

Formulation and Evaluation of Fast Dissolving Tablet Containing Vilazodone Nanocrystals for Solubility and Dissolution Enhancement Using Soluplus: *In vitro-In vivo* Study

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ABSTRACT

A major problem in the development of an efficacious formulation of the drug is its pitiable aqueous solubility which affects stability and bioavailability of drug formulation. There is a need for systematic formulation approaches to make poorly soluble drugs bioavailable. The present investigation aims to increase solubility and dissolution of Vilazodone (VLZ) an antidepressant drug by preparing its nanoparticles using graft copolymer Soluplus and polyvinylpyrrolidone K-30 (PVP K 30) by evaporative precipitation into aqueous solution method. The prepared nanoparticles were characterized by FTIR, DSC, XRD, SEM, Particle size by DLS and saturation solubility. The nanoparticles showed a remarkable increase in the aqueous saturation solubility i.e., NP1, NP2, NP3 and NP4 shows 4.4, 4.6, 7.7 and 7.8 folds respectively increase in aqueous solubility as compared to VLZ. The nanoparticles NP4 batch with the highest solubility is converted into fast dissolving tablet. The tablets were evaluated for different parameters and found to possess more dissolution (89.386% release) as compared to pure drug (51.652%). The rise in solubility and dissolution may be due to either reduction in particle size leads to increase surface area or micelles formation due to Soluplus and reduction in crystallinity of drug. *In vivo* study reveals that optimized Vilazodone nanoparticles (VLZNP) elicited significant antidepressant-like activity.

INTRODUCTION

Therapeutic efficacy depends upon bioavailability, solubility, and release of drug molecules from the formulation. The aqueous solubility of therapeutically active substance governs dissolution, absorption and has an essential role in bioavailability of oral drug formulations (Patel *et al.*, 2011). About more than 40% of drug molecules recognized during combinatorial selection programs are poorly water soluble. Low aqueous solubility is main trouble in formulation development, clinical testing and during screening new compounds for therapeutic activity (Lipinski, 2002). The low water solubility of many active pharmaceutical ingredients (APIs) excludes their use in certain clinical applications in spite of their efficacy. However, small particle formation technologies for these APIs may increase

their effectiveness for oral, injectable and inhalation delivery by increasing surface area, dissolution rates and overall bioavailability (Vaughn *et al.*, 2004). Systematic formulation approaches may make poorly soluble drugs bioavailable. Nanoparticle engineering technologies in formulation development of low water-soluble drugs is a promising strategy to enhance dissolution rates and thus bioavailability (Patel *et al.*, 2011). Vilazodone is an antidepressant agent with poor aqueous solubility use as an alternative for patients who cannot tolerate treatment with other antidepressants.

MATERIALS AND METHODS

Materials

Vilazodone was gifted by Clearsynth labs Pvt Ltd Mumbai, Soluplus a graft copolymer was a gift sample from BASF chemicals, Mumbai, PVP K-30, and microcrystalline cellulose was from Himedia Lab. Pvt. Ltd., Mumbai, all other materials and chemicals were procure from S D Fine chemicals Mumbai.

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Methods

Preparation of nanoparticles

Nanoparticles were prepared by evaporative precipitation into aqueous solution method. Vilazodone was dissolved in dimethyl sulfoxide with warm at 70-80°C under constant stirring at 1000 rpm. The prepared drug solution was injected dropwise by using syringe into water containing soluplus with stirring on a magnetic stirrer at 1000 rpm, particles precipitated and milk like suspension formed in which added solution of PVP K-30. Resultant was then filtered and dried. Nanoparticles were ground in mortar and pestle and pass through sieve no 170 to obtain desired uniform size. The Nanoparticles of the drug with polymer was denoted with symbol VLZNP.

Ratio optimization (drug: polymer) by solubility study

The solubility of VLZNP determined in distilled water. The solubility of NPs was determined by taking an excess amount of NPs and adding them to 10 ml of Millipore water and kept at equilibrium on a magnetic stirrer for a period of 48 hours (REMI Instruments, Mumbai) at room temperature. The resultant was filtered through 0.45 µm nylon syringe filter and analyzed by UV-Visible spectrophotometer (Shimadzu Corporation, Japan) at 224 nm wavelength. Ratio (drug: carrier) with higher solubility was said to be optimized and processed further.

Drug entrapment efficiency of NPs

The Vilazodone percentage entrapped within nanoparticles determined by measuring the concentration of free Vilazodone in the dispersion medium.

$$\% EE = \frac{([M_{\text{initial drug}}] - [M_{\text{free drug}}]) \times 100}{[M_{\text{initial drug}}]}$$

where $M_{\text{initial drug}}$ is the mass of initial drug used for the assay, $M_{\text{free drug}}$ is the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

In-vitro dissolution test for VLZ nanoparticles

Dissolution of optimized ratio performed using USP type II dissolution apparatus (Electrolab) in 900 ml of 0.1 N HCl. Powder containing 40 mg (or equivalent) of Vilazodone added in medium maintaining temperature $37 \pm 0.5^\circ\text{C}$ and 50 rpm paddle speed. About 5 ml of aliquot were withdrawn at 2.5, 5, 10, 15, 20, 25 and 30 minute and replaced with the same quantity of prewarmed fresh dissolution medium. Aliquots filtered through 0.45 µm nylon syringe filter and analyzed spectrophotometrically at a wavelength of 224 nm (Medina *et al.*, 2013; Javadzadeh *et al.*, 2007).

Characterization of nanoparticles

Nanoparticles which show better results in solubility and *in vitro* dissolution were further characterized to access interaction if any between drug and polymer during a month.

