Original Research Article

Solubility enhancement studies on lurasidone hydrochloride using mixed hydrotropy

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Abstract

Low aqueous solubility is a major problem faced during formulation development of new drug molecules. Lurasidone HCl (LRD) is an antipsychotic agent specially used in the treatments of schizophrenia and is a good example of the problems associated with low aqueous solubility. Lurasidone is practically insoluble in water, has poor bioavailability and slow onset of action and therefore cannot be given in emergency clinical situations like schizophrenia. Hence, purpose of this research was to provide a fast dissolving oral dosage form of Lurasidone. This dosage form can provide quick onset of action by using the concept of mixed hydrotropy. Initially, solubility of LRD was determined individually in nicotinamide, sodium citrate, urea and sodium benzoate at concentration of 10, 20, 30 and 40% w/v solutions using purified water as a solvent. Highest solubility was obtained in 40% sodium benzoate solution. In order to decrease the individual hydrotrope concentration mixed hydrotropic agents were used. Highest solubility was obtained in 15:20:5 ratio of Nicotinamide + sodium benzoate + sodium citrate. This optimized combination was utilized in the preparation of solid dispersions by using distilled water as a solvent. Solid dispersions were evaluated for X-ray diffraction, differential scanning calorimetry and Fourier-transform infrared to show no drug-hydrotropes interaction has occurred. This solid dispersion was compressed to form fast dissolving tablets. Dissolution studies of prepared tablets were done using USP Type II apparatus. The batch L3 tablets show 88% cumulative drug release within 14 min and *in vitro* dispersion time was 32 min. It was concluded that the concept of mixed hydrotropic solid dispersion is novel, safe and cost-effective technique for enhancing the bioavailability of poorly water-soluble drugs. The miraculous enhancement in solubility and bioavailability of Lurasidone is clear indication of the potential of mixed hydrotropy to be used in future for other poorly water-soluble drugs in which low bioavailability is a major concern.

Key words: Bioavailability, lurasidone, mixed hydrotropy, nicotinamide, solid dispersions

INTRODUCTION

About 45% of new chemical entities coming from the discovery are poorly bioavailable. This exerts strong limits to the performance of a drug by necessitating administering a much higher dose than strictly required from the pharmacological point of view. This can induce harmful side-effects or create problems related to cost of treatment. Due to poor bioavailability the formulator may have to select the injection route instead of the oral route.[1] For a better oral bioavailability drug must be soluble in gastro-intestinal fluids that is, drug should be soluble in an aqueous medium and also possess permeability properties for good membrane diffusion in order to reach the bloodstream.[2,3] Hydrotropy is a solubilization process where addition of a large amount of second solute exerts an increase in the aqueous solubility of another solute. The other solute can be a poorly soluble drug. Hydrotropes may be cationic, anionic or a neutral molecule, and possesses a hydrophobic as well as a hydrophilic group.[4] Finding the right hydrotropic agent for a poorly soluble drug requires screening of a large number of hydrotropic agents. However, significant solubility enhancement of drug can be easily achieved by selecting correct hydrotropic agent.[5] Hydrotropic solubilization technique is a promising approach with great potential for poorly soluble drugs. In this method, chemical modification of the drug, use of organic solvents and preparation of emulsion systems is not required.[6,7]

Lurasidone (LRD) is an antipsychotic agent specially used in the treatments of schizophrenia. It has a combined antagonism

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of serotonin (5HT2A) and dopamine (D2) and is thought to improve the negative symptoms of psychoses and reduce the incidence of extrapyramidal side-effects in comparison to typical antipsychotics. It is categorized as a high permeable ($\log P = 5.6$) and low soluble (aqueous solubility = 0.165 mg/ml). As for compounds with low aqueous solubility, LRD exhibits low and variable bioavailability (9-19%) associated with dissolution rate-limited absorption after oral administration.[8,9] Solubility of LRD increased by using mixed hydrotropic solid dispersion method. In this method we use two or more hydrotropic blends, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs. Utilization of this technique in the formulation of dosage forms of water insoluble drugs helps reduce the individual concentration of hydrotropic agents hence to minimize their side effects.

