Development and Characterization of Oral Disintegrating Tablet Containing Nanosuspension of Lurasidone Hydrochloride antipsychotic Drug

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Abstract

Background: Lurasidone hydrochloride, is BCS Class II drug with poor bioavailability of about 7% and lacking solubility to show quick response. The aim of the work was to develop oral disintegrating tablet containing nanosuspension of Lurasidone Hydrochloride thereby improve the solubility and overcome the poor bioavailability. **Material and Methods:** Nanosuspension of Lurasidone hydrochloride was prepared by media milling technique. HPMC and poloxamer were used as stabilizers to prevent from surface charge agglomeration. Kollidon, Croscarmellose sodium and ludipress were used as super disintegrants. The nanosuspension was optimized by evaluating the particle size analysis, zeta potential, milling time and concentration of stabilizer. **Results and Discussion:** The particle size and zeta potential of F4 formulation were found to be 245.4 nm, -3.24 mv respectively. The solubility studies proven the nanosuspension shows more solubility than pure drug. The Powder X-ray Diffraction (PXRD) results indicates that the drug exists as unchanged crystalline nature which improved the solubility by media milling technique. Further, the suspension was converted to oral disintegration tablets and evaluated. The results shows that *in vitro* release of disintegrating tablets with ludipress with more than 85% drug release than formulations with kollidon, Croscarmellose sodium. **Conclusion:** From the result it may be concluded that the formulated oral disintegrated tablet with uniform sized stable nanosuspension showed enhanced dissolution which may lead to enhanced oral bioavailability of Lurasidone HCl.

Key words: Hydroxypropyl methylcellulose, ludipress, lurasidone hydrochloride, media milling technique, nanosuspension, poloxamer, powder X-ray diffraction

INTRODUCTION

In the current situation, most of the new drug molecules coming to the market belongs to BCS-II, having low solubility and high permeability, these are unable to meet the drug concentration at respective organ within the time.[1] These candidates often have a partition coefficient of more than 1. To address these issues, many development strategies have been introduced, namely, solid dispersions, complexation, cosolvency, lipid nanoparticles, etc., have been tried. In these techniques, large quantities of organic solvents and other excipients were used which may result in the toxicity.[2] Nanosystems were used in recent times for production nanoparticles to improve the solubility and bioavailability-related issues. The increase surface area leads to increased dissolution rate which in turn as per Noyes-Whitney theory result in increased

bioavailability. Like bottom-up technologies, top-down methods were also shown to be a reliable method to increase the surface area and dissolution rate.[3] To name, media milling and homogenization have been successfully applied to produce nanosized particle. Media milling grinding with metallic pebbles is used to nanosized particles which will are free from solvents.

Nanosuspensions (NS) have gain interest to provide effective delivery of hydrophobic drugs using different techniques

such as media milling and high-pressure homogenization have been commercially used for producing NS.[4] These colloidal systems are easy to scale up with particle size 10-100 nm. When particle size reduction method is used, the major problem associated is particle agglomeration which can be reduced by addition of stabilizers. Once again the type and concentration of stabilizers along with milling parameters effects the particle size. Stabilization of particles (prevention of agglomeration) is achieved by the use of surfactants or by electrostatic repulsion techniques. Hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulfate (SLS) were proved to be good stabilizer in many of the media milling techniques.[5]

In this present work, NS was prepared by media milling technique; it has advantages other than alternative techniques to make NS. The important criteria are maintaining the uniform particle size of suspension to maintain the stability by manufacturing processes. The absence of particles with major differences in their size in NS prevents the existence of different saturation solubilities, concentration gradients, and preventing the Oswald ripening effect.[6,7] An attempt has been made for the drug molecule having crystalline nature belongs to BCS-II class to improve the solubility through NS.

Lurasidone hydrochloride is newer drug molecule to treat schizophrenia, IUPAC as (3aR,4S,7R,7aS)-2-[((1R,2R)-2-{[4-(1,2-benzisothiazol-3-yl)-piperazin-1yl]methyl}cyclohexyl)methyl] hexahydro-1H-4,7 methanisoindol-1,3-dione.[8] Common stabilizers are used such as HPMC and poloxamers to prevent from agglomeration of nanocrystals. The main actions of a stabilizer are wet the drug particles thoroughly and to prevent Ostwald's ripening.[9,10]

The aim of work is to prepare NS by media milling technique to improve the solubility, using zirconium beads with 0.4 and 0.2 mm mesh size evaluate for its particle size, zeta potential and *in vitro* studies and powder X-ray diffraction (PXRD) was performed; NS was prepared and formulated as the oral disintegration tablets and compared with lurasidone NS.

