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DEVELOPMENT AND EVALUATION OF NANOEMULSION FOR IMPROVED ORAL DELIVERY OF LURASIDONE HYDROCHLORIDE.

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ABSTRACT

Low aqueous solubility is a major problem faced during the formulation of NCE, Lurasidone Hydrochloride is an antipsychotic agent specially used in the treatment of schizophrenia. Lurasidone is practically insoluble in purified water, has poor bioavailability and slow onset of action. The purpose of the present study is to enhance the solubility and bioavailability of Lurasidone hydrochloride by Nanoemulsion technique. Different solubility studies were performed and the Nanoemulsion were prepared by using isopropyl myristate, Oleic acid, Capryol 90 Propylene glycol dicaprate as oil phase and selected surfactants and Co-Surfactants were used to formulate the Nanoemulsion. The formed Nanoemulsion were evaluated for different test. Based on the invitro drug release studies it is concluded the increase in the dissolution profile of the Nanoemulsion when compared to the pure API, which implies the increase in bioavailability of Lurasidone Hydrochloride, by using Capryol 90 as the oil phase, Tween 80 was used as surfactant and PEG 400 used as co-surfactant.

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INTRODUCTION

Schizopherenia is a serious mental disorder in which people interpret reality abnormally. Schizophrenia may result in some combination of hallucinations, delusions, and extremely disordered thinking and behavior that impairs daily functioning and can be disabling[1,3].

People with schizophrenia require lifelong treatment. Early treatment may help get symptoms under control before serious complications develop may help improve the long-term outlook[2].

Lurasidone is a new second-generation antipsychotic belonging to the chemical class of benzisothiazol derivatives indicated for the treatment of acute schizophrenia in adults. This medication was approved by the FDA in October 2010.

Lurasidone differs from other second-generation antipsychotics in its action profile for certain receptors. In vitro studies have shown that lurasidone is the second-generation antipsychotic that shows the greatest affinity for $5HT_7$ receptors (K_i = 0.495–2.10 nM) and a high affinity for $5HT_{1A}$ receptors. $5HT_7$ receptors[4] are abundant in the thalamic and hypothalamic regions involved in the regulation of sleep, and in the cortical areas and the regions of the hippocampus and raphe nuclei involved in memory and mood regulation[6]. Therefore, via these two receptors, lurasidone should have favorable effects on memory and cognitive functions, together with an antidepressive and anxiolytic action [7].

Lurasidone Hydrochloride belongs to BCS Class II molecule, which has poor aqueous solubility and high permeability, the bioavailability of Lurasidone hydrochloride is 9-19%, this represents that a mere amount of the drug is available for the onset of action. The present investigation is to improve the solubility and bioavailability of Lurasidone hydrochloride by formulating it into nanoemulsions by using suitable surfactants and cosurfactants.

Nanoemulsions are dispersed particles used for pharmaceutical and biomedical aids and vehicles. Size of the droplets is governed by the surfactant phase structure at the inversion point induced by either temperature or composition. They are composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios. The particles can exist as water in oil and oil-in- water forms, where the core of the particle is either water or oil, respectively.

MATERIALS AND METHODS

Lurasidone was a kind gift from Aurobindo pharma (Hyderabad, India), Isopropyl myristate was procured from Mohini Organics Pvt. Ltd, PEG- 400 was procured from Sigma Aldrich, Glycerine was procured from Arihant Chemicals, Transcutol P was gifted from Gattefosse, Mumbai, Propylene glycol was procured from Sigma Aldrich. Ultra Turrax homogenizer was supplied from IKA.

Solubility studies

The solubility of lurasidone hydrochloride in various oils (Isopropyl Myristate, Oleic acid, Capryol 90), Surfactants (Tween 20 and Tween 80) and Cosurfactants (Transcutol P, Propylene glycol, PEG 400 and Glycerol) was determined by adding an excess amount of drug in oils, surfactants and co surfactants separately in stopper vials and mixed [10]. The mixture vials were then kept at 25^0C in a sonicator to reach equilibrium. The samples were centrifuged at 3000 rpm for 15 minutes. The supernatant was taken and filtered through 0.45 micron membrane filter. The filtrate was solubilized in suitable solvent, diluted with pH 7.4 phosphate buffer and the concentration was determined using UV Spectrophotometer at 315 nm.

