	0.00042686	0.000564349
Cl/F_{obs}	(mg)/(µg/mL)/hr	1.90313E-05	1.14413E-05

and it effectively delivers LH across the blood brain barrier. The pharmacokinetic parameters for the NLC-LH show better bioavailability as compared to free LH. The results of the study can directly translate into a formulation development strategy that would ensure more efficient therapeutic dosing of LH in schizophrenic patients with better patient compliance owing to the use of intranasal administration.

CONCLUSION

The current study demonstrates the feasibility of using nano structured lipid carrier as an effective system to deliver LH through the intranasal route. The comparative pharmacokinetic study of the optimized NLC formulation and free drug of Lurasidone shows that intranasal administration of Lurasidone as nano structured lipid carrier formulation significantly increases bioavailability of Lurasidone. The pharmacokinetics of Lurasidone from the NLC formulation shows low elimination rate constant when compared with the pure LH from its API. The tissue distribution study confirms this increased bioavailability and provides evidence to the effective targeting of the brain tissue and successful penetration of BBB by the NLC formulation. The validated reverse phase HPLC method as developed in the current research is reproducible and more convenient than earlier reported methods for quantitation of Lurasidone from biological matrices. The application of the developed HPLC

method to quantitate LH from plasma and the brain tissue homogenate demonstrates the wide applicability of the HPLC method to different biological matrices. The results obtained in the current study, indicates that the administration of LH as NLC formulation through the nasal route can be explored as a possible alternative to oral administration of LH. Administration of LH as NLC formulation provides advantages of convenience of administration, increased patient compliance, faster onset of action, lower dosage, better safety and lesser systemic exposure. It can be concluded that the formulated NLC-based carrier system for lurasidone, has improved quality aspects and QbD approach, can effectively provide an efficient delivery system for the controlled release of lurasidone in treatment of psychosis. For future research, toxicity studies can be performed for identifying the lethal dose. Clinical research can be done for safe dosing. Future, working on scalability aspects of the formulation and its challenges can be evaluated.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

LH: Lurasidone Hydrochloride; **HPLC:** High Performance Liquid Chromatography; **NLC:** Nano Structured Lipid Carrier; **UV:** Ultra violet; **DAD:** Diode Array Detector; **RP-HPLC:** Reverse Phase High Performance Liquid Chromatography; **M:** Micrometer; **mM:** Millimeter; **mg:** Milligram; **kg:** Kilogram; **µg:** Micro gram; **mL:** Millilitre; **nm:** Nanometer; **hr:** Hour; **LOD:** Limit of Detection; **LOQ:** Limit of Quantification; **API:** Active Pharmaceutical Ingredient; **µ/g:** Micro gram per gram; **5-HT2A:** 5-hydroxytryptamine (serotonin) receptor 2A; **RLD:** Reference Listed Drug; **C_{max}:** Maximum concentration; **BBB:** Blood-Brain Barrier; **CNS:** Central Nervous System; **SLN:** Solid Lipid Nanoparticles; **QbD:** Quality by Design; **BBD:** Box Behnken experimental Design; **v/v:** Volume/Volume; **USFDA:** United States of America Food and Drug Administration**; OPA:** Ortho phosphoric acid; **% RSD:** Percentage Relative Standard Deviation; **min:** Minute; **EDTA:** Ethylenediamine tetra acetic acid; **rpm:** Revolutions per minute; **T_{max}:** Time to peak drug concentration; **$t_{1/2}$:** Half-life; **Tlag:** Lag time; **Obs:** Observed; **AUC:** Area Under the Curve; **inf:** infinity; **AUMC:** Area Under the Moment Curve; **MRT:** Mean Residence Time; **Vz/F:** Apparent volume of distribution during terminal phase; **CL/F:** Drug clearance during terminal phase.

SUMMARY

Lurasidone Hydrochloride (LH) is a benzothiazole derivative used as an antipsychotic drug for the treatment of schizophrenia. Due to low bioavailability, oral administration of Lurasidone hydrochloride, results in inadequate concentration of Lurasidone in the brain tissue. Therefore, there is a need to enhance the bioavailability of lurasidone by an alternate route of administration and / or a new drug delivery system to achieve the desired drug concentration at the site of action, in the brain. The current study involves development and evaluation of a Nano Structured Lipid Carrier (NLC) formulation of Lurasidone hydrochloride for intranasal administration. Pharmacological evaluation of the formulation has been carried out in the rat model and a validated reverse phase HPLC method for quantitation of Lurasidone from biological matrix was developed and validated to estimate the pharmacokinetic parameters after intranasal administration.

