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Design, Optimization and Evaluation of Lurasidone Hydrochloride Nanocrystals as Fast Disintegrating Tablets

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ABSTRACT

Formulation of poorly water-soluble drugs for oral drug delivery has always been a difficult task for formulation scientists. Lurasidone hydrochloride is one such agent which is used to control bipolar depression. The objective of this study was to formulate and optimize lurasidone nanosuspension, further formulating optimized nanosuspensions as fast disintegrating tablets for improved patient compliance. In the present study, lurasidone nanosuspension was prepared by nanomilling technique. Optimized nanosuspension has mean particle diameter of 248.9 nm, polydispersity index of 0.127 and zeta potential of 18.1 mV. The lyophilized optimized nanocrystals, optimize nanosuspension as granulating fluid and as top spraying dispersion for granulation in fluid bed granulator being used to formulate fast disintegrating tablets with suitable super disintegrant. Croscarmellose sodium was found to be best superdisintegrant compared to sodium starch glycolate and crospovidone, as its acts by both mechanism swelling and wicking. Its swells 4-8 folds in less than 10 s. Many folds increase in the rate of drug release observed compare to micronized lurasidone and marketed product. There was no change in crystalline nature after nanomilling as characterized by XRD and FTIR, and it was found to be chemically stable with high drug content. The developed fast disintegrating tablets would be an alternative better formulation than its conventional formulation to address its bioavailability issue and for improved patient compliance. However, this should be further confirmed by appropriate *in vivo* studies.

KEYWORDS

Nanosuspension, Lurasidone, Nanomilling, Fast disintegrating Tablets, Optimization.

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INTRODUCTION

Difficulty in swallowing called dysphagia is common in about 35 % of the general population across all the age groups [1]. Easy of swallowing the solid oral dosage forms is very important for geriatric, pediatric patients and also the travelling patients who may not have easy access to water. Therefore, for better patient compliance development of solid oral dosage forms which can be either dissolved or suspended with water in the mouth for easy swallowing are highly desirable. Chewable tablets are not the same as the new fast disintegrating tablets (FDTs), though they are available in the market for some time. Fast disintegrating tablet technologies designed to

TABLE-1
COMPOSITION OF NANOSUSPENSION OF LURASIDONE HCl

Formulation (code)	Polymer 1		40		API (%w/w)	Total solid content (%w/w)
	Name & Grade	% w/w	Name & Grade	% w/w		
L1A	HPMC E3	8.3	-	-	16.7	25
L1B	HPMC E3	11.1	-	-	13.9	25
L1C	HPMC E3	12.5	-	-	10	25
L2	HPMC E3	8.3	SLS	0.5	16.7	25.5
L3	HPMC E3	8.3	Span 20	0.5	16.7	25.5
L4	HPMC E3	11.1	Polysorbate 80	0.5	13.9	25.5

disintegrate the tablets in the mouth without chewing and without intake of additional water have drawn considerable attention in recent times. All the approved FDTs are classified as orally disintegrating tablets by Food and Drug Administration of United States (US-FDA). Recently, European Pharmacopeia defined a tablet that disperses or disintegrates in less than 3 min in the mouth before swallowing as orodispersible tablets. Such tablets after disintegrating into fine granules or melting in the mouth form a gel-like structure to a hard solid which in-turn allows easy swallowing by patients.

Lurasidone hydrochloride, a typical antipsychotic acts its pharmacological action by blocking central dopamine D2 neuroreceptors [2,3]. Food and Drug Administration of United States (US-FDA) approved its use in adults for the treatment of bipolar depression alone or in combination with lithium [4] and its available under the trade name Latuda™. It has minimal effects on body weight, low potential of sedation and also impacts across metabolic parameters is minimal [5]. Therefore, it is a drug of choice for the treatment of bipolar depression. But, its absorption is influenced by food consumption. Two-fold increase in absorption, three-fold increase in maximum concentration (C_{max}) and 0.5-1.5 h increased in T_{max} observed when taken with food. So, it is recommended to administer with food. The pK_a value is 7.6, Log P value is 5.6 in octanol/water and it has very low aqueous solubility which in-turn responsible for low bioavailability estimated to be 9 to 19 % [6]. Kesisoglou *et al*. [7] have critically reviewed the food interaction with dissolution of poorly soluble drug. Therefore, it is quite evident that the presence of food may interfere in the dissolution which in-turn uniform absorption of lurasidone hydrochloride from the gastrointestinal tract. So, the improvement of solubility and dissolution characteristics of lurasidone hydrochloride may help uniform absorption from gastrointestinal tract which in-turn enhances its bioavailability. The amorphous form of lurasidone hydrochloride exhibits higher bioavailability compared to the existing crystalline form of lurasidone hydrochloride. Madan *et al*. [8] prepared fast-disintegrating tablets of solid dispersion to improve the solubility of lurasidone hydrochloride.

Nanocrystal technology is an established and proven technology to improve the solubility of water insoluble drugs. Though different process reported to prepare nanocrystals, wet media milling (WMM) is the most used and convenient technique. About 20 nanocrystal products are available presently in the market and most of them are made by the WMM technique [9]. Several literature reviews available that discussed about the development, evaluation and advantage of drug nanocrystals over conventional methods like solid dispersions, co-solvency and amorphization of drug [10,11]. So, nanocrystals are the choice of formulation for the improvement of solubility, dissolution rate which in-turn improves the bioavailability of drug. These nanocrystals are 100 % drug particle without having any matrix material but stabilized by ionic or steric stabilizer. Therefore, the present investigation was carried out to develop and optimize lurasidone nanocrystal followed by converting the optimized nanocrystal as fast disintegrating tablets to get improved saturation solubility, dissolution rate and improved patient compliance which in-turn may improve bioavailability.