Fourier-transform infrared spectroscopy

Spectra of drug Vilazodone alone and its Nanoparticles

carried out to check compatibility of the drug with polymers. The nanoparticle of the drug with the polymer (VLZNPs) triturated with potassium bromide IR grade. The dispersion was scanned using FT-IR Spectrophotometer (Shimadzu, Japan). The spectra of nanoparticles compared with the Spectra of vilazodone.

Differential scanning calorimeters (DSC)

DSC thermograms of drug Vilazodone and its nanoparticles obtained (Diamond DSC, Perkin Elmer) by heating at a rate of 10°C/min from temperature 0-300°C.

X-ray diffraction studies (XRD)

XRD study of drug Vilazodone and Nanoparticles access the changes in crystallinity of drug alone and when combined with the polymer. XRD patterns recorded using (Bruker, D8) with Cu- α radiation. The scanning angle ranged from 20° to 80° of 2 θ .

Scanning electron microscopy (SEM)

The surface morphology of nanoparticle formulation was examined by Scanning Electron Microscopy with Gold ion coating for 5-6 min.

Particle size

Particle size was studied by Dynamic Light Scattering method (Hackley and Clogston, 2007).

Preparation of fast dissolving tablet

The ratio of NPs which shows best results in solubility and powder dissolution was selected for preparation of fast dissolving tablet, table 2. The tablets were compressed by direct compression method using 10 mm punch on rotary tablet Minipress (Karnavati Pvt. Ltd, Gujarat).

Table 1: Formulation design of nanoparticles.

Ingredients	NP1	NP2	NP3	NP4	NP5	NP6	NP7
Vilazodone	200	200	200	200	200	200	200
Soluplus	200	300	400	500	600	700	800
PVP K-30	100	100	100	100	100	100	100

Table 2: Composition of VLZNP Fast dissolving tablet.

Ingredients	Batches (All ingredients were in mg)		
	F ₁	F ₂	F ₃
VLZNP (equivalent to 40 mg Vilazodone)	160	160	160
Microcrystalline cellulose	80	80	80
Sodium starch glycolate	40	35	30
Magnesium stearate	6	6	6
Talc	4	4	4
Starch	10	15	20
Total final weight	300	300	300

Pre and post compression evaluation of tablet

Precompression and Post compression evaluation fast dissolving tablet were performed according to USP 30 NF 25 (Rockville, 2007).

In vitro dissolution test for fast dissolving tablet

In vitro dissolution test was performed according to USP apparatus Type II (Electrolab). Tablet containing 40 mg (or equivalent) of Vilazodone was added in dissolution media 900 ml gastric fluid maintaining the temperature at $37 \pm 0.5^\circ\text{C}$ and rotation speed of paddle at 50 rpm. About 5 ml of the aliquot were withdrawn at 2.5, 5, 10, 15, 20, 25, 30 and 35 minute and replaced with 5 ml of fresh prewarmed gastric fluid, filtered through 0.45 μm nylon syringe filter and analyzed at 224 nm wavelength.

Stability studies

Optimized tablet formulation containing nanoparticles subjected to stress conditions of $40^\circ\text{C}/75\%$ RH for six months in stability chamber (Photostability chamber S R Lab Instruments Pvt. Ltd. Mumbai).

In vivo antidepressant activity evaluation

The study was conducted in compliance the protocol approved by the institutional ethical committee. Immobility time in mice evaluated as per the method described by (Porsolt *et al.*, 1977). Mice were forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm) containing 19 cm of water (depth) at $25 \pm 1^\circ\text{C}$; and the immobility time recorded for 6 minutes. Individual mouse considered to be immobile when it ceased struggling and remained floating motionless in the water, showing only those movements essential to keep its head above water. An increase in immobility time was considered an indication of depressive behavior.

RESULT AND DISCUSSION

Drug: polymer ratio optimization

NPs of the drug with polymer were analyzed for solubility study and results are shown in table 3. Solubility study shows that soluplus have very good solubility enhancing property may because of its good surfactant property (Pandey

et al., 2012; Hardung *et al.*, 2010). From solubility studies, it is found that up to certain ratio i.e. 1:2.5 solubility goes increases constantly and further increase in polymer concentration leads to decrease in solubility. Prepared nanoparticle samples showed increased solubility in water more than seven-fold higher (9.36 $\mu\text{g}/\text{ml}$) than pure Vilazodone (1.48 $\mu\text{g}/\text{ml}$). This optimized ratio was then confirmed with powder dissolution and further used for formulation development. The increase solubility of Vilazodone from prepared nanoparticles may due to the reduction in particle size.

Table 3: Solubility of pure VLZ and VLZ nanoparticles.

Batch code	Water Solubility	
	In ($\mu\text{g}/\text{ml}$)	Increase (in fold)
Pure Drug	1.486	1.0
NP1	5.813	4.4
NP2	6.063	4.6
NP3	9.251	7.7
NP4	9.36	7.8
NP5	9.06	7.6
NP6	4.726	3.3
NP7	3.126	1.7

Drug entrapment efficiency of Nanoparticles

Percentage entrapment efficiency of NP4 was found to be maximum that is 95.32%.

In vitro dissolution studies of nanoparticles

VLZNP powder released 82.36% of the drug in solution compared to a pure drug which released only 53.75%. From the results fig. 1 it can be concluded that % drug release of VLZNP is faster than pure VLZ and hence nanoparticles used for the preparation of tablet formulation.