Fast dissolving drug delivery systems (FDDS) have gained popularity among the wide population because they are easily administered to the geriatrics, pediatrics and patients suffering from dysphasia and emesis. FDDS have rapidly gained acceptance as an important improved way of administering drugs orally. FDDS disintegrate and/or dissolve rapidly in the saliva without the need for water.[10,11] As drug dissolves in saliva, it bypasses enterohepatic circulation and prevents first-pass metabolism if it is absorbed in the mouth, which improves bioavailability of the drug and reduces dosing frequency and dose-related untoward effects.[12]

The objective of this study was to increase the solubility of Lurasidone in water using hydrotropes and their combinations so that oral bioavailability can be increased and to prepare fast dissolving tablets of the same.

MATERIALS AND METHODS

Materials

LRD was gifted by Wockhardt Ltd., Aurangabad, Sodium Benzoate, Tri-sodium citrate (TSC), Lactose, Urea, and Mannitol were gifted by Research-lab Fine Chem Industries, Mumbai and Nicotinamide was gifted by Loba Chemie Pvt. Ltd., Mumbai.

Determination of solubility

Saturation solubility of Lurasidone was determined in distilled water, Mcllvaine Buffer pH 3.8 solution (dissolution media of LRD). Mcllvaine Buffer pH 3.8 was prepared by mixing a solution of 0.0.025 M citric acid solution + 0.05M Na_2HPO_4 solution in the ratio of 3:2. The pH was adjusted to 3.8, and the solution was degassed before use. All media were prepared and excess of Lurasidone was added to each of them and kept in an incubator shaker at a speed of 200 rpm for 24 h at 37°C. After 24 h, solution was centrifuged at 2000 rpm for 15 min. Supernatants were diluted with the respective solution (i.e., distilled water, Mcllvaine Buffer 3.8). Absorbance was measured at 314 nm using ultraviolet (UV) visible spectrophotometer (Shimadzu V-630, Japan), and solubility was calculated.[13,14]

Lurasidone hydrotropic agent interference study

Ultraviolet spectrophotometric study

For determination of interference of hydrotropic agents in the spectrophotometric estimation of Lurasidone, the absorbances of the standard solutions of Lurasidone were determined in distilled water alone and in the presence of the hydrotropic blend employed for formulation purpose. The absorbances were recorded against respective reagent blank at appropriate wavelengths. A UV-visible recording spectrophotometer (JASCO V-630) with 1 cm matched silica cells were employed for spectrophotometric determinations.[15]

Fourier-transform infrared study

Fourier-transform infrared spectrum (FTIR) of Lurasidone and its physical mixture with hydrotropic agents was recorded over a range 4000-400 cm^{-1} to study principal peaks using FTIR spectrophotometer (Shimadzu Affinity-1).

Equilibrium solubility studies in different hydrotropic agents

10% w/v, 20% w/v, 30% w/v and 40%w/v solutions of each hydrotropic agent viz., urea (U), sodium benzoate (B), TSC, Nicotinamide (N) were prepared in water. For determination of solubility accurately measured 5 ml of above particular solution of hydrotropic agent was taken in a 10 ml vial and excess amount of drug (LRD) was added and mechanically shaken until saturated solution was formed. Each vial was shaken on the mechanical shaker for 12 h and hence that equilibrium solubility can be achieved, and the solution was allowed to equilibrate for 24 h. The solution was further centrifuged at 2000 r.p.m. for 10 min in ultra-centrifuge and further filtered through Whatman grade 41 filter paper. Aliquot was suitably diluted with distilled water and analyzed using UV spectrophotometer at 314 nm.[16] Enhancement ratios in solubility were calculated by the following formula:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in water}}$$

Equilibrium solubility studies in mixed hydrotropic blends

Initially 2-3 hydrotropic agents were mixed in 1:1 ratio and dissolved in water to get clear solution, excess amount of drug (LRD) was added in above solution and mechanically shaken until saturated solution was formed and solubility in water was determined as shown in Table 1. Further ratio of mixed hydrotropic agent was optimized as shown in Table 2 to achieve maximum solubility of LRD in water.

