Research Article

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ENHANCEMENT OF SOLUBILITY OF LURASIDONE HCL USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The present study was carried out to enhance solubility of Lurasidone HCl. Lurasidone HCl was selected as model drug and different carriers like Urea, Polyethylene Glycol 4000, Polyvinyl pyrrolidone K-30 were used in drug to carrier ratio 1:1, 1:3, 1:5 by weight respectively. Solid dispersions were prepared by physical mixing method and solvent evaporation method. Solid dispersions were evaluated by drug content, *in-vitro* release, FT-IR, DSC and XRD. The obtained data of solid dispersion prepared by solvent evaporation method were compared with physical mixing method. The result showed decrease in melting point change from crystalline to amorphous form and improved dissolution rate as compared to physical mixing as well as pure Lurasidone HCl. The finding of present study proposes that solid dispersion approach is beneficial in enhancing solubility of drug and bioavailability as well.

Keywords: Lurasidone HCl, solid dispersion, Urea, PVP K-30, PEG 4000.

INTRODUCTION

Enhancement of bioavailability of poorly water soluble drug is a big challenge for formulation scientist. Solid dispersion technique is useful in improving bioavailability by increasing solubility. Solid dispersion is defined as dispersion of drug in matrix of hydrophilic carrier. Solid dispersion technique is basically used for BCS class II drugs. Drugs which come under BCS class II have low water solubility and high permeability and these drugs have solubility as rate limiting step. Thus if we increase solubility of drug, then bioavailability of drug will also increases^{1,2}. Lurasidone Hydrochloride is atypical antipsychotic drug. This has low bioavailability (9-19 %) and high protein binding (98 %). It acts by antagonizing D₂ and 5-HT_{2A} receptor which improve negative of symptoms of psychoses and reduce extrapyramidal side effects which are associated with typical antipsychotics. It is used in treatment of schizophrenia³. There are various methods which are used for making solid dispersion like solvent evaporation method, melting method, spray drying method and other also. In present investigation physical mixing method and solvent evaporation method was employed for preparation of Lurasidone HCl solid dispersion. The carriers used were urea, polyethylene glycol 4000 and polyvinylene pyrrolidone K-30. The samples were formulated in different drug: carrier ratios.

MATERIAL AND METHOD

Drug and chemicals

Lurasidone HCl obtained as gift sample from Manus Akkteva Biopharma LLP, Ahamdabad, India. Urea, Polyethylene Glycol, Polyvinylene K-30 were procured from Merck chemical Ltd. All carriers and solvents used were of analytical grade.

Standard curve of Lurasidone HCl

Lurasidone HCl was estimated by UV spectroscopic method and absorbance was taken at 314 nm in 0.1 N HCl pH 3.8 which was used in present investigation. The stock solution of Lurasidone HCl was subsequently diluted to 5, 10, 15, 20, 25, 30 ug/ml using 0.1 N HCl pH 3.8 and observations was measured by UV spectroscopy. The method obeys beer laws in the concentration 0-50 ug/ml⁴.

Preparation of solid dispersion by physical mixing method

Physical mixtures were prepared by trituration of drug and carrier in mortar pestle then proper blending in poly bags. Then mixtures were sieved and stored in desiccator at room temperature for further evaluation⁵.

Preparation of solid dispersion by solvent evaporation method

Solid dispersions of Lurasidone HCl were prepared with drug and carrier (Urea, PVP K-30, PEG 4000) ratio 1:1, 1:3, 1:5 by weight, using solvent evaporation method. The drug was dissolved in ethanol then further carriers were dissolved in ethanol. Then solvent was removed by evaporation keeping at 40°C under proper stirring for 24 hours. Then solid dispersions were collected and dried at room temperature for 48 hours. Then solid mass was pulverized in porcelain mortar and pestle and then passed through sieve no. 80 and store at room temperature in desiccator for further use⁶.