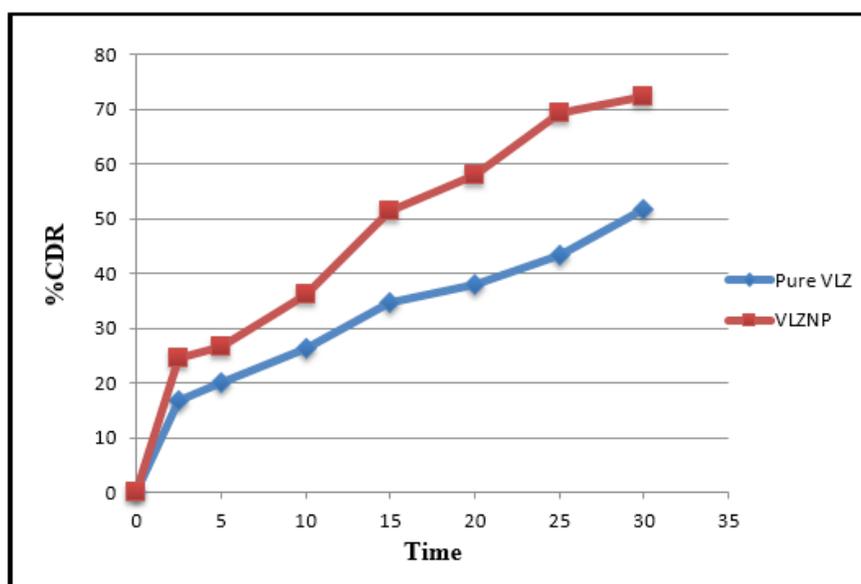


Fig. 1: Comparative Dissolution Profile of pure VLZ and VLZNP.

Characterization of VLZNPs

Fourier transformed infrared spectra

From the spectra of vilazodone and its nanoparticles, it can be concluded that principle peaks of the drug remained unchanged in soluplus treated nanoparticles demonstrating the compatibility between drug and polymer.

Differential scanning calorimetry

DSC analysis performed to observe the thermal behavior of components used in Nanoparticles formulation. The DSC thermograms of the VLZ and VLZNP fig. 4 and fig. 5 showed a sharp characteristic endothermic peak at 276.62°C and 277.31°C respectively indicating crystalline nature of materials and there is no appearance or disappearance of one or more peak.

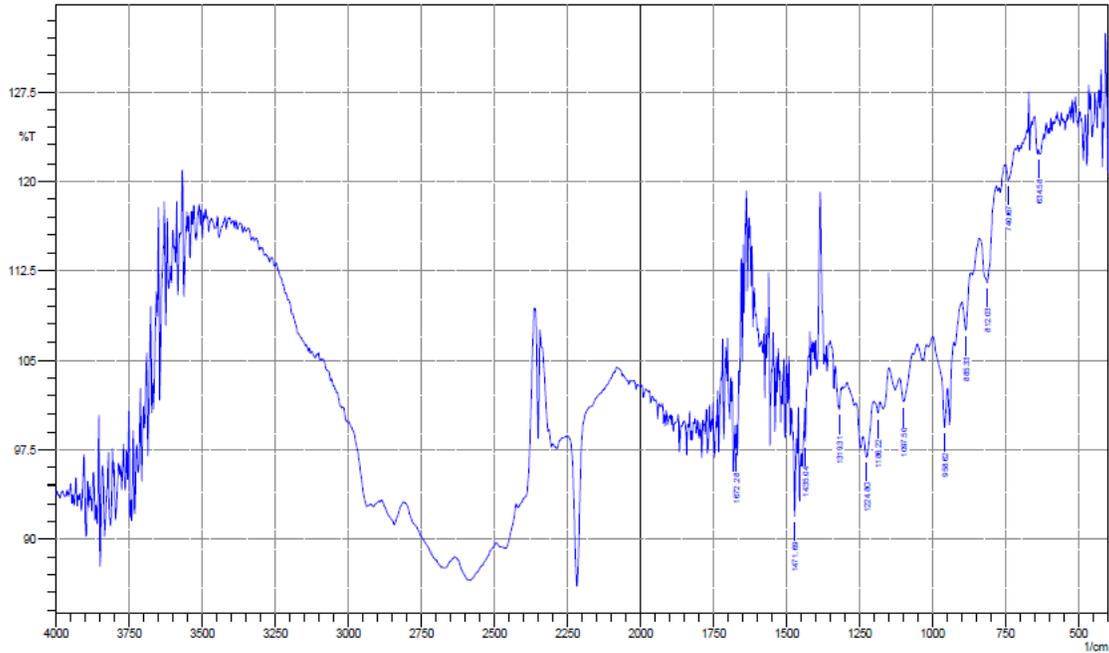


Fig. 2: IR-Spectrum of pure VLZ.