Formulation of hydrotropic solid dispersions of Lurasidone

For preparation of hydrotropic solid dispersion, accurately weighed 1.5 g nicotinamide, 2 g of sodium benzoate, 0.50 g of TSC (so that total weight of the mixture was 5 g) were taken in a 100 ml beaker and properly mixed. Further, minimum quantity of warm distilled water sufficient to dissolve the above hydrotropic

Table 1: Equilibrium solubility of lurasidone in mixed hydrotropic blends

Combination	Total concentration (%w/v)	Individual concentration (%w/v)	Solubility (mg/ml)	Solubility enhancement ratio
U*+N*	40	20	2.85±0.21	17.27
U+B*	40	20	4.7±0.54	28.48
U+C*	40	20	02±0.11	12.12
N+B	40	20	5.01±0.69	30.36
N+C	40	20	2.32±0.33	14.06
B+C	40	20	3.5±0.77	21.21
U+N+B	40	13.33	6.5±0.87	39.39
U+N+C	40	13.33	6±0.95	36.36
U+B+C	40	13.33	6.9±0.67	41.81
N+B+C	40	13.33	8±0.58	48.48

*N: Nicotinamide, B: Sodium benzoate, U: Urea, C: Tri sodium citrate

Table 2: Equilibrium solubility of lurasidone in mixed of hydrotropic blends

Combination	Total concentration (%w/v)	Ratio	Solubility (mg/ml)	Solubility enhancement ratio
N+B+C	40.00	10:20:10	8.6±0.54	52.12
N+B+C	40.00	10:10:20	7.5±0.36	45.45
N+B+C	40.00	15:20:5	10.22±0.97	61.93
N+B+C	40.00	5:20:15	8.93±0.87	54.12

N: Nicotinamide, B: Sodium benzoate, C: Tri sodium citrate

blend was added, If minimum amount of water (approximately 5 ml) is used lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely during removal of the water.

Dissolution of the hydrotropic mixture was facilitated by agitation of a teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of above hydrotropic mixture, 1 g of Lurasidone (drug to carrier ratio was 1:4) was dissolved in the above solution and temperature was maintained in the range of 55-60°C so as to facilitate the water evaporation. As soon as evaporation of water increases speed of rice magnetic bead automatically decreased due to increased viscosity and it stopped stirring when most of the water was evaporated, this indicates the formation of hydrotropic solid dispersion (wet). The wet solid dispersion thus obtained were spread on several watch glasses and the watch glasses were kept in hot air dry oven maintained at 50°C ± 2°C so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, hydrotropic solid dispersions were crushed using a glass pestle mortar and passed through sieve no. 60 and were finally stored in an air tight glass bottle.[15]

Evaluation of hydrotropic solid dispersion of Lurasidone

Micromeritic properties of hydrotropic solid dispersions

Micromeritic properties of the hydrotropic solid dispersions studied were Hausner ratio, bulk density, compressibility index, tapped density and angle of repose. The results are reported in Table 3.

X-ray powder diffraction analysis of LRD

The X-ray powder diffraction (XRPD) spectra of Lurasidone was recorded using Model D8 Advance high power powder X-ray diffractometer with Cu as target filter having a voltage/current of 40 kV/40 mA at a scan speed of 4°/min. The samples were analyzed at 2θ angle range of 10-89°. Step time was 0.5 s and time of acquisition was 1 h.

Differential scanning calorimetry analysis

Thermogram of the Lurasidone was recorded by using differential scanning calorimetry (DSC) 60 Shimadzu, Japan. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate of 1000°C/min from 30°C to 300°C.