Experimental rats were administered with a dose equivalent to free LH of 0.81 mg/kg per body as pure API and as NLC-LH by intra nasal route. Nine blood samples were collected from the retroorbital plexus at 0.00 hr (pre-dose) till 24 hr post dose. After 24 hr, the brain tissue from the treated rats was excised under anaesthesia. LH was quantified from the blood plasma and the brain tissue homogenate using the validated RP-HPLC method.

The developed method was found to be specific, accurate, precise and robust in quantitating LH from rat plasma. The validated method provided linear response in the range from 10 µg/mL to 50 µg/mL. The LOD and LOQ of the method were found to be 0.527 µg/mL and 1.598 µg/mL respectively. After intranasal administration, the concentration of LH in the brain tissue was 111.465 µ/g while after administration of free form of LH as API, the concentration was found to be 27.49 µ/g. This indicates better delivery of the Lurasidone across the blood-brain-barrier with the nano sized drug carrier vehicles in the NLC formulation. It is concluded that in the current study, the validated reverse phase HPLC method developed to detect and quantify LH, has good precision and accuracy. The method can be successfully applied to quantify LH from API, NLC formulations and biological matrix. The NLC formulation developed is novel and it effectively delivers LH across the Blood Brain Barrier. The NLC formulation is thus a as a possible alternative to oral administration of LH which provides advantages of convenience of administration, increased patient compliance, faster onset of action, lower dosage, better safety and lesser systemic exposure.

REFERENCES

1. Rahman H, Haque SM, Siddiqui MR. A comprehensive review on importance and quantitation of atypical antipsychotic drugs and their active metabolites in commercial dosage forms. Current Pharmaceutical Analysis. 2020; 16(8): 989-1019.
2. Grislain L, Couvreur P, Lenaerts V, Roland M, Deprez-Decampeneere D, Speiser P. Pharmacokinetics and distribution of a biodegradable drug-carrier. International journal of pharmaceutics. 1983; 15(3): 335-45.
3. Katteboina MY, Pilli NR, Mullangi R, Seelam RR, Satla SR. LC-MS/MS assay for the determination of lurasidone and its active metabolite, ID-14283 in human plasma

and its application to a clinical pharmacokinetic study. Biomedical Chromatography. 2016; 30(7): 1065-74.