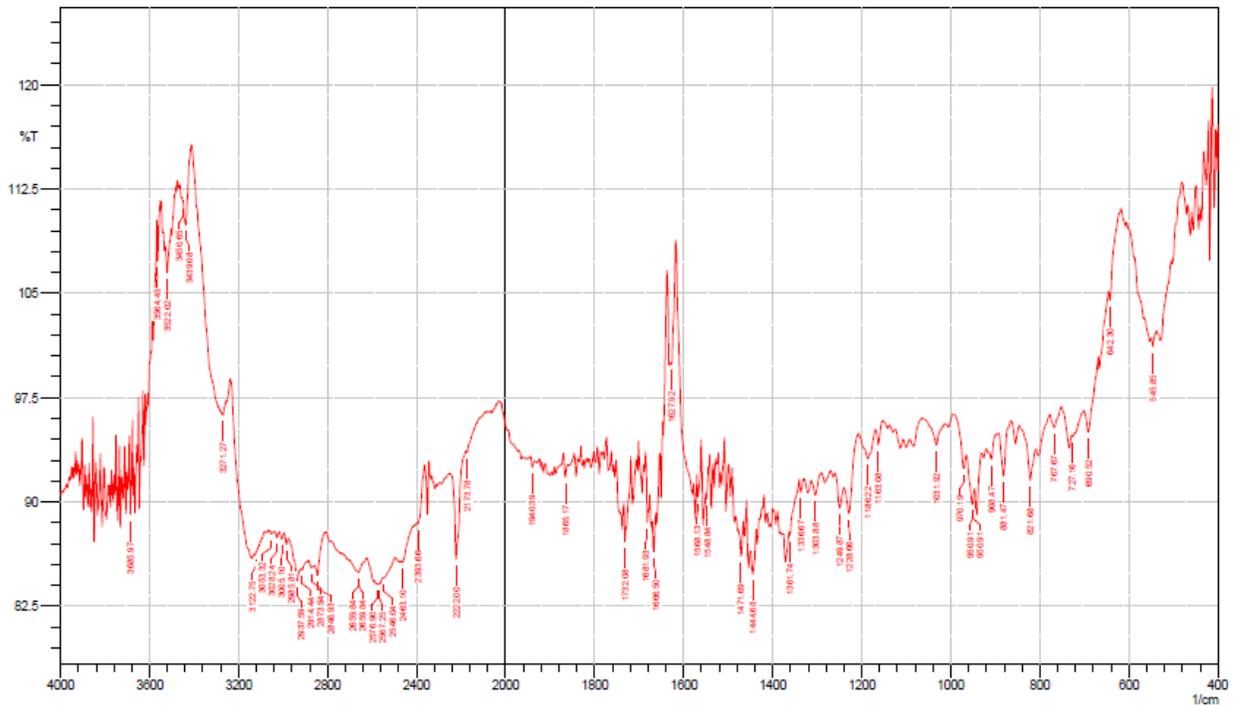


Fig. 3: IR-Spectrum of VLZNPs.

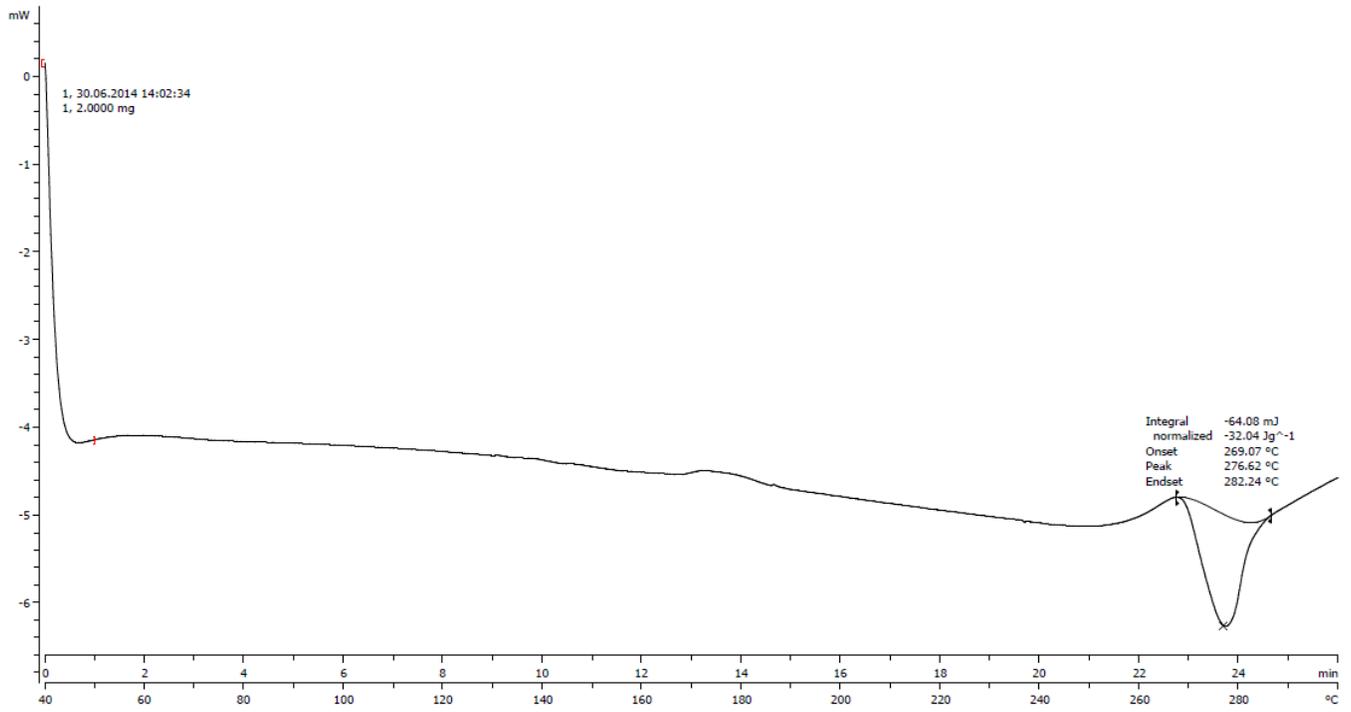


Fig. 4: DSC thermogram of Pure VLZ.

