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Solubility and Bioavailability Enhancement of Lurasidone Hydrochloride by SMEDDS

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Abstract: The purpose of the present study is to prepare SMEDDS of Lurasidone Hydrochloride. The SMEDDS were prepared by using Propylene glycol dicaprate as oil phase and TPGS and TBCP were selected as emulsifiers, the formed SMEDDS were evaluated for different test. Based on the invitro drug release studies it is confirmed that the increase in the dissolution profile of the SMEDDS when compared to the pure API, which directly implies that increase in the bioavailability of the Lurasidone Hydrochloride.

Keywords: Propylene glycol dicaprate, TPGS, TBCP, SMEDDS.

INTRODUCTION

Schizophrenia [1] is a major mental illness that causes changes in perception, thoughts and behavior. Lurasidone [2,3] 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[4].

Lurasidone is a powerful antagonist of D_2 dopamine and $5HT_{2A}$ serotonin receptors but differs from the other second-generation antipsychotics in its action profile for certain receptors [5,6]. Lurasidone [7,9] is the second-generation antipsychotic with the greatest affinity for $5HT_7$ receptors and has a high affinity for $5HT_{1A}$ serotonin receptors, compatible with favorable effects on cognitive function and an antidepressant action.

By contrast, lurasidone has a low affinity for α_1 α_{2C}-adrenergic and $5HT_{2C}$ serotonin receptors, and no affinity for histaminergic H_1 or muscarinic M_1 receptors, suggesting a better tolerability profile than the other second-generation antipsychotics [8].

The present investigation is to increase the solubility and bioavailability of Lurasidone hydrochloride by formulating it into SMEDDS. SMEDDS help in increasing the absorption of lipophilic drugs taken orally. They spread readily in the GI tract, and the digestive motility of the stomach and the intestine provides the agitation necessary for self-emulsification.

MATERIALS AND METHODS

Lurasidone was a kind gift from Aurobindo pharma (Hyderabad, India). Propylene glycol monocaprylate was gifted by Gattefosse, Mumbai, India. TPGS was gifted by Isochem, France.

Poloxamer 407, a triblock copolymer of the type polyethyleneoxide- polypropyleneoxide-poyethyleneoxide with average formula EO101–PO56EO101 (abbreviated in what follows as triblock copolymer TBCP) was offered by Signet Chemicals, Mumbai, India.

Ultra Turrax homogenizer was supplied from IKA,

Preparation of Emulsion

Based on the RHLB value and solubility results, propylene glycol dicaprate was selected as oil phase and TPGS and TBCP were selected as emulsifiers. Total surfactant blend concentration of 1.5 % w/w was used to achieve an RHLB of 15 for preparing the emulsions. The required amount of TPGS was dissolved in the selected oil followed by the drug. TBCP was dissolved in the aqueous phase. Both phases were heated to 40°C and the oil phase was added in a dropwise manner to the aqueous phase with vigorous stirring for 15 min using mechanical stirrer at 3,000 RPM.

The emulsion was then homogenized using Ultra Turrax at 24,000 RPM for 5 min. A set of three

emulsions were prepared containing different amounts of the oil (Table No.1).

Table-1: Formulation of Lurasidone Hydrochloride SMEDDS

Batch Code	F1	F2	F3	F4
Lurasidone (%)	0.5	0.5	0.5	0.5
Propylene glycol dicaprate (%)	5	3	4	7.5
TPGS (%)	1.3	1.5	1.4	1.7
TBCP (%)	0.2	0.25	0.3	0.2
Water up to (%)	100	100	100	100

EVALUATION OF LIQUID EMULSIONS

The liquid emulsions (before spray drying) and the reconstituted emulsions were evaluated for the following parameters.

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.

Precipitation analysis

The prepared SMEDDS were diluted with 0.1N HCl upto 250 times. The diluted microemulsion was observed at 1 hour and 6 hours for any sign of phase separation or drug precipitation.

Cloud point measurement

The formulation was compared for cloud point. Each formulation was diluted with water in the ratio of 1:100 and placed in a water bath with a gradual increase in temperature, at the cloud point, drop in sample % transmittance was measured spectrophotometrically.

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.