EXPERIMENTAL

Lurasidone hydrochloride was obtained from Mylan Laboratories Ltd., India. Hydroxypropyl methyl cellulose (Hypromellose 2910, Methocel® E3 LV) was gift sample from Dow Chemicals, USA. All other materials used were of pharmaceutical grade and produced from commercial sources.

Preparation of nanosuspension: For nanogrinding lurasidone, solutions of surfactant (SLS, span 20, polysorbate 80) and polymer stabilizers (methocel E3) in purified water were first prepared. Lurasidone hydrochloride (d_{90}: 18.5 µm) was then dispersed in the stabilizer solution. The composition of different formulation with polymer stabilizer and surfactant are mentioned in Table-1. The resulting dispersion was comminuted using colloidal mill (Make: Pharmatech) for 30 min with zero clearance. The colloidal mill passed dispersion was further milled in a high-energy Nanomill (LabStar, Netzsch, Germany) filled (to 70 %, v/v) with yttrium-stabilized zirconium oxide beads (0.4 mm in diameter). Nanomilling was performed in circulation mode using 325 g of drug suspension. The nanomill was refrigerated to control the product temperature below 37 ºC. The details of nanomilling parameters for different trails are given in Table-2.

TABLE-2
MILLING PARAMETERS OF
NANOSUSPENSION OF LURASIDONE

Formulation code	Pump speed (rpm)	Milling speed (rpm)	Agitator speed (rpm)	Bead volume (mL)	Pressure (bar)
L1A	40	3000	120	130	0.23
L1B	40	3000	120	130	0.28
L1C	40	3000	120	130	0.28

Lyophilization: The optimized nanosuspension was lyophilized. The vials of Nanosuspension were freeze-dried (FTS Lyostar II freeze drying system, SP Industries Inc., Warminster, USA). The primary drying was operated in -30 ºC for 20 h and secondary drying was completed stepwise from -25 ºC to 45 ºC.

Solubility studies: The study was done before and after nano milling to study the effect of nano sizing on the solubility and dissolution rate of the drug. Saturation solubility studies were performed by adding known excess amount of drug and optimized lyophilized nanocrystal in 250 mL of water, pH 1.2 (0.1 N HCl), pH 2.0 (0.01 N HCl), pH 3.8 Mcllavaine buffer, pH 4.5 acetate buffer and pH 6.8 phosphate vuffer respectively. These flasks were hermitically sealed and incubated at 37 ºC in an incubator shared rotated at 50 rpm for 48 h. Then, the samples were filtered and subsequently diluted with same media and absorbance was noted at 315 nm.

Characterization of nanosuspension: The characterization of nanosuspension are in similar ways as those used for conventional suspensions like evaluation of physical, chemical and flow properties. Physical evaluation includes appearance of phases, particle size analysis, zeta potential and solubility studies. Assay, dissolution and related substance were checked as part of chemical evaluation. For flow properties, determination of sedimentation volume, pourability and redispersibility were carried out.

Particle size analysis: The size distribution and average particle diameter of the prepared nanosuspensions were measured by laser photon correlation spectroscopy using Zetasizer Ver. 7.02 (Malvern Instruments, Worcestershire, UK) [12,13]. Nanosuspensions were appropriately diluted with deionized water as dispersant. Further, sonicated for 2 min to reduce any interparticle aggregation. Then, the samples were analyzed by placing in disposable sizing cuvette. The 50 and 90 % volume percentiles (d_{50} and d_{90}) were being used to exhibit the particle size of nanosuspension. Samples were analyzed in duplicate per batch and the measurements were taken in triplicate for each sample. Similarly, particles size also determined after lyophilization of optimized nanosuspension.

Zeta-potential measurement of nanosuspensions: Zetasizer Ver. 7.02 (Malvern Instruments, Worcestershire, UK) was being used to measure the zeta-potential of prepared nanosuspensions. The samples were appropriately diluted with deionized water and analyzed by keeping in disposable zeta cells. The Smoluchowski equation [14] of the electrophoretic mobility was being used to measure the mean zeta potential in mV .

FTIR analysis: The FTIR spectra was recorded for micronized drug of lurasidone hydrochloride, polymer (HPMC E3) and lyophilized nanocrystal of optimized nanosuspension formulation using KBr pellet technique. The spectra were scanned over 3600-400 cm^{-1} at ambient temperature with a resolution of 4 cm^{-1}.

Sedimentation volume: Each suspension (50 mL) was being kept in stoppered measuring cylinder and stored undisturbed at room temperature. Further, the separation of clear liquid was noted at an interval of 2 and 4 h. The following equation was being used to calculate the sedimentation volume (F %):

$$F\ (\%) = \frac{V_u}{V_o} \times 100$$

where, V_u is the end volume of the sediment, V_o is the initial volume of the suspension.

Pourability: This test assures that the final nanosuspension is pourable and will not encounter any problem during filling and handling by end user.

Redispersability: In calibrated tubes fixed volume of each suspension (50 mL) was stored at room temperature for different intervals (2 and 4 h). One tube was removed at regular interval of 2 h and shaken vigorously to redistribute the sediment. Further, the presence of deposit if any was recorded. The time taken to redisperse the sedimented suspension was recorded.

Assay: Lurasidone nanosuspension (1 mL) was taken and dissolved in about 60 mL methanol and sonicated for 60 min, the volume was adjusted to 100 mL using 0.1N HCl continuous sonication for 15 min. Further, 5 mL of this solution was diluted to 100 mL with 0.1N HCl. Filtered through a 0.45 µm membrane filter and analyzed by measuring the absorbance at 315 nm against blank using UV spectrophotometer. The readings were taken in triplicate (Shimandzu UV-1700).