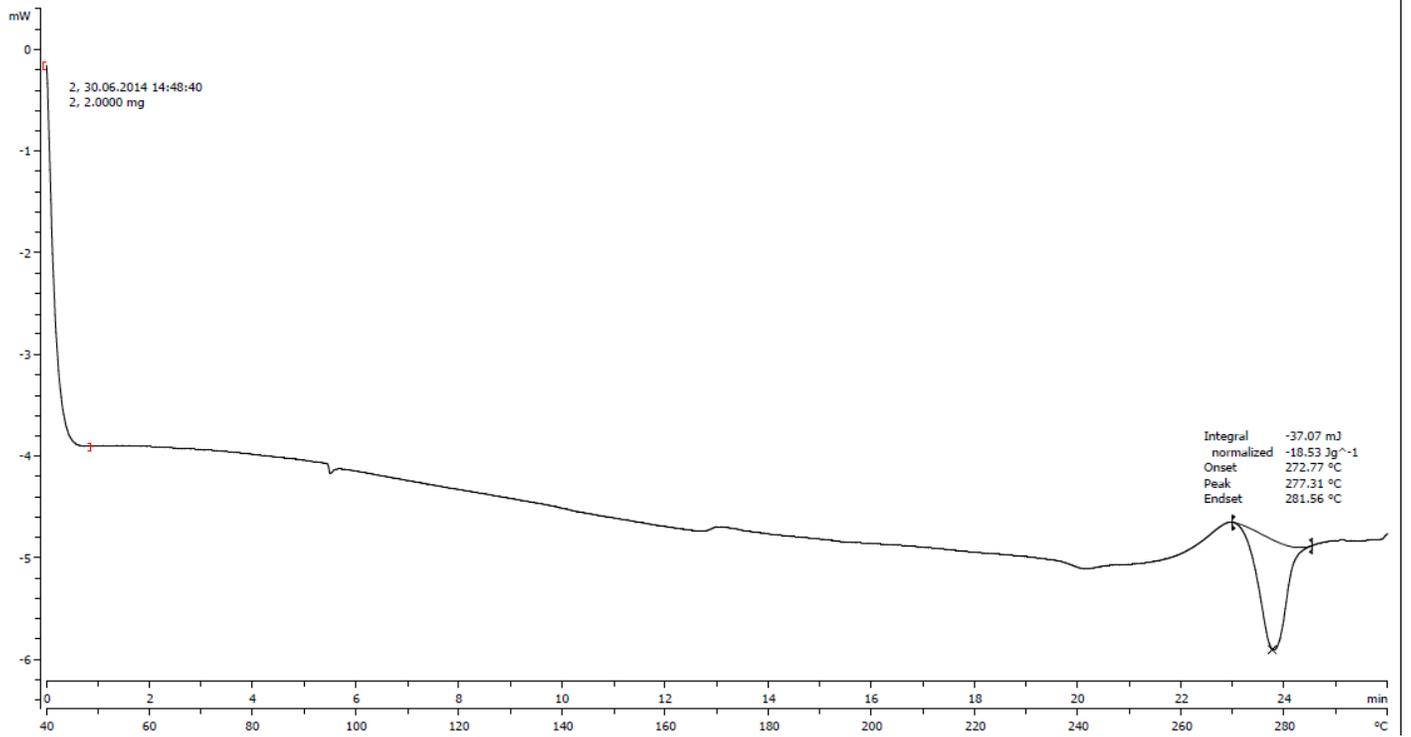


Fig. 5: DSC thermogram of VLZNP.

X-ray powder diffraction (XRD)

Diffraction pattern of Vilazodone showed numerous sharp peaks between 24.56 to 28.85 at 2θ and VLZNP showed the presence of less intense peaks between 24.76 to 20.57 at 2θ . The intensity of the peaks reduces indicating that soluplus interferes with the Vilazodone by forming H-bonding and thus reduces the

crystallinity of the drug and indicates amorphization of the drug.

Scanning electron microscopy (SEM)

Pure drug particles are tabular while optimized NPs were found to be irregular in shape and size below 1000 nm. The SEM images (fig. 8) clearly indicate a complex form of Vilazodone in Soluplus.