Drug content

The HPLC system made was 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

Liquid SMEDDS was filled in capsule shell and invitro release profile was taken in a USP apparatus 2 at 37 ± 0.5^0C 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

Thermodynamic stability studies

Thermodynamic stability studies were performed to observe the ability of the formulation to withstand different stress conditions. A stable SMEDDS formulation should not lose its ability of spontaneous emulsification upon dilution. All liquid formulations were found to be stable in the centrifugation test and in the freeze- thaw cycle. There was no sign of phase separation as reported in Table No. 2

Cloud point

The cloud point is the temperature above which the formulation clarity turns into cloudiness. At higher temperatures, phase separation can occur. Since both drug solubilization and formulation stability will decline with this phase separation, the cloud point of the formulation should be over 37^0C. in this study, the cloud points of all formulations were very high as reported in Table No. 2

Precipitation analysis

Out of four different formulations, the F1 was precipitated on dilution with 0.1N HCL at 250 times after 6 hours. Although there was no sign of precipitation upto 2 hours in all formulations. Table No. 2

Drug content

All SMEDDS showed drug content within 97-99%, Table No.3

In vitro dissolution

The pure API powder showed that only 20% drug was released within 45 minutes and 28% in the recovery period for 90 minutes. Invitro release profile of liquid F1 showed that 99.15% drug was released within 45 minutes. It might be quick emulsification

properties of SMEDDS and its ability to keep drug in solubilized state upon dilution.

Globule size analysis

Droplet size of SMEDDS is a critical step in the pathway of enhancing drug bioavailability. For F1 the globule size was found to be 113.5 nm

Table-2: Thermodynamic stability, Cloud point, Precipitation studies

Formulation	Centrifugation test	Freeze thaw cycle	Cloud point (Temp^{0}C)	Precipitation	
				After 1 h	After 6 h
F1	No phase separation	No phase separation	71	Clear	Clear
F2	No phase separation	No phase separation	65	Clear	Clear
F3	No phase separation	No phase separation	63	Clear	Clear
F4	No phase separation	No phase separation	69	Clear	Clear

Table-3: Drug content

Sample	Drug content (%)
F1	99.15
F2	98.24
F3	97.83
F4	97.21

Table-4: Invitro Dissolution studies

Time (In Minutes)	% Drug release				
	Pure API	F1	F2	F3	F4
5	2.36	4.19	4.27	5.64	4.96
10	3.45	14.51	14.58	15.47	12.64
15	6.87	31.25	27.64	32.51	24.87
20	10.22	44.20	35.10	35.39	31.54
30	16.54	71.28	50.76	54.12	48.97
45	20.16	79.58	62.54	73.64	69.85

Table-5: Globule size analysis

Sample	Particle size (nm)
F1	105.98
F2	148.34
F3	163.87
F4	187..17

Dilution 250 times in 0.1N HCL

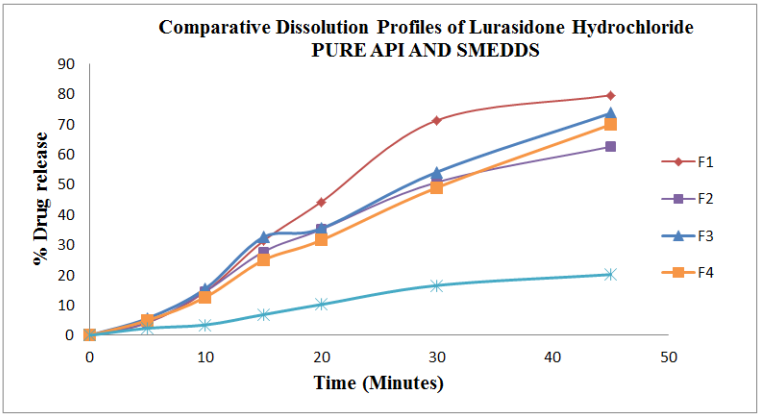

Fig-1: Invitro dissolution profile

CONCLUSION

Liquid SMEDDS were prepared for antipsychotic Lurasidone hydrochloride. Optimized liquid SMEDDS contains 5% Propylene glycol dicaprate, 1.3% TPGS, 0.2% TBCP and Purified water upto 100%, which showed spontaneous emulsification properties and good thermodynamic stability. Liquid SMEDDS showed a better in vitro drug release profile compared with pure API. The present study confirmed that the new self microemulsifying systems containing bio- enhancer excepients are promising strategies for enhancing dissolution rate and thereby oral bioavailability of the Lurasidone Hydrochloride.

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