Dissolution study: *in vitro* Dissolution study was carried out using USP dissolution test Apparatus-2 (Paddle assembly, Make: Electrolab). The dissolution was performed using 900 mL of pH 3.8 Mcllavaine buffer (official FDA listed dissolution media) maintained at 37± 0.5 ºC, agitation speed of 50 rpm for lyophilized lurasidone nanocrystals, optimized FDTs formulation and marketed product (Latuda™ marketed by Sunovion Pharmaceuticals, USA). Samples (10 mL) were withdrawn at regular intervals of 10 min for 60 min and replaced with fresh dissolution medium. This solution (5 mL) was diluted to 10 mL with the medium and filtered through 0.22 µm Nylon filters (Millipore) and assayed on Shimadzu UV-visible spectrophotometer UV-1601 at 315 nm wavelength. Dissolution for each formulation was performed in triplicates.

Related substances: To check the impact of nano-grinding process on the chemical stability of lurasidone, related substances analysis was performed using HPLC method. Following chromatographic conditions for related substances analysis of lurasidone nanosuspension samples were done by using HPLC method where Inertsil ODS-3, 250 × 4.6 mm, 3.0 µm column was used for separation. Detector wavelength was set at 230 nm with flow rate of 1.0 mL/min. Degassed and filtered pH 2.0-0.02 M potassium dihydrogen phosphate buffer was used as mobile phase A. Mixture of acetonitrile and methanol in the ratio of 80:20 was used as mobile phase B. Gradient program was set as 85/0, 65/20, 60/25, 60/35, 50/40, 30/50, 25/60, 15/70, 15/85, 85/90 and 85/100 (mobile phase A/min). Mixture of 0.1 % orthophosphoric acid in water and acetonitrile in the ratio of 70:30 was used a diluent for test preparation. Test preparations of lurasidone were prepared at the concentration of 1 mg/mL.

Microscopy test: The samples (before and after nanomilling) were visualized by using optical microscope (LEICA, DFC 395) at 40X zoom. Air-dried samples of nanosuspensions were mounted on the aluminum stubs with the help of carbon double-sided tape (Nisshin EM Co. Ltd., Tokyo) and sputter coated with platinum by using Auto fine coater (JEOL, JFC-1600) for 90 s under vacuum (3Pa) and observed under the scanning electron microscope (JEOL, JSM-6380) at a magnification of 500X.

Solid state analysis: The pure drug, physical mixture and lyophilized optimized nanocrystals were analyzed by using Bruker D8 Advance X-ray diffractometer (Bruker, Germany). The pattern of spectra was collected in the range of 3º to 45º

TABLE-3
COMPOSITION OF LURASIDONE FDT FORMULATIONS

Ingredients (mg/tablet)	Formulation code										
	LT1	LT2	LT3	LT4	LT5	LT6	LT7	LT8	LT9	LT10	LT11
Lurasidone HCl micronized	40	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Lurasidone as lyophilized powder eqv to 40 mg of lurasidone	Nil	144	144	144	144	144	144	144	144	144	144
CCS	28	–	14	21	28	–	–	–	–	–	–
SSG	–	–	–	–	–	14	21	28	–	–	–
CP	–	–	–	–	–	–	–	–	14	21	28
Aspartame	2	2	2	2	2	2	2	2	2	2	2
Directly compressible mannitol	276	200	186	179	172	186	179	172	186	179	172
Masgnesium stearate	4	4	4	4	4	4	4	4	4	4	4
Total weight of the tablet (mg)	350	350	350	350	350	350	350	350	350	350	350

2θ. Cu with Kα = 1.5405 Å was used as anode X-ray source, the voltage was kept as 40 kV and tube current as 40 mA. In continuous mode, scanning was performed with time/step of 0.4 s and step size of 0.01.

Conversion of lyophilized nanocrystal into FDT dosage form: The optimized lyophilized nanocrystals of lurasidone (L1C) were further formulated as fast disintegrating tablets by using various proportions of croscarmellose, sodium starch glycolate and crospovidone as superdisintegrant. The superdisintegrant proportion in various formulations were taken at 4 , 6 and 8 % of the total tablet weight (Table-3). All the excipients were passed through sieve no 40 and blended for 15 min in double cone blender. Then lubricated by blending with #60 mesh passed lubricant for 5 min in double cone blender. Finally, the final blends were compressed into tablets using 10 mm standard round concave punches using Cadmach 8 station compression machine.

Conversion of nanosuspension into FDT dosage form by top spray granulation: The top spray granulation of nanosuspensions onto cellulose, sugar or other inert excipients increases the bulk density of granulated powder which in turn gives good followability and helps in downstream processing of these powders, like direct capsules filling or compressing them into tablets after blending with additional excipients [15]. Therefore, the optimized nanosuspension of lurasidone (L1C) were further formulated as fast disintegrating tablets by spraying the nanosuspension onto either mannitol (Pearlitol SD 200), microcrystalline cellulose (Avicel pH 101), mixture of mannitol and microcrystalline cellulose using fluid bed granulator and also used as granulating fluid to granulate the mass containing microcrystalline cellulose (Avicel pH 101) along with other tableting excipients (Tables 4 and 5). The parameters were carefully monitored by maintaining the product temperature at 30-35 ºC and the spray rate was maintained at 2-3 mL/min to obtain a free flowing powder. All the excipients were passed through sieve no. 40 and blended for 15 min in double cone blender. Then lubricated by blending with #60 mesh passed lubricant for 5 min in double cone blender. Finally, both the above said final blends were compressed into tablets using 10 mm standard round concave punches using Cadmach 8 station compression machine.