Drug content

Samples equivalent to 40 mg Lurasidone HCl was placed in 100 ml volumetric flask containing some quantity of 0.1 N HCl pH 3.8 and then finally volume was made up to mark. Then it was shaken for some time to dissolve the sample, and then filtered through Whatman filter paper number 42 and suitably diluted and analyzed with double

beam UV-VIS spectrophotometer at 314 nm⁵. Drug content was determined by following formula:

$$\text{Percentage drug content} = \frac{\text{Mact}}{\text{Mes}} \times 100$$

$$= \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

In vitro dissolution study of Lurasidone HCl and its formulations

It was performed in USP type II apparatus (Paddle type). Accurately weighed solid dispersion containing 40 mg Lurasidone HCl was used for dissolution study. 0.1 N HCl pH 3.8 solution was used as dissolution medium at $37 \pm 0.5^\circ\text{C}$ and paddle speed was 100 rpm. Dissolution study was carried out for 60 minutes. 10 ml sample was withdrawn at predetermined time interval of 5, 10, 15, 30, 45, 60 min. Sink condition was maintained by adding 10 ml fresh medium. Samples were filtered by Whatman filter paper no. 42 and analyzed by UV- visible spectrophotometer at 314 nm¹.

Infrared spectroscopy

Infrared spectroscopy was performed to determine interaction between drug and carrier. Sample (fine pure drug or prepared solid dispersion) was mixed with potassium bromide and then compressed into pellet. Spectra were recorded on shimadzu FTIR 8700 at 4000 to 400 cm⁻¹.⁷

Differential scanning calorimetric studies

It was performed on scanning calorimetry (DSC Q20 V24.11 build 124). The instrument was calibrated with standard indium. Sample (2-5) were placed in sealed aluminium pans and heated from 40°C to 390°C at rate of $10^\circ\text{C}/\text{in.}$ in nitrogen atmosphere with reference to empty pan⁸.

X-Ray Diffraction Studies

The powder x-ray diffraction (XRD) was performed by X'pert Pro with Spinner PW3064 using Ni-filtered, CuK α radiation, a voltage of 45 kV, and a current of 40 mA with a scintillation counter. The instrument was operated in the continuous scanning speed of $4^\circ/\text{min}$ over a range of 5°C to 40°C .⁹

Drug Release Kinetics

For understanding kinetics of drug release, the results of *in-vitro* dissolution study were fitted in various linear kinetic equations like zero order, first order, Hixson-Crowell's cube root model and Higuchi model. Dissolution data of best formulation were fitted and the value of regression coefficient was determined and compared to each other. The model which gave highest value of Regression Co-efficient (r^2), the release of drug follows that kinetics¹⁰.

Stability Study

Accelerated stability studies were carried out on the F-18 formulation as per ICH Guidelines Q1C. The most satisfactory formulation was stored and sealed in aluminum foil. The samples were stored $40 \pm 2^\circ\text{C}$ ($75 \pm 5\%$ RH) for 3 months. Solid dispersion formulation was evaluated for physical characteristics, and *in-vitro* drug release study, drug content study, solubility.¹¹

RESULT AND DISCUSSION

Calibration curve

Estimation of Lurasidone HCl was carried out in 0.1 N HCl buffer pH 3.8 ranging from 5-50 ug/ml at 314 nm absorbance. The standard curve was linear with regression coefficient 0.9967. Lurasidone HCl is very slightly soluble in water and having poor bioavailability and comes under BCS class II. To improve its bioavailability, solid dispersions of drug were prepared. (Table 1)

Preparation of formulation (Table 2)

Drug content (Table 3)

In-vitro release study (Table 4)

FT-IR study (Figure 1-4)

Interpretation of IR Spectra (Table 5)

DSC Study (Figure 10,11)

Powder XRD Study (Figure 12,13)

Stability Study

Formulation was found to be stable with insignificant change in physical appearance, *In-vitro* release study, drug content and solubility.

Table 1: Observation table of standard curve

S.No.	Concentration (ug/ml)	Absorbance 314 nm
1	5	0.0417
2	10	0.0785
3	15	0.1002
4	20	0.1345
5	25	0.1701
6	30	0.2011