MATERIALS AND METHODS

Materials

Lurasidone hydrochloride was a gift sample from Mylan Laboratories, Ltd. (Hyderabad, India). Sodium lauryl sulfate, and poloxamer 188 was purchased from sigma-Aldrich Corporation, (Bengaluru, India). HPMC E3 and HPMC E5 purchased from Merck Chemicals India Pvt. Ltd. (Mumbai). All the other chemicals used in this study were of analytical grade.

Solubility studies

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug. Saturation solubility studies were performed by adding known excess quantity of drug in 250 ml of respective media, namely, pH 0.1 N hydrochloric acid, pH 3.8 Mcilvaine, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer and subjected to agitation incubator at 100 rpm for 24 h at 37°C. The resultant saturated solutions were collected and filtered through 0.45 μ membrane filter, and the concentration of drug was determined spectrophotometrically at λ_{max} of 230 nm. The procedure was followed to study the increase insolubility for NS.[11-13]

Drug excipients compatibility

Fourier transform infrared (FTIR) study

Compatibility of drug and excipients were studied using FTIR. A physical mixture of drug and polymers (either alone or in combination) was prepared and mixed with anhydrous potassium bromide (KBr) in 1:4 ratio. About 100 mg of this mixture was ground into fine powder using mortar and pestle followed by compression to form a transparent KBr pellet using a hydraulic press at 15 tons pressure. Each KBr pellet was scanned at 4 mm/s at a resolution of 2 cm over a wavenumber region from 4000 to 400 cm^{-1} in a FTIR spectrophotometer (Shimadzu, Japan). The IR spectrum of the physical mixture (1:4 ratio) was compared with those of pure drug, lipid, and surfactant and IR peak matching were done to detect any appearance or disappearance of peaks.[14-16]

XRD study

Crystallinity of the drug was determined using the Bruker D8 advance XRD with copper target. The conditions were 40 mA current; 40 KV voltages; at room temperature. The drug was loaded onto the diffractometer and scanned over a range of 20 values from 3° to 45° at a scan rate of 0.1°/s.[16]

Formulation development[17-20]

Preparation of NS

The drug was dispersed in aqueous purified water with a different ratio of stabilizer (HPMC E3, poloxamer) in 130 ml. The resultant coarse pre-dispersion drug sample was comminuted using zirconium oxide beads (milling media) on a magnetic stirrer with a diameter of 0.4 mm. Various parameters such as the effect of stirring time and pressure bar were optimized by keeping the drug, stabilizing agent, and milling media volume as constant initially. The optimized conditions of stirring time and pressure bar were used throughout the study to optimize the concentration of stabilizing agent to achieve minimum particle size. The stirring was continued for 2 h at 3000 rpm. The formulation charts for preparing NS were shown in Table 1.

Preparation of granules

Top spray granulation technique was followed for the preparation of granules. The optimized NS formulation was sprayed on mannitol and microcrystalline cellulose (2:1)

Formulation	Ingredient 1		Ingredient 2		API (% w/w)	Total solid content (% w/w)
	Name and grade	% w/w	Name and grade	% w/w		
NS1	HPMC E3	8.33	-	-	16.66	25.00
NS2	HPMC E3	8.33	SLS	0.5	16.66	25.49
NS3	HPMC E3	8.33	Span 20	0.5	16.66	25.49
NS4	HPMC E3	12.0	Polysorbate 80	0.5	12.5	25.49
NS5	HPMC E5	12.5	-	-	12.5	25.00
NS6	Poloxamer 188	12.5	-	-	12.0	25.00
NS7	Poloxamer 188	8.33	Labrasol	1	16.66	25.99

Table 1: Formulation parameters for preparation of nanosuspension

HPMC: Hydroxypropyl methylcellulose, SLS: Sodium lauryl sulfate, NS: Nanosuspension

ratio using fluid bed dryer. The parameters maintained are shown in Table 2.

Formulation of oral disintegrating tablets

The prepared granules were taken and blended with Kollidon CL-M, lactose monohydrate, Celous 802, and aerosil for 10 min followed by lubrication with magnesium stearate for 5 min. The blend was directly compressed into tablets using 16 station rotary punching machine with 13 mm round punch at compression force of 3-5 kp.