Evaluation of fast disintegrating tablets (FDTs)

Physical appearance: The physical attributes of tablets such as tablet size, shape, taste, colour, presence or absence of odor, and surface texture were observed which in turn gives patient compliance and acceptance.

TABLE-4
COMPOSITION OF TABLETS PRODUCED BY USING LURASIDONE NANOSUSPENSION AS GRANULATING FLUID

Ingredients (mg/tab)	Formulation code		
	LT12	LT13	LT14
Lurasidone nanosuspension (L1C)	72.0	72.0	72.0
Avicel PH 101			
Croscarmellose	21.000	28.000	35.000
Aspartame	2	2	2
Magnesium stearate	4	4	4
Total	350	350	350

TABLE-5
COMPOSITION OF TABLETS PRODUCED BY USING OPTIMIZED L NANOSUSPENSION AS TOP SPRAYING DISPERSION FOR GRANULATION

Ingredients (mg/tab)	Formulation code		
	LT15	LT16	LT17
Lurasidone nanosuspension (L1C)	72.0	72.0	72.0
Avicel PH 101	150		75
Mannitol SD 200		150	75
Croscarmellose	28	28	28
Aspartame	2	2	2
Magnesium stearate	4	4	4
Total	350	350	350

Hardness test: The hardness of tablet of each formulation was checked by using Dr. Schleuniger Hardness tester in terms of kilopounds (Kp).

Friability test: Initial weight of 20 tablets is taken and placed in the friabilator, further rotates at 25 rpm for 4 min. The difference in the weight was expressed as percentage. The desirable value should be below 1.0 %.

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

where, W_1 = weight of tablets before test, W_2 = weight of tablets after test.

Weight variation: Individually 20 tablets were taken and weighed on a digital weighing balance. Average weight was calculated as per formula given below:

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Disintegration test: Six tablets were selected randomly from each batch for disintegration test. Disintegration test was

performed by placing each tablet in a basket sinker just below the water surface containing 900 mL of water maintained at 37 ± 0.5 ºC and the paddle rotating at 100 rpm. The time noted for a tablet to disintegrate completely into fine particles.

Wetting time: The tablet was placed on the double folded piece of tissue paper placed in clean and dry petri-plates containing 10 mL of water paper and the time for complete wetting of the tablet was measured in seconds.

Dispersion time: In 100 mL of water, two tablets were placed and stirred till completely dispersed. The dispersion time was noted for different formulations.

Assay: Twenty tablets were crushed into fine powder using pestle and mortar. The powdered sample equivalent to 40 mg of lurasidone drug was dissolved in about 400 mL methanol and sonicated for 60 min, the volume was adjusted to 500 mL using 0.1N HCl and continue sonication for 15 min. Further 3 mL of this solution was diluted to 100 mL with 0.1 N HCl. Filtered through a 0.45 µm membrane filter and analyzed by measuring the absorbance at 315 nm against blank using UV spectrophotometer. The readings were taken in triplicate (Shimandzu UV-1700).

Stability studies: The optimized Lurasidone FDTs was filled in HDPE containers sealed and loaded into stability chamber at 40 ± 2 ºC/75 ± 5 RH (Newtronics stability chamber) [14]. The samples were withdrawn after 3 months and analyzed for particle size, assay, dissolution studies, related substances.

RESULTS AND DISCUSSION

The effect of different polymers on the milling efficiency was evaluated. Formulations L2 (HPMC E3 with SLS), L3 (HPMC E3 with Span 20) showed physical incompatibility leading to coagulation and precipitation of solid material forming a cake. Formulation L1C was therefore considered for further studies. Effect of different percentage of polymer (HPMC E3) with respect to API on milling efficiency were performed and detailed given in Table-6. In L1A and L1B, the percentage of polymer was 50 % and 80 % respectively with respect to amount of API and milled for 60 min. It was found that milling efficiency increased from 17.17 % for D-90 values. This observation can be attributed to the intensity of particle number fall under D-90 value and therefore be inferred that 80 % of HPMC with respect to API proves to have optimum milling efficiency. L1A has lesser polymer compared to that of L1B. However, L1B has significantly higher solid content and has therefore been chosen for further experimental studies.

TABLE-6
OPTIMIZATION OF POLYMER CONCENTRATION

Formulation	% HPMC wrt API	Z-average (nm)	D-90 (nm)	PDI
L1A	50	353.2	757	0.231
L1B	80	348.4	677	0.247
L1C	125	338.4	627	0.237

Optimization of milling time: For optimizing the milling time, L1C was milled for 120 min. Samples were taken in-between to characterize. Upon characterization, it was found that particle size reduction was significant till 120 min and desired particle size is obtained for 120 min milling time (Table-7). Therefore, milling time was optimized as 120 min.

TABLE-7
CHARACTERIZATION FOR MILLING TIME OPTIMIZATION

Time (min)	L1C		
	Z-average (nm)	D-90 (nm)	PDI
30	748.4	1070	0.308
45	483.2	1000	0.28
60	338.4	627	0.237
90	311.8	588	0.194
120	248.7	420	0.127

Evaluation of nanosuspension: The average particle size and particle size distribution are the two important characteristic parameters that affect the saturation solubility, dissolution rate, physical stability even *in-vivo* behaviour of nanosuspensions [16]. The prerequisite for long term stability of nanosuspensions is narrow polydispersity index (PDI). A PDI value of 0.1 to 0.25 indicates a narrow size distribution (Table-8) [17].