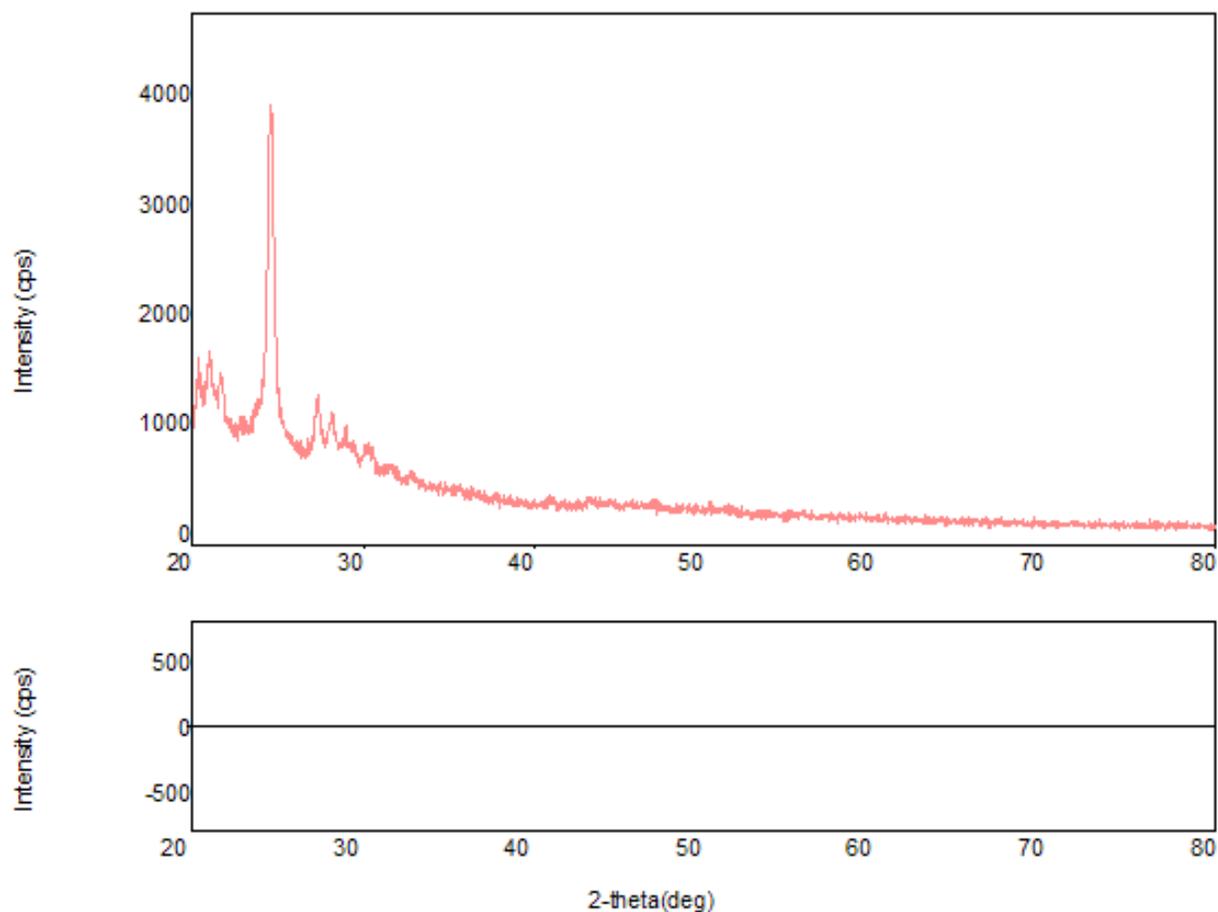


Fig. 6: XRD pattern of Pure VLZ.

Particle size

The Dynamic Light Scattering measurements as depicted in fig. 9, show 90% of particles falls below 100 nm and 10% of particle found coarser.

Pre and post-compression evaluation of fast dissolving tablet

All the pre and post compression evaluation parameters are found to be within the limit as per USP 30 NF25 results depicted in table 4 and 5.

In vitro dissolution of VLZNPs fast dissolving tablet

Release of VLZNPs tablet formulation F_2 (89.386%) exhibited improved dissolution behavior than formulation F_1 (86.74%), F_3 (84.581) and VLZ (51.65%) at the end of 30 min, this may due to decreased particle size, increased surface area and micellar effect of soluplus (Gattani *et al.*, 2018). Results of the *in-vitro* drug release depicted in fig. 10.

Table 4: Pre compression studies.

Formulation code	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
F_1	21.26 ± 1.653	10.56 ± 0.961	1.312 ± 0.026
F_2	20.56 ± 1.681	12.64 ± 0.674	0.989 ± 0.069
F_3	22.11 ± 1.388	13.76 ± 0.766	1.213 ± 0.156

Data are means \pm SD, $n = 3$.

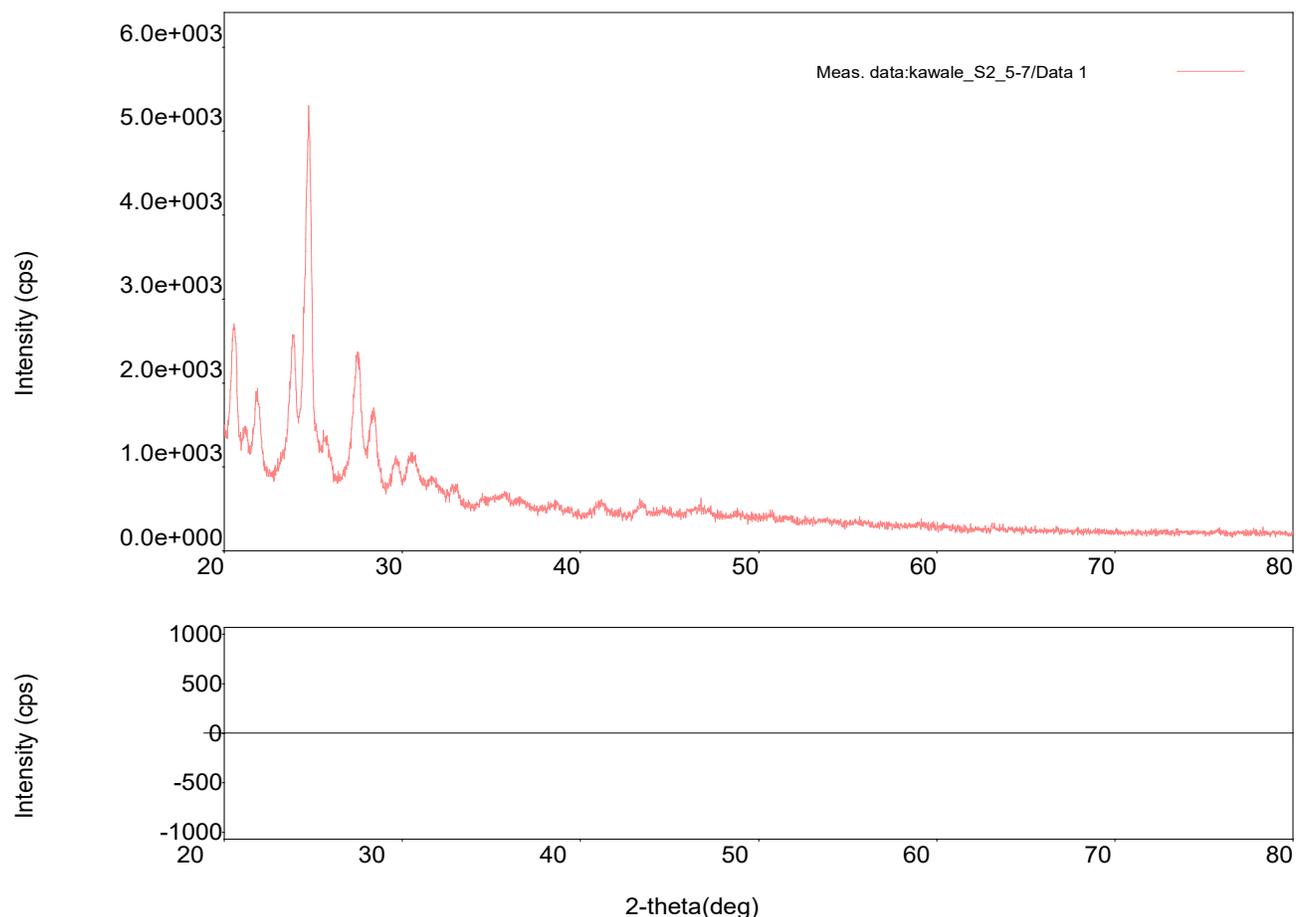
Stability study of vilazodone nanoparticles tablet

Optimized formulation (F_2) subjected to stability conditions (40°C/75% RH) and parameters such as color, odor, assay, and release were studied during 180 days of exposure. No significant change was observed in the stability parameters during exposure and formulation said to be stable and not much affected by stress conditions.