The same procedure was repeated by replacing the Kollidon CL-M with Croscarmellose sodium (CCS) and ludipress with their respective trials, to formulate into oral disintegrating tablets. Control tablet of pure drug was prepared with respective composition and optimized formula to compare with the developed formulation. The compositions of NS as oral disintegrating tablets are shown in Table 3.

Physical characterization of NS

Mean particle size and size distribution (polydispersity index [PDI]) and zeta potential of the prepared NS were determined using Malvern Zetasizer (Nano Series Nano-ZS, Malvern Instruments, UK). Before the measurement, the samples were appropriately diluted with water to a suitable scattering intensity and re-dispersed by shaking. Zeta potential was determined by the electrophoretic mobility of the particles.[21]

Evaluation of oral disintegrating tablets[22-25]

Physical appearance

The tablets were observed for its size, shape, color, presence or absence of odor, taste, surface texture, and consistency.

Weight variation

Twenty tablets were taken and weighed individually, and average weight of the tablets was calculated.

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

Hardness test

The hardness of tablet of each formulation was checked using Dr. Schleuniger hardness tester in terms of kilopounds.

Thickness

Thickness was measured using vernier caliper. It was determined by checking six tablets from each formulation.

Friability test

The initial weight of 20 tablets is taken and placed in the Roche friabilator, rotating speed at 25 rpm for 4 min. The difference in the weight is noted and expressed as percentage.

$$\% \text{ Friability} = [(W_1 - W_2)/W_1] \times 100$$

Where W_1 = Weight of tablets before test and W_2 = Weight of tablets after test.

Content uniformity test

10 tablets from each formulation were powdered. The powdered sample equivalent to 100 mg of drug was transferred to a volumetric flask and dissolved in methanol, mixed, and filtered. Required amount of pH 3.8 Mcilvaine buffer was added to the filtrate to make suitable dilution with media, and drug content was analyzed against blank by ultraviolet (UV) spectrophotometer at 230 nm. The percentage of drug present in the tablets was calculated.

Disintegration test

Each formulation orally disintegrating tablets (ODTs) are placed in a Basket Sinker just below the water surface containing 900 mL of water at 37°C and the paddle rotating at 100 rpm. The time taken for a tablet to disintegrate completely into fine particles was noted.

Wetting time

The wetting time of the tablets was measured using a simple procedure. 10 cm diameter of five circular tissue papers was placed in a Petri dish containing 0.2% w/v solution

Table 2: Parameter for preparation of granules

Parameter	Maintained at
Inlet temperature	42°C
Product temperature	38°C
Exhaust temperature	36°C
Blower speed	45 m/s
Atomization	1.2 mPa
Spray speed	10 rpm

Table 3: Composition of oral disintegrating tablets with granulated nanosuspension and controlled tablet

Ingredients	Quantity (mg/tab)						
	F1	F2	F3	F4	F5	F6	F7
Pure drug	40	-	-	-	-	-	-
Granulated nanosuspension	-	340	340	340	340	340	340
Lactose monohydrate	450	125	100	125	100	125	100
Celous 802	100	100	100	100	100	100	100
Kollidon CL-M	-	25	50	-	-	-	-
Croscarmellose sodium	-	-	-	25	50		
Ludipress	-	-	-	-	-	25	50
Aerosilpharma 200	4	4	4	4	4	4	4
Magnesium state	6	6	6	6	6	6	6
Final weight of tablet	600	600	600	600	600	600	600

of amaranth (10 ml). One tablet was carefully placed on the surface of the tissue paper. The time required for the development of blue color on the upper surface of the tablets was noted as the wetting time.

In vitro studies[26]

The *in vitro* study was performed in paddle USP-II apparatus. The sample was withdrawn at different time intervals and analyzed.

Preparation pH 3.8 Mcilavine buffer

Mix 645 ml of 0.1 M citric acid and 355 ml of 0.2 M disodium hydrogen phosphate in 1000 ml of volumetric flask. pH of the resultant medium was adjusted with 0.1 M citric acid.

Procedure

The *in vitro* drug release studies for the prepared formulation were conducted for a period of 1 h using an electrolab model dissolution tester USP Type - II apparatus (paddle). The

formulation was placed in 900 ml of the dissolution medium set of 50 rpm at $37 \pm 0.5°C$. At definite time intervals, 10 ml samples were withdrawn from the dissolution medium and replaced with fresh dissolution medium to keep the volume constant. The absorbance of the sample solution was analyzed by UV-visible spectrophotometer at 230 nm to know the amount of drug released from the formulation at a particular time interval.