TABLE-8
CHARACTERIZATION OF NANOSUSPENSION FORMULATIONS

Batch details	Milling time: 120 min			
	Z-average (nm)	D-90 (nm)	PDI	Zeta potential
L1A	333.2	707	0.231	12.5 Mv
L1B	308.4	627	0.237	13.5 Mv
L1C	248.7	420	0.127	18.1 Mv

The particle size of lurasidone nanosuspension formulations were evaluated by Malvern particle size analyzer (Zetasizer) and the results showed that the particle size of formulations L1C (drug:13.88 % w/w and HPMC E3: 11.11 % w/w) was reduced to nanometric range. The particle size distribution of formulation L1C was found to be around 250 nm with polydispersity index of 0.127 as shown in Fig. 1. Hence, the formulation L1C was used for further formulation development of lurasidone fast disintegrating tablets.

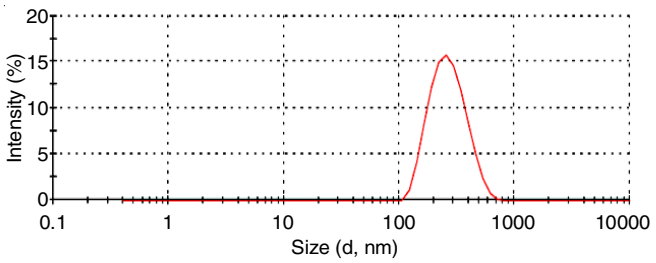

Fig. 1. Particle size distribution of optimized lurasidone nanosuspension

There was no significant change in particle size distribution on dilution of nanosuspension (Table-9). PDI values were not altered after dilution which shows that the particles are within narrow size range. After 4 weeks, nanosuspension formulation were again tested for particle size distribution to check whether any cluster/growth/ agglomeration and found to be 250 nm. The physical stability study results at room temperature for 4 weeks was found to be satisfactory. A slight sedimentation was observed after 4 weeks which were readily

TABLE-9
EFFECT OF DILUTION ON PARTICLE SIZE OF LURASIDONE NANOSUSPENSION

Dilution	Z-average (nm)	PDI
1:1	248.7	0.127
1:10	242.5	0.135
1:100	232.4	0.148
1:500	238.5	0.135
1:1000	249.5	0.148

redispersible. Formulation L1C was found to be stable over a period of 4 weeks. It was characterized for PSD and PDI and was found to have no significant change during this period as seen in Table-10.

TABLE-10
CHARACTERIZATION FOR STABILITY OF OPTIMIZED LURASIDONE NANOSUSPENSION (L1C)

Particulars	0 Day	1 week	2 weeks	4 weeks
Z-average (nm)	248.7	255.5	260.4	267.3
PDI	0.148	0.178	0.211	0.248
Redispersibility (%)	100	100	100	100
Time taken to redisperse (s)	6	8	10	10
Sedimentation volume (F)	0.92	0.9	0.9	0.8

The determination of zeta potential of nanosuspension is essential as it gives an idea about the physical stability of nanosuspension [18]. The zeta potential of nanosuspension is controlled by both stabilizer and the drug itself. Circulation of nanonised particles in blood stream and absorption into body membrane, also effected by zeta potential. Zeta potential of final formulation was found to be increasing with the time of milling (Table-11). After 90 min, change in zeta potential was negligible. As the zeta potential of optimized lurasidone nanosuspension (L1C) (Fig. 2) is greater than ± 15 mV, henceforth, it can be concluded that nanosuspensions of lurasidone nanosuspension are deemed to be stable [19].

TABLE-11
ZETA POTENTIAL OF LURASIDONE NANOSUSPENSION

Time (min)	Mill speed (rpm)	Pump (rpm)	Zeta potential (mV)
45	3000	40	7.8
90	3000	40	16.5
120	3000	40	18.1

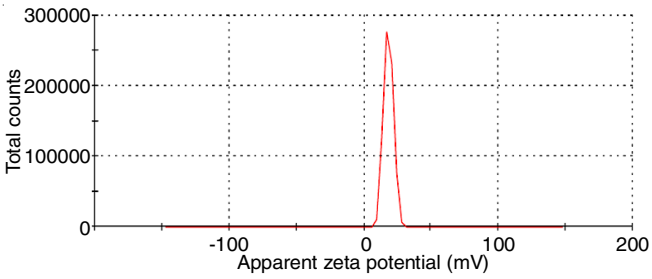

Fig. 2. Zeta potential of optimized lurasidone nanosuspension

SEM has been used to determine PSD, surface topography, texture and examine the morphology of fractured or sectioned surface. The nanonised dried optimized formulation were screened through SEM to show the better particulate nature of the drug. The SEM image of the dried optimized nanosuspensions is shown in Fig. 3.

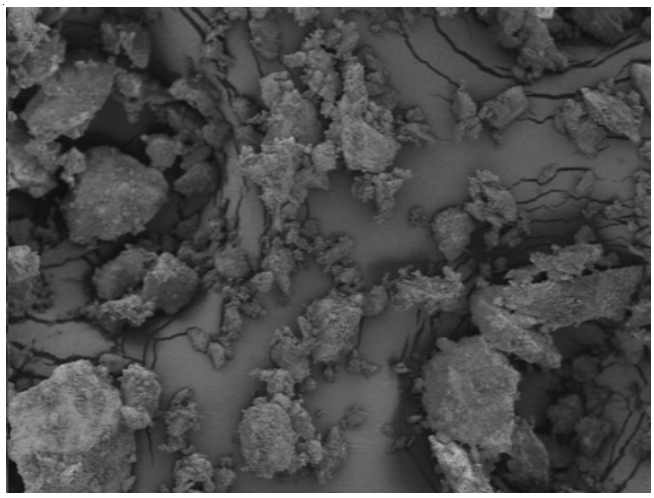

Fig. 3. SEM image of optimized lyophilized nanocrystal of L1C at 500X

To understand, the polymorphic or morphological changes that a drug might undergo when subjected to nanomilling, the assessment of the crystalline state and particle morphology are required. Therefore, the X-ray diffraction analysis was performed for lurasidone pure drug and optimized lyophilized nanocrystal. The obtained patterns reveal that the crystallinity of the drug in nanosuspension formulation was not affected. The characteristic peaks of lurasidone drug molecule were found to be present in nanosuspensions and final blend prepared using optimized lurasidone nanosuspension. The comparative diffractograms are shown in Figs. 4 and 5.