Table 2: List of formulations containing different carriers in different ratios

Formulation	Method of Formulation	Drug (Lurasidone HCl)	Carrier used		
			Urea	PVP K-30	PEG 4000
F-1	PM method	400 mg	400 mg	-	-
F-2	PM method	400 mg	800 mg	-	-
F-3	PM method	400 mg	1200 mg	-	-
F-4	PM method	400 mg	-	400 mg	-
F-5	PM method	400 mg	-	800 mg	-
F-6	PM method	400 mg	-	1200 mg	-
F-7	PM method	400 mg	-	-	400 mg
F-8	PM method	400 mg	-	-	800 mg
F-9	PM method	400 mg	-	-	1200 mg
F-10	SE method	400 mg	400 mg	-	-
F-11	SE method	400 mg	800 mg	-	-
F-12	SE method	400 mg	1200 mg	-	-
F-13	SE method	400 mg	-	400 mg	-
F-14	SE method	400 mg	-	800 mg	-
F-15	SE method	400 mg	-	1200 mg	-
F-16	SE method	400 mg	-	-	400 mg
F-17	SE method	400 mg	-	-	800 mg
F-18	SE method	400 mg	-	-	1200 mg

Table 3: Drug content of all formulations

Formulation code	Drug content
F-1	63.74
F-2	55.29
F-3	54.73
F-4	59.33
F-5	53.50
F-6	44.99
F-7	54.31
F-8	60.70
F-9	50.24
F-10	75.24
F-11	80.70
F-12	82.49
F-13	79.95
F-14	76.02
F-15	78.70
F-16	84.69
F-17	86.85
F-18	88.45

Table 4: In-vitro release of drug and all formulations

Formulation	Cumulative % release of drug at 60 minutes
Drug	23.92
F-1	22.18
F-2	25.22
F-3	28.87
F-4	32.66
F-5	36.31
F-6	39.47
F-7	44.23
F-8	48.92
F-9	54.85
F-10	59.06
F-11	61.77
F-12	64.82
F-13	68.65
F-14	71.58
F-15	74.30
F-16	77.31
F-17	82.53
F-18	92.41

Table 5: Interpretation of IR spectra Release Kinetics Study

Peaks	Description	Range	IR peaks of drug	IR peaks of drug and urea	IR peaks of drug and PVP K-30	IR peaks of drug and PEG 4000
2914.24	C-H stretching	2962-2853	Present	Present	Present	Present
2258.49	Aryl Nitrile	2260-2240	Present	Present	Present	Present
2229.58	Isocyanide	2220-2070	Present	Present	Present	Present
1760.89	A β unsaturated gamma lactones	1780-1760	Present	present	Present	Present
1685.67	Aryl group	1700-1680	Present	Present	Present	Present
1502.44	Aromatic group	1500-1520	Present	Present	present	Present

Table 6: Value of Regression Coefficient of all release kinetics models

Type of linear kinetic	value of Regression Coefficient
Zero Order Curve	0.4364
First Order Release Curve	-1.62
Higuchi Model Curve	0.7652
Korsmeyer Model Curve	-0.331
Hixson Crowell Cube Root Curve	-1.568

Figure 1: FTIR Spectrum of Lurasidone HCl

Figure 2: FTIR Spectrum of physical mixture of Lurasidone HCl and urea

Figure 3: FTIR Spectrum of Lurasidone HCl and PVP K-30

Figure 4: FTIR Spectrum of Lurasidone HCl and PEG 4000

Figure 5: Zero order curve of F18 Formulation

Figure 6: First order curve of F18 Formulation

Figure 7: Higuchi Model Curve of F18 Formulation

Figure 8: Korsmeyer Model curve of F18 formulation

Figure 9: Hixson Crowell Cube root Curve of F18 Formulation

Figure 10: DSC spectrum of Lurasidone HCl

Figure 11: DSC spectrum of F18 formulation

Figure 12: Powder XRD spectrum of Lurasidone HCl

Figure 13: DSC spectrum of solid dispersion of Lurasidone HCl: PEG 4000

CONCLUSION

Among all formulations F-18 showed highest release rate F-18 was selected as optimized formulation. I.R. spectroscopy of F-18 shows that there is no incompatibility between drug and different polymers. D.S.C. study of F-18 shows that melting point of F-18 formulation has decreased, thus after formulation drug is converted in amorphous form from crystalline form. Release kinetics of F-18 was determined by different models like zero order, First order, Higuchi, Korsmeyer and Hixson-Crowell Mode. The Correlation co-efficient (R^2) value of F-18 formulation was found to be 0.4364, -

.162, 0.7652, -0.331, -1.568. Formulation F-18 follow Higuchi model curve. Solubility of Lurasidone HCl was increased thus solid dispersion formulation of Lurasidone HCl was found to be significant.

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