RESULTS AND DISCUSSION

Solubility studies

The solubility study for optimized NS was done in various physiological body conditions. The solubility data indicate that the drug is having a highest solubility in pH 3.8 phosphate buffer followed by 0.1 N HCl, whereas in pH 6.8 phosphate buffer, the drug is completely insoluble. Based on the solubility data of NS, it was compared with pure form of drug. The solubility of NS was increased by 5-folds in pH 3.8 Mcilvaine buffer. The results were evidenced from Figure 1.

Drug excipients compatibility by FTIR study

Drug excipients' compatibility was carried out by FTIR study to know any physical or chemical interaction occurs between drug and excipients. From the results of it indicated that there was no interaction between drug and excipients. The frequencies of functional groups of drug remained intact in physical mixture containing different excipients. Hence, it was concluded that there were no major interactions occurred. The results were evidenced from Figure 2.

PXRD

PXRD study was conducted to know the polymorphic or any morphological changes occurred in the formulation, by assessing the crystalline state and particle morphology. From the results, it confirmed that crystalline state of the drug and NS did not induce a crystalline or polymorphic transition of the drug during milling and drying process. Therefore, the prepared granulated NSs were physicochemically stable during the storage. It can also be safely assumed that better physicochemical properties such as enhanced solubility and dissolution velocity can be attributed to the particle size reduction and without altering in crystalline state. The results were shown in Figure 3.

Preparation of NS

The different ratios of polymer and stabilizers are used to prepare NS formulation. Zirconium oxide beads were used in the preparation due to their low cost and easy availability in lab scale for the production of NS in comparison to silver

beads. The formulations F2 and F3 with HPMC E3, SLS, and HPMC E3, Span 20 showed physical incompatibility after milling, i.e., leading to coagulation and precipitation of solid material forming a cake. Formulation F7 with poloxomer and labrosol showed good milling efficiency but producing a highly viscous suspension upon milling and leading to aggregation of particles. Formulation F5 with HPMC E5 was found to be less efficient than formulation F1. Formulation F4 was milled with 0.5% w/w polysorbate 80 to evaluate its effect on milling. It was found that polysorbate 80 at the selected concentration increases milling efficiency. Formulation F1 with HPMC E3 does not give efficient milling than F4. This could be due to the lack of stabilizer in formulation F1 and F6 with poloxamer 188 gives the good milling efficiency.
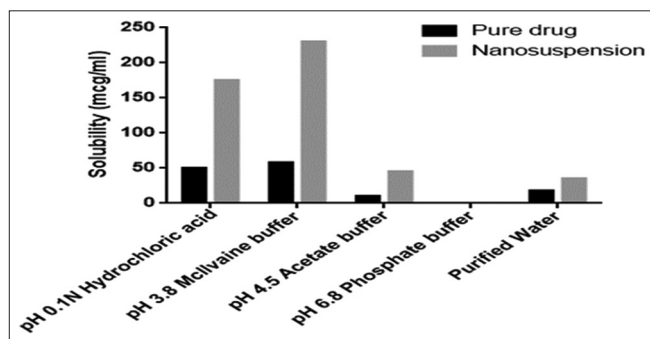
Figure 1: Solubility of pure drug and nanosuspension in various pH conditions

Preparation of granules

The optimized NS was selected from the characterization study. The granules are prepared using fluid bed dryer and evaluated for the flow property of the prepared granules. From the results, it was confirmed that the prepared granules show excellent flow property. The results were shown in Table 4.

## Characterization and optimization of NS

Optimization of milling parameter of NS

Milling parameters which are considered to optimize for the preparation of the NS are shown in Table 5.

For optimizing the milling time, the prepared NS formulation was milled for 60 min and 120 min, respectively. From the characterization, it was found that the particle size reduction was significant till 120 min to obtain desired particle size. Therefore, the milling time was optimized as 120 min. The results were given in Table 6.