The FTIR spectrum of lurasidone drug substance, physical mixture and optimized lyophilized Lurasidone nanocrystal was recorded on Perkin-Elmer spectrum FTIR spectrophotometer by using KBR pellet method and the spectrum is shown in Fig. 6. The peaks at wavenumbers 3430, 2896, 2696, 1340, 1323, 768 cm^{-1} in lurasidone drug substance are considered to be characteristic peaks (Table-12). All these characteristic peaks are also observed in lyophilized nanocrystal indicating that there is no interaction between drug substance lurasidone and excipients due to the process of nanomilling. The sedimentation volume was measured for the suspensions and was found that the suspensions showed the F values from 0.92 to 0.83

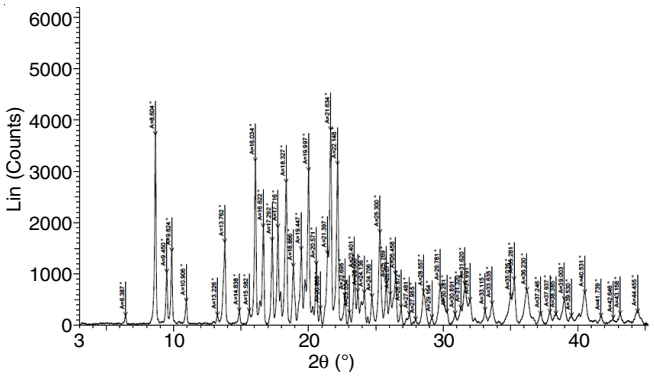

Fig. 4. PXRD spectra of lurasidone hydrochloride

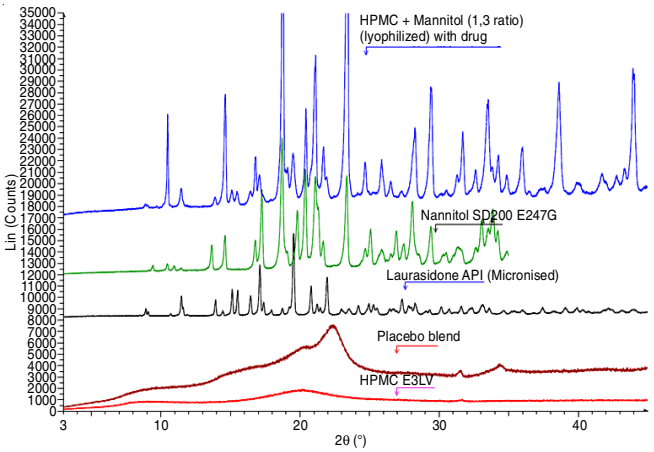

Fig. 5. PXRD data of micronized lurasidone API, mannitol SD200, HPMC E3LV, placebo blend and optimized lyophilized lurasidone nanocrystal

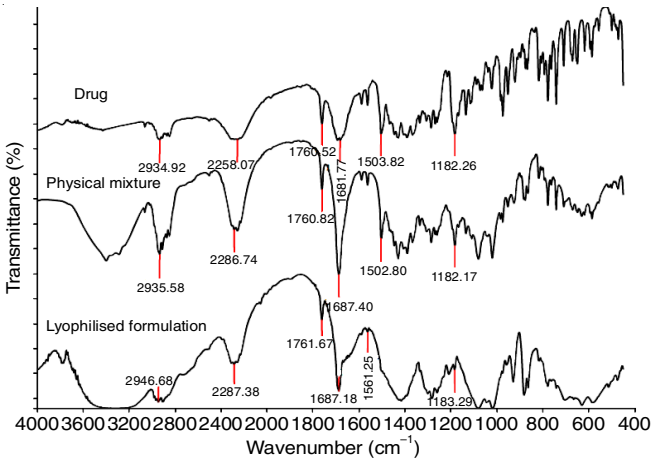

Fig. 6. FTIR pattern comparing micronized lurasidone, physical mixture and optimized lyophilized nanocrystal

TABLE-12
FT-IR ABSORBANCE VALUES

Functional group	Expected absorbance value (cm^{-1})	Model drug (cm^{-1})	Nanosuspension (cm^{-1})
C=O	1670-1820	11761.04	1687.07
C-S	705-570	768.56	708.76
C-CH_3	2900-3100	2896.13	2925.3
C-N (2° aromatic amine)	1340-1280	1340.74	1340.15
C-N (3° aromatic amine)	1360-1310	1323.25	1358.60
N-H (amide)	3000-3200	3430.6	3003.86
S-H	2600-2500	2696.3	2288.2
C-N	1000-1300	1034.67	1040.23

for the optimized lurasidone nanosuspension which ensures easy pourability from the bottle.