Selection of Surfactant

Surfactant selection was done on the basis of percentage of transparency and ease of emulsification. Briefly 0.4 ml of each surfactant was added to the selected 0.4 ml of oil phase. The mixture was gently heated at 50^0C for homogenization of the component. Each 0.05 ml mixture was then diluted with water. Ease of emulsification was judged by the number of flask inversion required to yield a homogenous emulsion. Emulsion is allowed to stand for 2 hours and their % transparency was evaluated by UV spectrophotometer using distilled water as a blank at 315 nm.

Selection of Co- Surfactant

Screening of Co- Surfactant was conducted on the basis of % transparency and ease of emulsification. 0.1 ml of each cosurfactant mixed with 0.2 ml of selected surfactant and 0.3 ml of selected oil phase was added and evaluated in a similar manner.

Construction of phase diagrams

Pseudo ternary phase diagrams were constructed for 1:1, 1:2, 1:3 surfactant to co surfactant ratios (S_{mix}) so that nanoemulsion regions could be identified. In construction of phase diagram Capryol 90 was used as oil, Tween 80 was used as surfactant and PEG 400 used as co-surfactant.

Preparation of Nanoemulsions

Nanoemulsions were prepared by aqueous phase titration method. The composition of the nanoemulsion was shown in Table No: 01. The drug was dissolved in oil, surfactant and co-surfactant mixture was added in the chosen according to the pseudo ternary phase diagram. The drug was dissolved in oil, surfactant and co-surfactant mixture was added in the chosen concentration, and water was added dropwise with continuous stirring until clear nanoemulsion was formed. Resulting Lurasidone Hydrochloride containing nanoemsulsion was subjected to homogenization for 15 min using mechanical stirrer at 3,000 RPM. The emulsion was then homogenized using Ultra Turrax at 10,000 RPM for 5 minutes to get uniform and stable nanoemulsion[11].

Table No.: 01: Different S_{mix} Ratio (Capryol 90, Tween 80, PEG 400).

Code	Oil (%)	S_{mix} (%)	Water (%)
F1	2	30	68
F2	2	35	63
F3	2	40	58
F4	2	45	53
F5	2	30	68
F6	3	35	62
F7	3	40	57
F8	3	45	52
F9	3	35	62
F10	3	35	62

EVALUATION OF NANOEMULSIONS

Nanoemulsions are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking.

Nanoemulsions were evaluated for following parameters.

Centrifugation Test

Nanoemulsions were centrifuged for 20 minutes at 3000 rpm and checked for phase separation, creaming or cracking[12].

Thermodynamic Stability Study of Emulsion

To assess the thermodynamic stability, the emulsions were subjected to thermodynamic stress of heating and cooling cycles at temperatures of 4°C and 45°C for 48 hours and a freeze–thaw cycle comprising six cycles between -20°C and 25°C with storage at each temperature for not less than 48 hours. This was followed by centrifugation at 3,500 rpm for 30 min and the emulsions were observed for any change in homogeneity previously calibrated with 0.1N Potassium chloride solution.

Determination of pH

pH value plays an important role in determination of the stability of the nanoemulsion. Change in pH means occurrence of chemical reaction that can impair the quality of the final product. The digital pH meter was used to determine the pH of the formulations.

Viscosity

Viscosity of the sample was measured as such without dilution using Brookfield viscometer at 25^0C. A sample volume of 10 ml was used. The nanoemulsion formulations were subjected to different rpm.