Optimization of polymer type

The effect of different polymers on the milling efficiency was evaluated. Formulation F2 and F3 with HPMC, SLS, and HPMC, Span 20 showed physical incompatibility leading to
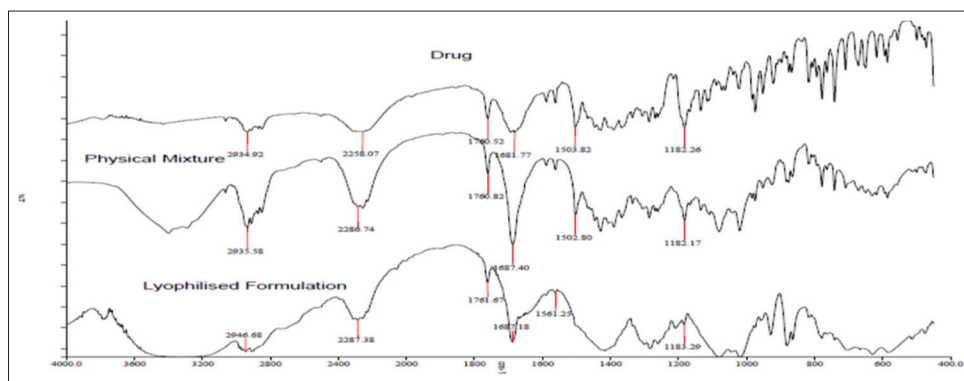
Figure 2: Fourier transform infrared overlay of pure drug, physical mixture, and nanosuspension
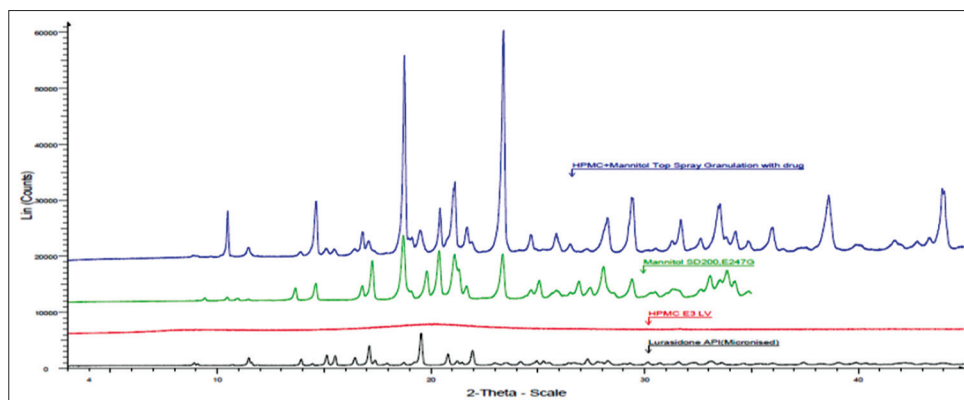
Figure 3: Powder X-ray diffraction of pure drug, hydroxypropyl methylcellulose E3, mannitol, granulated nanosuspension mixture

			Table 4: Milling parameters for the preparation of NS			
Formulation	Pump speed (rpm)	Milling speed (rpm)	Agitator speed (rpm)	Bead volume (ml)	Pressure (bar)	Temperature (°C)
NS1	40	3000	-	130	0.23	28
NS2	-	-	-	-	-	-
NS3	-	-	-	-	-	-
NS4	40	3000	-	130	0.32	34
NS5	40	3000	-	130	0.37	36
NS6	40	3000	-	130	0.21	25
NS7	40	3000	60	130	0.37	30

Pressure observed is pressure buildup in milling chamber and should not exceed 1. Milled samples were collected at desired time intervals and stored for analysis. NS: Nanosuspension

		Table 5: Flow property of granulated NS		
Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
F1	0.44	0.51	13.72	1.15
F2	0.45	0.52	15.09	1.17
F3	0.44	0.51	13.72	1.15
F4	0.45	0.52	15.38	1.11
F5	0.44	0.51	13.72	1.15
F6	0.45	0.52	15.09	1.17
F7	0.45	0.50	10.00	1.11

NS: Nanosuspension

	Table 6: Optimization of milling time	
Time (min)	Z-average (nm)	PDI
30	748.4	0.308
45	483.2	0.28
60	338.4	0.237
90	311.8	0.194
120	296	0.177

PDI: Polydispersity index

coagulation and precipitation of solid material forming a cake. Formulation F7 with poloxamer and labrosol showed good milling efficiency but producing a high viscous suspension upon milling and leading to formation of settling aggregates. Formulation F5 with HPMC E5 was found to be less efficient than formulation F1. This could be due to low viscosity. Formulation F4 was milled with 0.5%w/w polysorbate 80 to evaluate its effect on milling. It was found that F4 with HPMC E3: Polysorbate 80 and F6 with poloxamer 188 at the chosen concentration shows increase in milling efficiency.

Formulations F4 and F6 with HPMC E3 and poloxamer 188 were, therefore, considered for further studies.