The assay values of lurasidone nanosuspensions were found to be 98.7, 99.5 and 99.2 %, respectively for L1A, L1B and L1C. Nanosuspension of this experimental drug increase both the dissolution velocity and saturation solubility as shown in Fig. 7. Size reduction indicates the enhancement of effective surface area which in-turn increase dissolution pressure as well as dissolution velocity. Because of reduction in particle size due to nanomilling solubility increases which change the surface tension leading to increase saturation solubility [18]. Dissolution

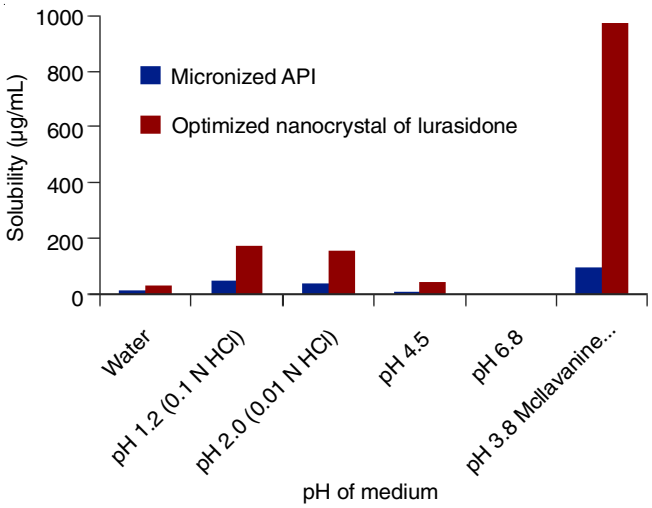

Fig. 7. Solubility of micronized API and optimized nanocrystal of lurasidone in different pH

studies were performed on plain lurasidone drug, optimized nanosuspension of lurasidone in wet and dry form and lurasidone suspension in pH 3.8 Mcilvaine buffer. The results were found to be 95.1, 99.8, 12.7 and 11.8 % for lurasidone nanosuspension (wet/dry), lurasidone suspension before milling and lurasidone plain API respectively at 20 min (Fig. 8).

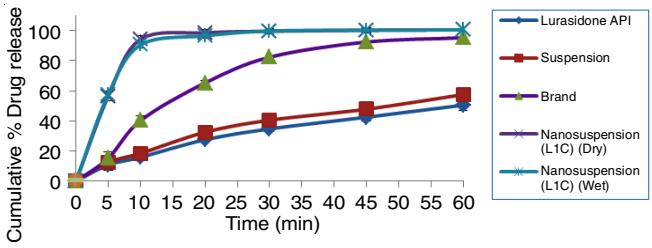

Fig. 8. Dissolution profiles of micronized drug, brand and optimized nanosuspension

Conversion of optimized nanouspension into FDT dosage form: The optimized lyophilized nanocrystals of lurasidone were further formulated as fast disintegrating tablets (FDTs) by using various proportions of superdisintegrant. Three different disintegrant croscarmellose sodium, sodium starch glycoalte and crospovidone in three different concentrations were used to get the desired quality attributes of FDTs. The formulation LT5 with 8 % w/w of croscarmellose sodium been finalized based on desired physical attributes of FDTs and faster drug release profiles (Fig. 9). Croscarmellose sodium was

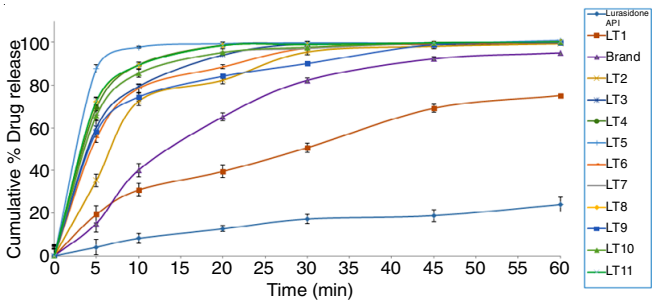

Fig. 9. Dissolution profiles of micronized drug, brand and lurasidone FDT using optimized nanocrystals

found to be best superdisintegrant compared to sodium starch glycolate and cross povidone, as its acts by both mechanism swelling and wicking. In less than 10 s, it swells 4-8 folds, therefore it's been selected for further studies.

Considering the process of lyophilization is costly and time taken, wet granulation of drug nanosuspension using inert excipients such as sugar, cellulose, or other inert excipient also been evaluated to formulate the FDTs. Mannitol (Pearlitol SD 200) resulted in a free flowing powder upon top spraying the optimized lurasidone nanosuspension (L1C) in comparison to that of microcrystalline cellulose (Avicel pH 101) and mannitol did not even result in any lump formation with increase in the spray rate of nanosuspension which was not the case with microcrystalline cellulose. The average weight of the tablets for different lurasidone FDT tablet formulations was found to be satisfactory and well within the acceptable range. The hardness for different simvastatin FDT tablet formulations was found to be between 5 to 7 kP. The friability was below 1 % for all the lurasidone FDT tablet formulations, which is an indication of good mechanical strength of the tablet. The disintegration time for different formulations varied from 27 to 195 s. The assay values for lurasidone FDT formulations were found to be between 98.8 to 101.5 %. Content uniformity results were found to be satisfactory. The lower standard deviation value signifies the content uniformity of the tablets (Table-13, Figs. 9 and 10). The drug release

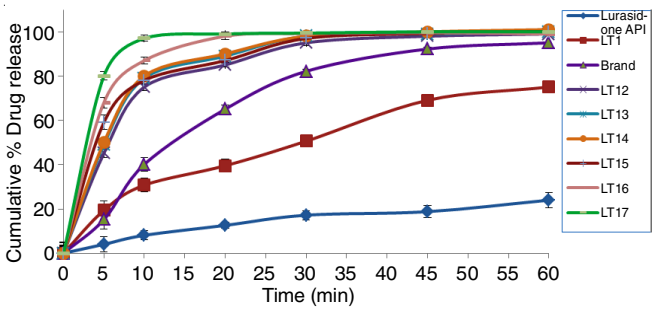

Fig. 10. Dissolution profiles of micronized drug, brand and lurasidone FDT using optimized nanosuspension as granulating fluid and as top spray dispersion

pattern of optimized FDTs formulation found to be first-order with correlation coefficient value of 0.962, 0.942,0.970 and 0.970 respectively for optimized formulation L1C, LT5, LT14 and LT17 respectively (figures not shown) indicating that the drug release rate is concentration dependent.