Particle size and Zeta potential measurement

0.1 ml of each tested formulation was dispersed in 50 ml of water in volumetric flask and then mixed by inverting the flask. Globule size and zeta potential of the nanoemulsion was determined by particle size analyzer, that analyzes the fluctuations in light scattering due to Brownian motion of the particles. Light scattering was monitored at 25^oC at 90^o angle.

Globule size analysis

The globule size and size distribution were analyzed by the dynamic light scattering with a globule size apparatus, SMEEDs were diluted 250 times with 0.1N Hcl at 25^0C under gentle shaking. After equilibrium, the emulsions were filtered through Whatman filter paper. The filtrates were analyzed by zeta sizer. A laser beam was used and light scattering was monitored at 25^0C at 90^0 angle.

Poly dispersity index (PDI) assay

The assay is used to measure the uniformity of globule size in nanoemulsion. It can be obtained by nanolase particle size analyzer. The higher the polydispersity value refers to the lower uniformity of the globule size of nanoemulsion[13].

Refractive index

Refractive index was determined using Mettler refractometer at 25^oC

Drug content

Drug content was measured by HPLC system made Waters Alliance e 2695 (Waters, Milford, MA, USA) using Water's C18 250 x 4.6 mm, 5µm column maintained at ambient temperature, a quaternary gradient system (600 Controller), in line degasser (Waters, model AF). The system was equipped with a photodiode array detector (Water, 996 model) and auto sampler (Waters, model 717 plus). Data was processed using Empower Pro 2 software (Waters, Milford, MA, USA).

Invitro dissolution

Nanoemulsion was filled in capsule shell and invitro release profile was taken in a USP apparatus 2 at 37 ± 0.5^{0}C at 100 RPM in 900 ml of 0.1 N Hydrochloric acid. Aliquots were withdrawn after 5, 10, 15, 20, 30 and 45 minutes, and analyzed at 315 nm.

RESULTS AND DISCUSSION

Solubility

Solubility plays an important role, as the ability of the nanoemulsion to maintain the drug in solubilized form depends on the solubility of the drug in the oil phase. After screening of Lurasidone Hydrochloride solubility, it was found that lurasidone hydrochloride exhibit maximum solubility in Capryol 90. Hence Capryol 90 was chosen as the oil phase. Similarly based on solubility parameter, Tween 80 was used as surfactant and PEG 400 used as co-surfactant. Data represented in Table No:02

Table No.02: Solubility of Lurasidone Hydrochloride in different Oils, Surfactants and Cosurfactants.

Excipients	Solubility (mg/ml)
Oils	
Isopropyl Myristate	17.54±0.3
Oleic acid	25.46±0.5
Capryol 90	34.16±0.4
Surfactants	
Tween 20	12.34±0.6
Tween 80	27.83±0.4
Co-Surfactants	
Transcutol P	50.14±0.5
Propylene glycol	36.85±0.2
PEG 400	82.67±0.4
Glycerol	71.54±0.3

Thermodynamic stability studies

Thermodynamic stability studies were performed to observe the ability of the formulation to withstand different stress conditions. A stable nanoemulsion formulation should not lose its ability of spontaneous emulsification upon dilution. Based on the results of thermodynamic stability tests as shown in table no.03, four formulations were selected for preparation of Lurasidone Hydrochloride loaded Nanoemulsions were subjected for characterization.

Table No. 03: Thermodynamic stability tests for Nanoemulsion formulations.

Formulation	Centrifugation test	Freeze thaw cycle	Heating- cooling	Results
F1	√	X	√	Fail
F2	√	√	√	Pass
F3	X	√	√	Fail
F4	√	√	√	Pass
F5	X	√	√	Fail
F6	√	√	X	Fail
F7	√	√	√	Pass
F8	X	√	√	Fail
F9	√	X	√	Fail
F10	√	√	√	Pass

Droplet size, Polydispersity index (PDI), pH, % Transmittance, Zeta potential, were shown in table no:04

Drug content

All Nanoemulsion formulations showed drug content within 97-99%, Table No.04

Tablet No: 04 Characterization of Nanoemulsions.