Physical characterization of NS

Mean particle size, size distribution, and zeta potential were determined using Malvern Zetasizer. The zeta potential is a measure of the electric charge at the surface of the particles, representing the physical stability of colloidal systems. Formulation F4 was found to have a mean globule size of 245.54 nm with a PDI 0.154, and zeta potential −3.24 mV was selected as the optimized formulation. Since the particles are uniformly distributed, and there was no agglomeration or aggregation between the particles. The results were evidence from Figures 4 and 5. Since in the formulation F6, the mean droplet size and PDI were found to be larger exceeding to 100 nm and wide range of particle size distribution which is not desirable. The results were given in Table 7. Other parameters for all the formulations were found to be good. The optimized formulation F4 was selected to prepare granules for further step.

Evaluation of oral disintegrating tablets

The general appearance of tablets, its visual identity, and overall elegance is essential for consumer acceptance. The physical characteristics of oral disintegrating tablets were performed to evaluate the parameters such as average weight of tablet, average thickness, average hardness, friability, disintegration time, and wetting time. The average weight of tablet varies from the 598.5 to 602.5 mg, the average thickness varies from 6.02 to 6.07 mm, the hardness of tablet varies from 3.5 to 4.2 kp, friability of tablets varies from the 0.50% to 0.70%, the disintegration time for prepared tablets varies from the 22 to 190 s, and the wetting time for 10-20 s.
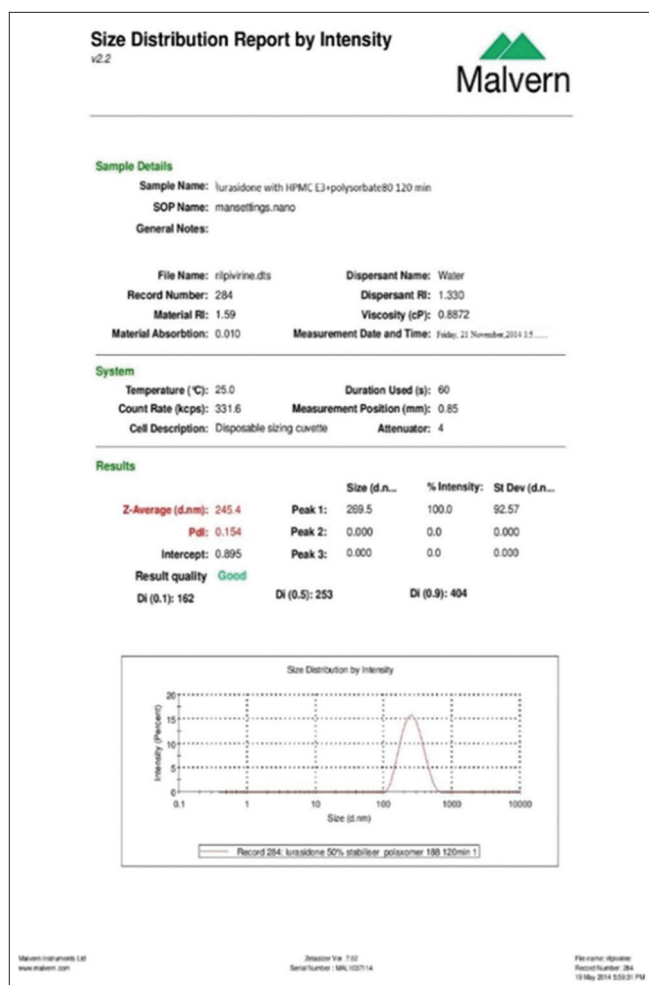
Figure 4: Size distribution study for optimized formulation (nanosuspension 4)