Preparation of fast dissolving tablets by direct compression technique

Three batches of tablets were prepared as shown in Table 4. All the ingredients were passed through 60 mesh sieve separately. Solid dispersion equivalent to 20 mg of Lurasidone and microcrystalline cellulose were mixed in geometric proportion to get an uniform mixture. Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using flat round punch of 8 mm sizes on a Rimek Compression Machine.[17]

Evaluation of fast dissolving tablets

Postcompression parameters

Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester. Its unit is expressed in kg/cm^2. Three tablets were randomly picked from each formulation and hardness was determined, the mean and standard deviation value was calculated.[18]

Friability

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Twenty tablets

were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (Wfinal). The percentage friability was then calculated by,

F = W initial-W final/W initial × 100
(% Friability of tablets <1% is considered acceptable)[19]

Drug content uniformity
Twenty tablets were weighed and crushed in a mortar then powder containing equivalent to 100 mg of LRD was dissolved in 100 ml of methanol to achieve a solution that has a concentration of 1000 μg/ml. 10 ml from this stock solution was taken and diluted to 100 ml using methanol, to get concentration 100 μg/ml. Further, 20 μg/ml solution was prepared by taking 2 ml from the stock solution and diluting to 10 ml. Absorbance was measured at 314 nm.[20]

Wetting time
The method was applied to measure tablet wetting time. In a petri plate (i.d. = 6.5 cm), 10 ml of water was taken and a piece of tissue paper folded twice was placed. A tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed, and standard deviation was determined.[21]

In vitro dispersion time
Tablet was added to 10 ml of Mcllavaine buffer pH 3.8 at 37°C ± 0.5°C. Time required for complete dispersion of a tablet was measured.

In vitro dissolution studies
Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900 ml of Mcllavaine buffer 3.8 as dissolution medium. Temperature of the dissolution medium was maintained at 37°C ± 0.5°C, 10 ml aliquot of dissolution medium was withdrawn at every 2 min interval and filtered and the absorbance of filtered solution was measured by UV spectrophotometric method at 314 nm and concentration of the drug was determined from standard calibration curve.[22]

RESULTS AND DISCUSSION

Determination of solubility

The solubility of LRD as observed in distilled water, and Mcllavaine buffer pH 3.8 is presented in Table 5.

Lurasidone hydrotropic agent interference study

Ultraviolet spectrophotometric study

The UV absorbance spectra of LRD was determined in distilled water alone and in the presence of the hydrotropic blend solutions as shown in Table 6. The results indicate no change in the wavelength of maximum absorbance (λ_{max}) of LRD in any of the solutions. Hence, it was concluded there were no drug-hydrotrope interference.

Fourier-transform infrared study

Fourier-transform infrared was employed to characterize the possible interaction of LRD and the hydrotropes. FTIR spectrum of the LRD showed characteristic peak at 2935 of Ar-H stretch, 1686 of C = O stretch (Aryl ketone), 1503 of Ar C = C stretch, 1400 of C-H bending, 2259 of CN stretch, 1200 of C-N stretch (ter. Amine), 750 of C-Cl stretch. All peaks are within the reported range indicating purity of LRD. All the major peaks of LRD can also be seen in hydrotropic physical mixture. Hence, there were no drug-excipients interactions [Figure 1].

Equilibrium solubility studies in different hydrotropic agents

Equilibrium solubility of Lurasidone in different hydrotropic solutions was evaluated as shown in Table 7. All hydrotropes