Code	Droplet size (nm)	Polydispersity index (PDI)	Viscosity (mPas)	RI	% Transmittance	ZP (Mv)	pH	%Drug Content
F2	89.15±0.52	0.168	130.54±1.2	1.408±0.001	97.33±0.21	-25.67±1.65	5.84	98.26
F4	77.24±0.38	0.162	76.81±2.6	1.293±0.003	98.24±0.09	-21.36±1.39	5.62	99.10
F7	85.68±0.47	0.171	98.53±1.9	1.325±0.004	94.32±0.82	-26.28±1.52	6.13	98.14
F10	79.39±0.81	0.165	124.91±6.4	1.320±0.008	96.41±0.09	-24.14±2.47	6.59	98.52

In vitro dissolution

The pure API powder showed that only 20% drug was released within 45 minutes. Invitro release profile of F4 showed that 90.67% drug was released within 45 minutes. It might be quick emulsification properties of nanoemulsions and its ability to keep drug in solubilized state upon dilution. Results shown in Table No. 05.

Table No: 05 Invitro Dissolution studies.

Time (In Minutes)	% Drug release				
	Pure API	F2	F4	F7	F10
5	2.36	5.29	6.35	4.21	5.34
10	3.45	20.34	23.91	19.67	21.64
15	6.87	38.59	40.59	36.39	35.46
20	10.22	50.17	55.18	49.67	49.46
30	16.54	75.54	80.64	73.10	76.46
45	20.16	82.64	90.67	80.93	85.61

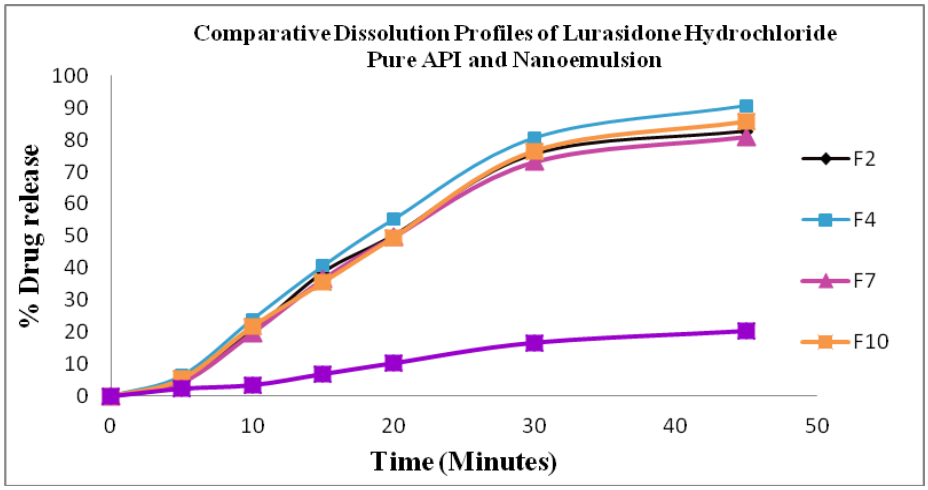

Figure No.01 Invitro dissolution profile.

CONCLUSION

Nanoemulsion are considered as an advance technique for improving the bioavailability of poorly water soluble drugs by enhancing the solubility and minimizing the first pass metabolism. A correct combination of oil, surfactant, cosurfactant and water is a major consideration factor in nanoemulsion preparation. Capryol 90 was chosen as the oil phase, Tween 80 was used as surfactant and PEG 400 used as Co-surfactant were selected for preparation of nanoemulsion by aqueous phase titration method. Based on different invitro release study, Lurasidone Hydrochloride nanoemulsion formulation of batch F4 was found to be optimum formulation. The optimized formulation showed low particle size, low viscosity and high percentage transmittance.

The present study clearly indicates the improvement of solubility, dissolution rate and there by oral bioavailability of Lurasidone Hydrochloride by formulating it into Nanoemulsions.

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