The stability studies were performed on optimized FDTs dosage form of lurasidone at 40 ± 2 ºC / 75 ± 5 RH for 3 months. The results obtained from stability studies shown that there was no significant change in given parameters evaluated and it can be concluded that the formulation was found to be stable (Table-14). No significant change in related substances observed after storage at accelerated storage condition for 3 months (Fig. 11).

TABLE-13
PHYSICAL AND CHEMICAL EVALUATION OF LURASIDONE FDT FORMULATIONS

Formulation code	Average weight (mg)	Crushing strength (Kp)	Friability (%)	Wetting time (s)	Dispersion time (s)	Assay (%)
Lurasidone conventional tablet formulation						
LT1	350.6	5-7	0.20	98 ± 2	205 ± 2	99.0 ± 1.1
Tablets prepared by optimized lurasidone nanocrystals						
LT2	350.8	5-7	0.18	195 ± 2	210 ± 2	99.4 ± 1.5
LT3	351.2	5-7	0.16	78 ± 2	82 ± 2	100.2 ± 1.0
LT4	351.0	5-7	0.17	55 ± 2	62 ± 2	99.2 ± 1.3
LT5	351.0	5-7	0.18	27 ± 2	32 ± 2	99.0 ± 1.5
LT6	351.0	5-7	0.19	94 ± 2	98 ± 2	100.6 ± 1.8
LT7	350.4	5-7	0.17	76 ± 2	78 ± 2	98.8 ± 1.5
LT8	350.4	5-7	0.18	58 ± 2	74 ± 2	99.5 ± 1.4
LT9	351.2	5-7	0.16	98 ± 2	105 ± 2	100.8 ± 1.5
LT10	350.8	5-7	0.19	78 ± 2	84 ± 2	100.2 ± 1.6
LT11	350.6	5-7	0.17	52 ± 2	60 ± 2	100.8 ± 1.4
Tablets prepared by optimized lurasidone nanosuspension as granulating fluid						
LT12	351.2	5-7	0.20	98 ± 2	105 ± 2	100.8 ± 1.3
LT13	351.0	5-7	0.16	78 ± 2	86 ± 2	100.5 ± 1.5
LT14	350.8	5-7	0.18	52 ± 2	60 ± 2	99.8 ± 1.2
Tablets prepared by optimized lurasidone nanosuspension as top spray solution						
LT15	350.0	5-7	0.16	95 ± 2	102 ± 2	99.8 ± 1.5
LT16	350.0	5-7	0.19	75 ± 2	84 ± 2	101.5 ± 1.8
LT17	349.8	5-7	0.15	52 ± 2	58 ± 2	100.8 ± 1.3

TABLE-14
STABILITY OPTIMIZED FDT

Time point	Assay	Dissolution in pH 3.8, Mcilvaine Buffer, USP II, 900 mL, 50 rpm			Related Substances			
		10 min	20 min	30 min	Epoxy lurasidone	*cis*-Isomer	Highest unknown	Total impurity
Initial	100.2	98	99	100	0.07	0.06	0.05	0.42
1 Month	100.8	95	98	99	0.1	0.1	0.07	0.58
3 Months	100.5	96	99	100	0.12	0.12	0.09	0.82

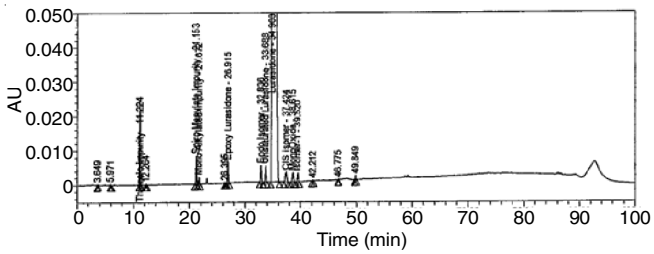

Fig. 11. Chromatogram of lurasidone related substances

Conclusion

The optimized nanosuspension (L1C) was formulated using HPMC E3 as stabilizer, solid content of 20 %, milling speed of 3000 rpm, milling time of 120 min and bead volume of 130 mL. Saturated solubility studies performed on lurasidone in micronized form and with nanocrystal of optimized nanosuspension. The study found to exhibit highest solubility in pH 3.8 Mcllavaine buffer and selected as dissolution media for further studies. These dissolution media also recommended by Office of Generic Frug, US FDA for the respective marketed product Latuda in USA [20]. In this study, the optimized nanosuspension and lyophilized nanocrystals have been used as an attractive alternative formulation type containing nanosized drug particles with increased dissolution rate (according to Noyes-Whitney model) and solubility (according to Ostwald-Freundlich and Kelvin equations) [21]. Further, the optimized nanocrystals are formulated as fast disintegrating tablets (FDTs) which help for pediatric, geriatric patient and also has ease of administration for normal travelling patient who may not have easy access to water. FTIR and XRD spectra indicated that there was no physical or chemical interaction in between drug and selected excipients, further the drug retains its form after nanomilling. The optimized formulation FDTs also has acceptable physical and chemical attributes. The optimized formulation being stable when stored at accelerated stability condition up to 3 months. Therefore, the developed optimized FDTs would be an alternative better formulation than its conventional formulation to address its bioavailability issue and improved patient compliance for geriatric, pediatric and travelling patient who may not have access to water. However, this should be further confirmed by appropriate *in vivo* studies.

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