Table 5: Post compression studies.

Batch	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content uniformity (%)	Disintegration time (Sec)
F ₁	297 ± 4.621	3.8 ± 0.125	0.39 ± 0.082	93	19 ± 1.269
F ₂	301 ± 3.625	3.6 ± 0.168	0.43 ± 0.063	95	18 ± 2.365
F ₃	293 ± 3.591	3.7 ± 0.215	0.38 ± 0.051	92	20 ± 1.874

Data are means ± SD, *n* = 3.

**Fig. 7:** XRD pattern of VLZNP.**Table 6:** Stability data of VLZNPs tablet formulation F₂.

Time (days)	% drug content	% <i>In vitro</i> drug release
0	95	89.38
30	95.30	89.43
180	95.19	89.40

In vivo antidepressant activity evaluation

Experimental data revealed that mice treated with VLZNP antidepressant agent attenuate significantly ($P < 0.001$) immobility time compared to VLZ and vehicle-treated group (Table 7 & fig 11). From the data, it seems that VLZ and VLZNP elicited significant antidepressant-like activity. This improvement in the effect of VLZNP may govern by the

decreased particle size and increased surface area and also may due to the micellar action of Soluplus. Thus raised solubility and the *in vitro* dissolution are supported by *in vivo* data and also kinetics.

Table 7: Effects of the vehicle, or VLZ and VLZNP on immobility time in mice.

Treatment and dose (mg/kg, p.o.)	Immobility time (Sec)
Vehicle (10 ml/kg)	52.3 ± 6.9
VLZ	46.5 ± 7.5 ^{ns}
VLZNP	24.5 ± 3.2 ^{**}

Results are expressed as Mean ± SEM, (*n* = 6), Data was analyzed by one-way ANOVA followed by Dunnett's test, * $P < 0.05$, ** $P < 0.001$, NS-Nonsignificant when compared to vehicle-treated group.

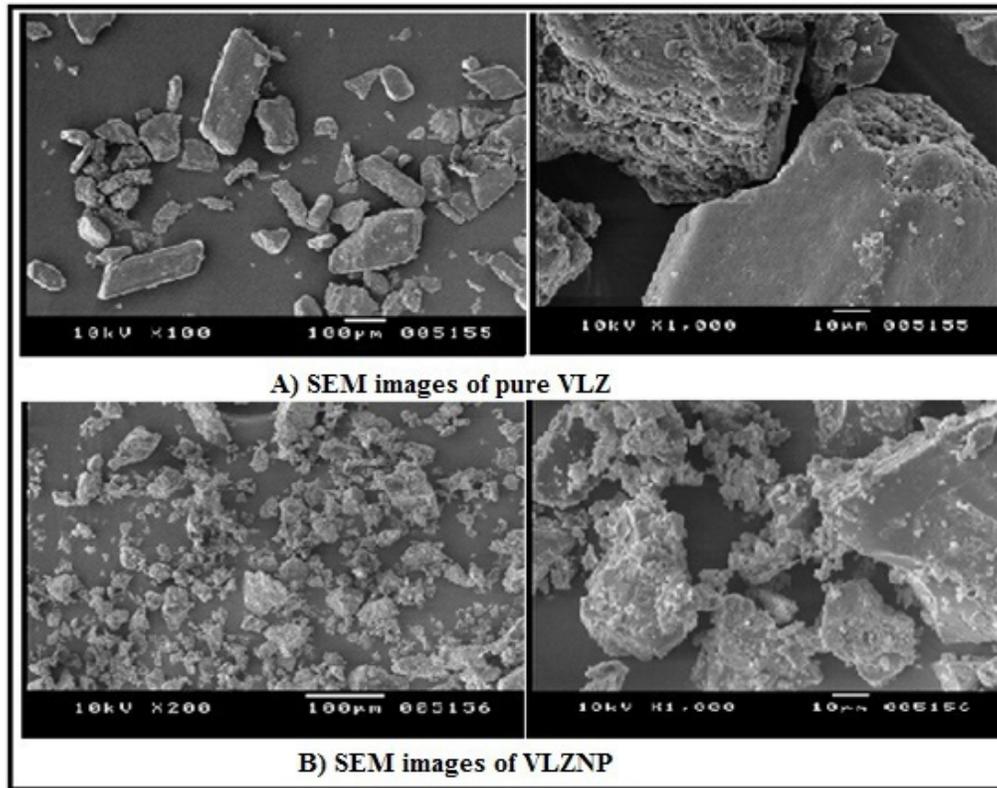


Fig. 8: SEM images of pure VLZ and VLZNP.