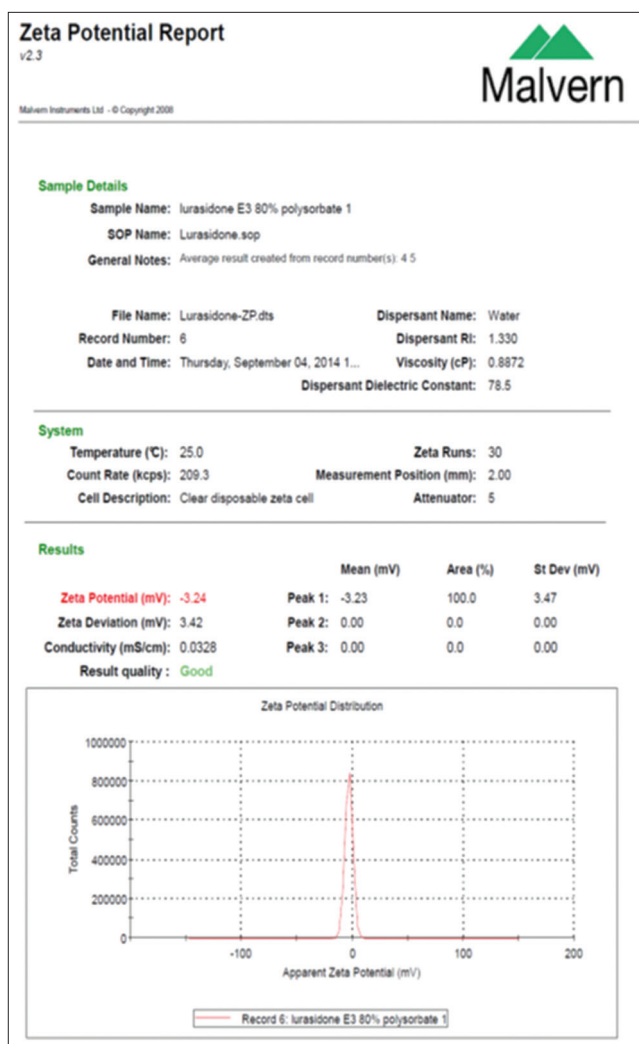**Figure 5:** Zeta potential study for optimized formulation (nanosuspension 4)

The time for oral disintegrating tablets to disintegrate is generally <1 min and actual disintegration time that patient can experience ranges from 5 to 30 s. The optimized formulation shows the average of tablet in the range of 600.5-602.2 mg, wetting time 10-12 s, and disintegration time about 22-24 s. Physicochemical properties (average weight, thickness, hardness, friability, and disintegration time) of all tablet formulations were found to be within USP specifications. The results were shown in Table 8.

Drug content

The drug content of oral disintegration tablets containing NS gives the drug content in the range of 99.92-100%. From the result, it confirms that the drug has been uniformly distributed in all the tablets.

In vitro dissolution studies

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium

Table 7: Characterization of NS formulations

Formulation	Z-average (nm)	PDI	Zeta potential
NS4	245.4 nm	0.154	–3.24 mv
NS6	325.4nm	0.68	29.5 mv

PDI: Polydispersity index

or solvent under standardized conditions of liquid/solid interface, temperature, and solvent composition. The *in vitro* dissolution study performed for oral disintegration tablets containing NS using USP–II paddle apparatus with medium as pH Mcilvaine buffer which simulates the *in vivo* conditions (actual physiological conditions). The drug release rate at 5 min shows for pure controlled tablet is 5.34%, formulation with 4% Kollidon CL-M as disintegrant shows 32.06%, and formulation with 8% Kollidon CL-M as disintegrant shows 46.87%. More than 80% drug release observed at 45min in both the formulations. At the 60 min, drug release observed for F2 is 81.93% and F3 is 92.06%. The results were shown in Figure 6.

The drug release rate at 5 min resulted for pure control tablet is 5.34%, formulation with 4% CCS as disintegrant shows 53.7%, and formulation with 8% CCS as disintegrant shows 60.56%. The more than 80% drug release observed at 30 min for both the formulations. At the 60 min, drug release observed for F4 is 96.18% and F5 is 98.62%. The results were evidence from Figure 7.

The drug release rate at 5 min shows for pure controlled tablet is 5.34%, formulation with 4% ludipress as disintegrant shows 73.5%, and formulation with 8% ludipress as disintegrant shows 77.06%. The more than 80% drug release observed at 15 min for both the formulations. At the 60 min, drug release observed for F6 is 97.87% and F7 is 99.37%. The results were evidence from Figure 8. The percentage cumulative drug release of Kollidon CL-M, CCS, and ludipress results was given in Table 9.