4. Smith QR. A review of blood-brain barrier transport techniques. The Blood-Brain Barrier: Biology and Research Protocols. 2003: 193-208.
5. Ahmad N, Ahmad R, Abbas Naqvi A, Ashafaq M, Alam MA, Ahmad FJ, *et al.* RETRACTED ARTICLE: The effect of safranal loaded mucoadhesive nanoemulsion on oxidative stress markers in cerebral ischemia. Artificial cells, nanomedicine and biotechnology. 2017; 45(4): 775-87.
6. Fernandez-Urrusuno R, Romani D, Vila-Jato JL, Alonso MJ. Development of a freeze-dried formulation of insulin-loaded chitosan nanoparticles intended for nasal administration. STP pharma sciences. 1999; 9(5): 429-36.
7. Ahmad N, Ahmad R, Alam MA, Ahmad FJ, Amir M. Impact of ultra-sonication techniques on the preparation of novel Amiloride-nanoemulsion used for intranasal delivery in the treatment of epilepsy. Artif Cells Nanomed Biotechnol, 2018a; 23: 1-16
8. Ahmad N, Ahmad R, Naqvi AA, Alam MA, Ashafaq M, Abdur Rub R, *et al.* RETRACTED ARTICLE: Intranasal delivery of quercetin-loaded mucoadhesive nanoemulsion for treatment of cerebral ischaemia. Artificial Cells, Nanomedicine and Biotechnology. 2018; 46(4): 717-29.
9. Kumar M, Misra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. International journal of pharmaceutics. 2008; 358(1-2): 285-91.
10. Phachonpai W, Wattanathorn J, Muchimapura S, Tong-Un T, Preechagoon D. Neuroprotective effect of quercetin encapsulated liposomes: a novel therapeutic strategy against Alzheimer's disease.
11. Kakkar V, Singh S, Singla D, Kaur IP. Exploring solid lipid nanoparticles to enhance the oral bioavailability of curcumin. Molecular nutrition and food research. 2011; 55(3): 495-503
12. Seju U, Kumar A, Sawant KK. Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: *in vitro* and *in vivo* studies. Acta biomaterialia. 2011; 7(12): 4169-76.
13. Alam MI, Baboota S, Ahuja A, Ali M, Ali J, Sahni JK. Intranasal infusion of nanostructured lipid carriers (NLC) containing CNS acting drug and estimation in brain and blood. Drug delivery. 2013; 20(6): 247-51.
14. Müller RH, Radtke M, Wissing S. Nanostructured lipid matrices for improved microencapsulation of drugs. International journal of pharmaceutics. 2002; 242(1-2): 121-8.
15. Ahmad N, Ahmad R, Al Qatifi S, Alessa M, Al Hajji H, Sarafroz M. A bioanalytical UHPLC based method used for the quantification of Thymoquinone-loaded-PLGA-nanoparticles in the treatment of epilepsy. BMC chemistry. 2020; 14: 1-5.
16. Ingle A, Code QR. Bio-analytical method validation and its importance in Pharma research-A Review Article.
17. Food FD. Guidance for industry: bioanalytical method validation. http://www. fda. gov/cder/Guidance/4252fnl. pdf. 2001.
18. Koo TS, Kim SJ, Lee J, Ha DJ, Baek M, Moon H. Quantification of lurasidone, an atypical antipsychotic drug, in rat plasma with high-performance liquid chromatography with tandem mass spectrometry. Biomedical Chromatography. 2011; 25(12): 1389-94.
19. LK T, NT R, UN M. A review on bioanalytical method development and validation. Asian J Pharm Clin Res. 2016; 9(3): 6-10.
20. Moein MM, El Beqqali A, Abdel-Rehim M. Bioanalytical method development and validation: Critical concepts and strategies. Journal of Chromatography B. 2017; 1043: 3-11.
21. Yang Y, Ying S, Li T, Zhen J, Chen D, Wang J. A sensitive LC-MS/MS-based bioanalytical method for quantification of salviaflaside and rosmarinic acid in rat plasma and its application in a pharmacokinetic study. Biomedical Chromatography. 2018; 32(8): e4259.
22. Remmerie BM, Sips LL, De Vries R, De Jong J, Schothuis AM, Hooijschuur EW, *et al.* Validated method for the determination of risperidone and 9-hydroxyrisperidone in human plasma by liquid chromatography-tandem mass spectrometry. Journal of Chromatography B. 2003; 783(2): 461-72.
23. Jain K, Sood S, Gowthamarajan K. Optimization of artemether-loaded NLC for intranasal delivery using central composite design. Drug delivery. 2015; 22(7): 940-54.
24. Shinde RL, Bharkad GP, Devarajan PV. Intranasal microemulsion for targeted nose to brain delivery in neurocysticercosis: role of docosahexaenoic acid. European Journal of Pharmaceutics and Biopharmaceutics. 2015; 96: 363-79.
25. Madane RG, Mahajan HS. Curcumin-loaded nanostructured lipid carriers (NLCs) for nasal administration: design, characterization and *in vivo* study. Drug delivery. 2016; 23(4): 1326-34.
26. Gabal YM, Kamel AO, Sammour OA, Elshafeey AH. Effect of surface charge on the brain delivery of nanostructured lipid carriers *in situ* gels via the nasal route. International journal of pharmaceutics. 2014; 473(1-2): 442-57.
27. Alam, Tausif and Pandit, Jayamanti and Vohora, Divya and Aqil, Mohd and Ali, Asgar and Sultana, Yasmin; Optimization of nanostructured lipid carriers of lamotrigine for brain delivery: *In vitro* characterization and *in vivo* efficacy in epilepsy. Expert opinion on drug delivery. 2014; 12: 1-14.

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