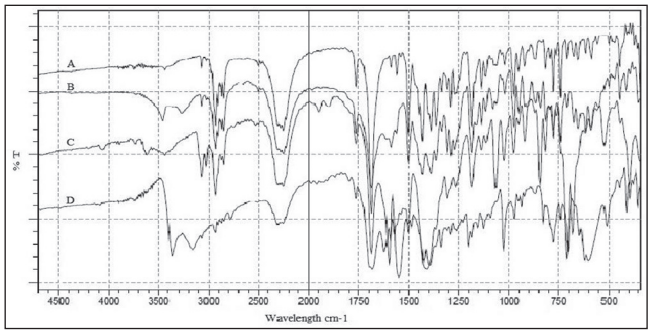

Figure 1: Fourier transform-infrared spectra of (a) lurasidone (LRD) active pharmaceutical ingredients, (b) Lurasidone + Nicotinamide, (c) Lurasidone + Sodium benzoate, (d) Lurasidone + Trisodium citrate

Table 3: Micromeritic properties of LRD solid dispersions

Parameter	Result
Bulk density (g/cm³)	0.862
Tapped density (g/cm³)	0.943
Compressibility index	8.621
Hausner ratio	1.09
Angle of repose	30°

Table 4: Formulation of lurasidone fast dissolving tablets prepared by direct compression method

Ingredients (mg/tablet)	L1	L2	L3
Solid dispersion equivalent to 20 mg of lurasidone	100	100	100
Crospovidone	1.5	4.5	7.5
Microcrystalline cellulose	15.5	12.5	9.5
Mannitol	30	30	30
Talc	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5
Total weight (mg)	150	150	150

Table 5: Solubility data of LRD

Solvent	Solubility (mg/ml)
Distilled water	0.165±0.015
Mcllavaine buffer pH 3.8	0.285±0.025

are able to enhance solubility of LRD. Highest solubility enhancement ratio was obtained in 40% sodium benzoate solution. Further, in order to decrease the concentration of sodium benzoate, different combinations of above mentioned four hydrotropic agents in different ratios were tried to determine enhancement in solubility. All blends were also found to increase the solubility of LRD as shown in Table 1.

The blend with maximum solubility enhancement (N + B + C) was further explored by changing the ratio so that maximum solubility can be obtained with minimum quantity of each hydrotropic agent to decrease their toxic potential [Table 2].

The blend N + B + C in the ratio of 15:20:5 gave the highest solubility enhancement of 61.93 when compared to distill water, and therefore, this optimized combination of hydrotropes was selected for the preparation of solid dispersions.

Formulation and evaluation of hydrotropic solid dispersions of Lurasidone

Micromeritic properties of solid dispersions

The closeness of values of tapped density and bulk density as shown in Table 3 indicate the free flowing property. The values of angle of repose, compressibility index and Hausner ratio indicate that the flow character of solid dispersion is good and no aid is needed to increase the flow properties, hence it can be used for direct compression of tablets.

X-ray powder diffraction analysis of LRD

The XRPD pattern of LRD and its solid dispersion is shown in Figure 2. XRPD pattern of LRD showed sharp, intense peak which confirms the crystalline nature of LRD. All major peak of pure drug can be seen in the physical mixture of LRD and hydrotropes, but the intensity of peak decreases that indicates formation of amorphous form of drug that increases the solubility. Based on XRPD results it can be presumed that formation of hydrotropic solid dispersion or a physical mixture does not cause any physical and chemical interaction between Lurasidone and hydrotropes at molecular level [Figures 2 and 3].

Differential scanning calorimetry analysis

The DSC thermogram of LRD is shown in Figure 4. The onset temperature was reported in the graph. The melting point of LRD was 205-210°C and DSC thermogram of LRD shows endothermic melting peak at 205.75°C. DSC thermogram of LRD solid dispersion is shown in Figure 5. There was no shift in the LRD endothermic peak hence; there was no drug excipients interaction. The separate endothermic peak of excipients was found at 139°C near to its melting point.