CONCLUSION

The ODTs tablet containing lurasidone HCl loaded NS formulated and optimized for their physical characterization. The particle size and zeta potential are 245.4 nm and −3.24 mV. The solubility studies have proven the NS get more solubility than pure drug. The PXRD results show the no change in crystalline nature of drug molecule improves the solubility by media milling technique. In conclusion, results of this work confirm that the improvement of lurasidone HCl dissolution rate using ODT is mainly caused by the increased surface-to-volume ratio due to the submicron dimension

of the drug particles. The present study showed that NS ODTs are the promising alternative method for improving dissolution rate and bioavailability of drug. The results suggest that the particle size reduction by media milling
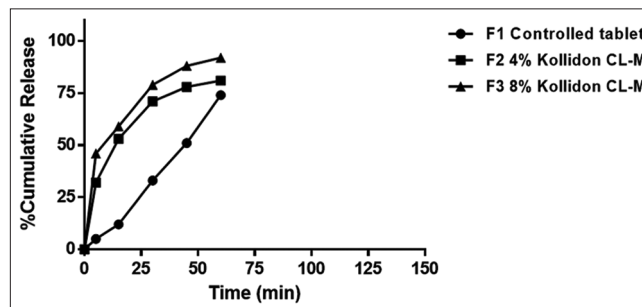
Figure 6: Dissolution profile for nanosuspension as orally disintegrating tablet with Kollidon CL-M
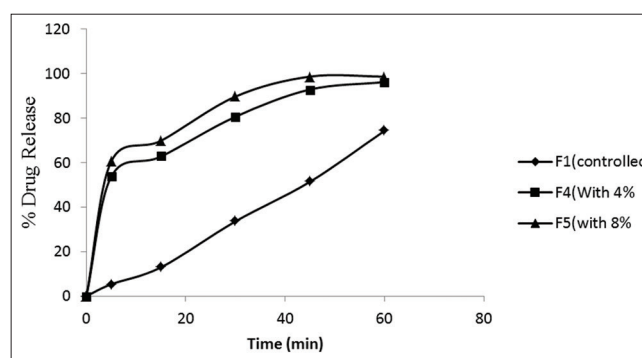
Figure 7: Dissolution profile for nanosuspension as orally disintegrating tablet with Croscarmellose sodium

Table 8: Physical characterization of ODTs

Formulation	Average weight (mg)	Average thickness (mm)	Average hardness (kp)	Friabilty (%)	Disintegration time (s)	Wetting time (s)
F1	600.1-601.2	6.02-6.07	3.5-4.2	0.52	30-40	15-20
F2	599.1-600.1	6.03-6.07	3.5-4.2	0.70	175-190	20-25
F3	600.5-603.5	6.03-6.07	3.5-4.1	0.68	70-85	15-20
F4	599.5-600.4	6.02-6.05	3.5-4.2	0.50	65-75	20-25
F5	598.5-600.1	6.02-6.06	3.5-4.3	0.69	40-45	10-15
F6	600.8-603.3	6.02-6.07	3.5-4.2	0.52	35-45	15-20
F7	600.5-602.2	6.04-6.07	3.5-4.1	0.53	22-24	10-12

ODT: Orally disintegrating tablets

Table 9: The percentage cumulative drug release of Kollidon CL-M, CCS, and ludipress

Time (min)	Cumulative percentage drug release						
	F1 controlled tablet (%)	F2 (with 4% kollidon CL-M)	F2 (with 8% kollidon CL-M)	F3 (with 4% CCS)	F3 (with 8% CCS)	F6 (with 4% Ludipress)	F6 (with 4% Ludipress)
5	5.34	32.06	46.87	53.7	60.56	73.5	77.06
15	12.93	53.62	59.87	62.70	69.8	80.62	95.12
30	33.56	71.25	79.87	80.58	89.65	90.25	99.37
45	51.37	78.18	88.5	92.81	98.62	97.87	99.37
60	74.25	81.93	92.06	96.18	98.62	97.87	99.37
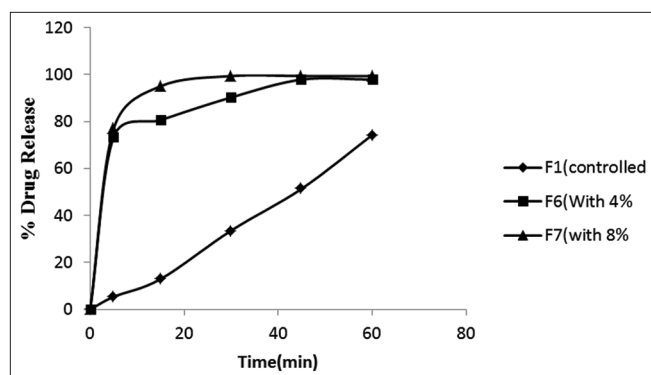
Figure 8: Dissolution profile for nanosuspension as orally disintegrating tablet with ludipress

technique can be utilized for reducing particle size and thereby improving solubility-related issues. Further *in vivo* studies are recommended to support the *in vitro* results.

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