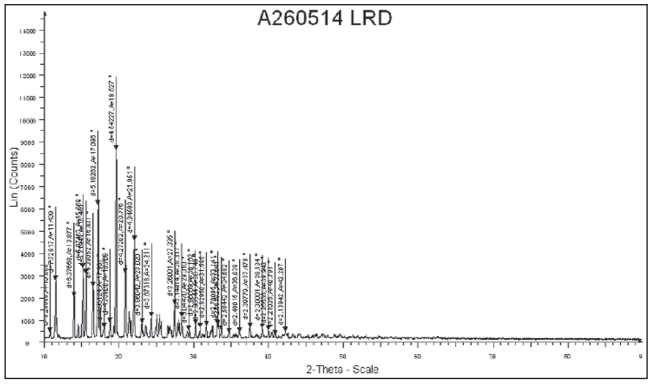

Figure 2: X-ray powder diffraction spectra of LRD

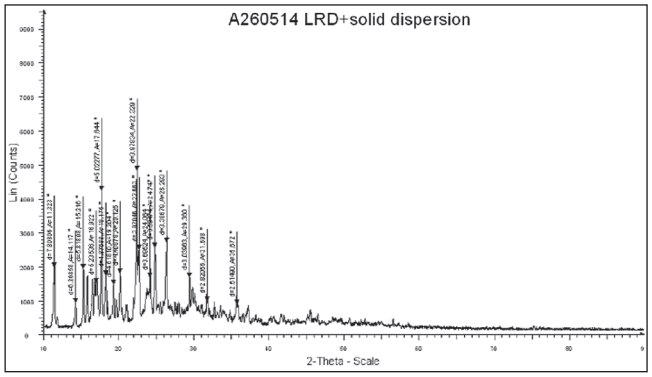

Figure 3: X-ray powder diffraction of hydrotropic solid dispersion of LRD

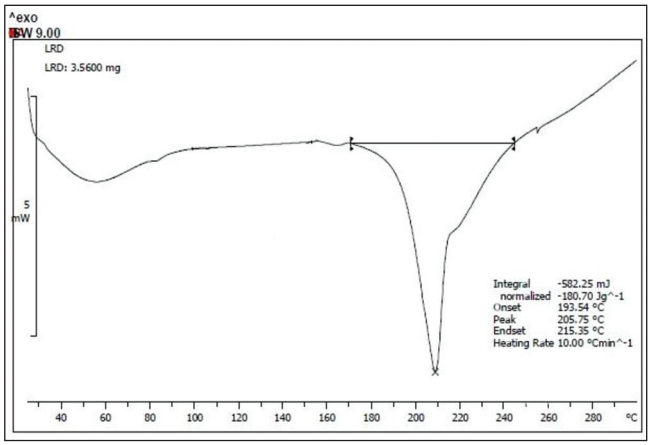

Figure 4: Differential scanning calorimetry thermogram of LRD

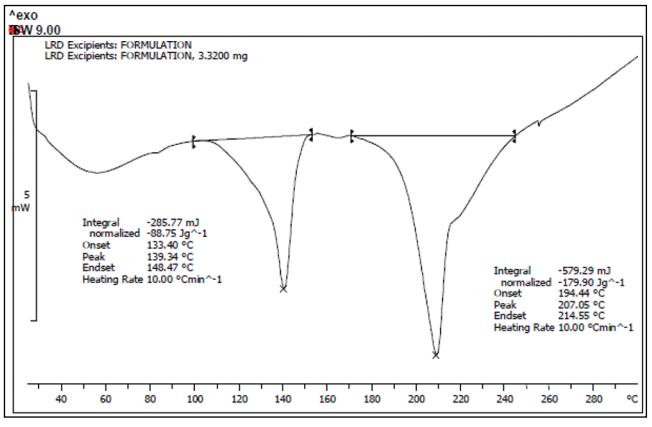

Figure 5: Differential scanning calorimetry of physical mixture of LRD and hydrotropic solid dispersion

Table 6: Drug-hydrotropes interference study by UV method

Drug	Solvent system used	Drug concentration (µg/ml)	Hydrotrope concentration (µg/ml)	Wavelength (nm)	Absorbance against respective blank
Lurasidone	Distilled water + sodium benzoate	20	1000	314	0.312
Lurasidone	Distilled water + urea	20	1000	314	0.310
Lurasidone	Distilled water + nicotinamide	20	1000	314	0.308
Lurasidone	Distilled water + trisodium citrate	20	1000	314	0.309
Lurasidone	Distilled water	20	1000	314	0.303

UV: Ultraviolet

Table 7: Equilibrium solubility of lurasidone in different hydrotropic agents

Hydrotropic agents	Concentration (w/v)				Solubility enhancement ratio
	10%	20%	30%	40%	
Urea (U)	0.22±0.05*	0.51±0.08	1.03±0.18	2.5±0.54	15.15
Sodium benzoate (B)	0.54±0.06	0.98±0.12	2.12±0.48	04±0.89	24.24
Nicotinamide (N)	0.23±0.02	0.60±0.49	1.20±0.25	02±0.65	12.12
Tri sodium citrate (C)	0.13±0.05	0.23±0.04	0.68±0.08	1.2±0.35	7.27

*Solubility in mg/ml

Table 8: Evaluation of fast dissolving lurasidone tablets

Formulation code	Hardness kg/cm²	Friability (%)	Drug content (%)	Wetting time (s)	Average weight (mg)	In vitro dispersion time (s)
L1	2.0±0.12	0.65	97±0.82	67±1.05	149±1.54	49±1.54
L2	2.5±0.18	0.58	97.50±0.98	65±1.54	148±1.42	38±1.24
L3	3.0±0.16	0.47	98±0.96	56±1.75	150±1.63	32±1.65

Evaluation of fast dissolving tablets

Postcompression parameters

Table 8 shows the hardness and friability of tablets are in an acceptable range. The wetting time and *in vitro* dispersion time was found to be minimum that is, within a minute hence tablets disintegrate, dissolve fast. Drug uniformity study results show that there was uniform distribution of drug throughout the batch. The L3 batch was found to be best because it showed maximum hardness, less *in vitro* dispersion time and good friability.

In vitro *dissolution studies*

The L3 batch showed good dissolution profile shown in Figure 6. 88% of the drug release takes place within 14 min. When the tablet enters into dissolution medium tablet disintegrates, further due to hydrotropic solid dispersion, soluble carrier releases the drug in molecular form due to which the dissolution of tablet increased and drug is released quickly from tablets and absorb rapidly by oral route resulting in increased bioavailability.

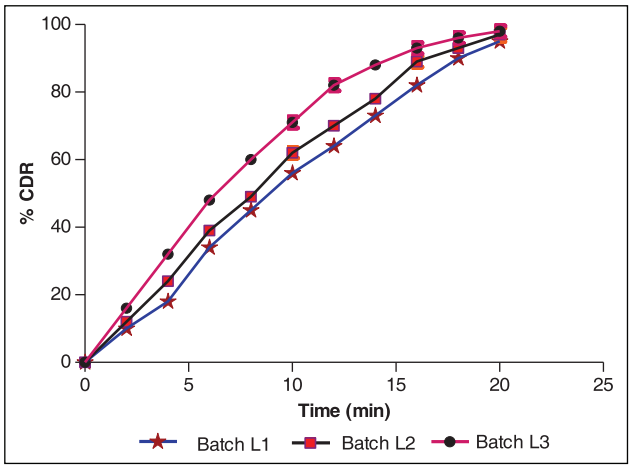

Figure 6: *In vitro* dissolution studies of batch L3

CONCLUSION

The present research work concludes that the hydrotropy is a novel, safe and effective way to enhance solubility of poorly aqueous soluble drugs. Immediate dissolution of practically insoluble drug LRD in aqueous dissolution media indicates its great potential to solubilize the drug in biological fluids, and thus appreciable enhancement in bioavailability and onset of action can be expected. Thus, the concept of mixed hydrotropy is an emerging field which can serve as a milestone for solubility enhancement and therefore deserves an urgent attention of the scientific community to assess its efficiency and applicability.

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