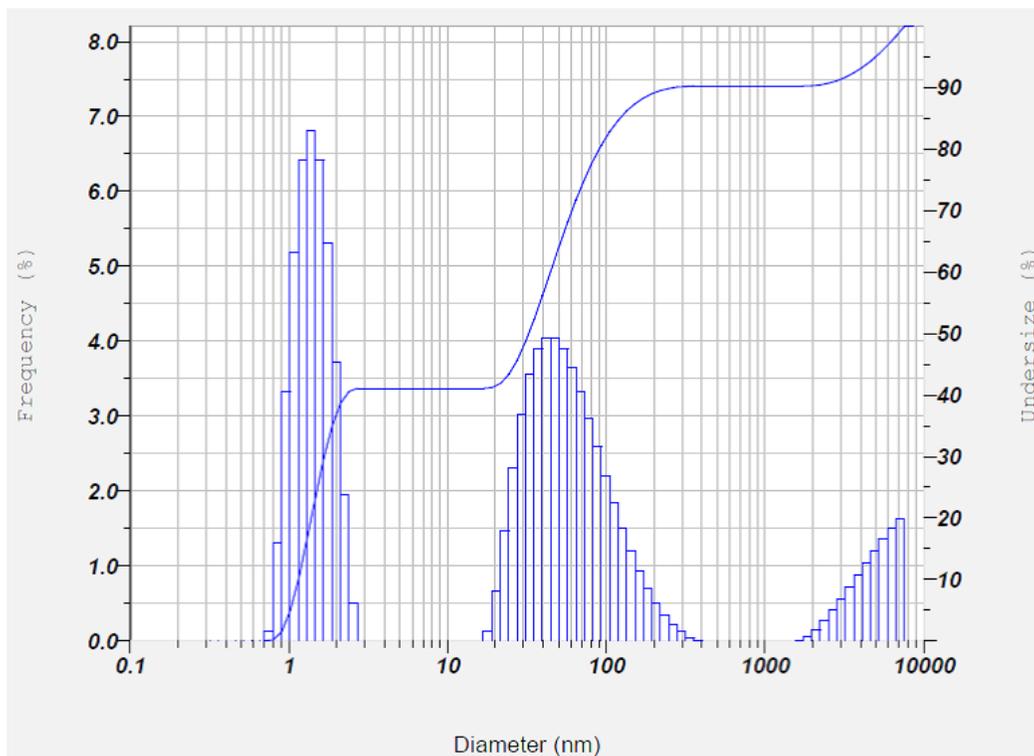


Fig. 9: Particle size of VLZNP.

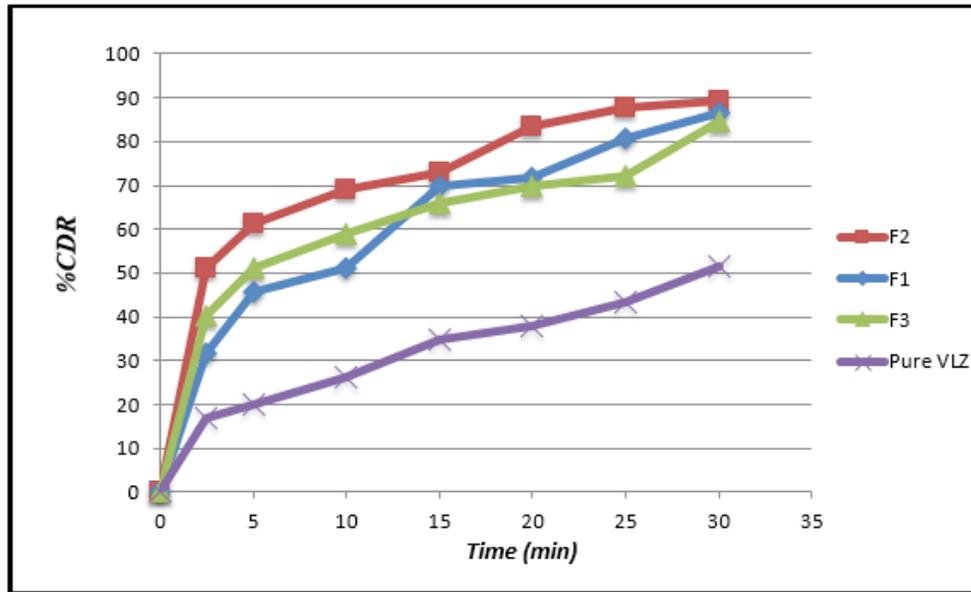


Fig. 10: Comparative Dissolution Profile of VLZ and VLZNPs tablet Formulation.

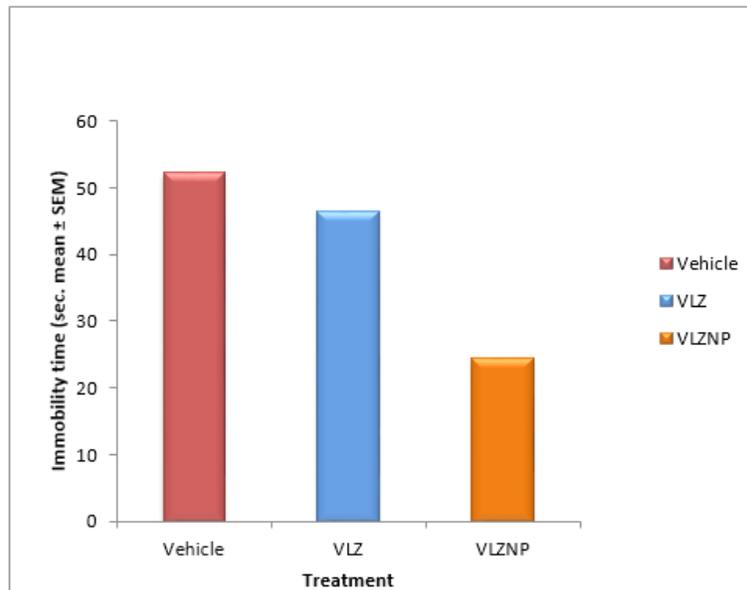


Fig. 11: The Comparative effect of Vehicle, VLZ, and VLZNP on immobility time.

CONCLUSION

Vilazodone was successfully formulated in nanoparticles with desired characteristics of size, shape, with reasonable stability and high entrapment efficiency and significantly greater solubility with faster drug dissolution compared to pure drug. The characterization parameters DSC, XRD, IR, SEM, and particle size confirm that the particles are crystalline in nature with irregular shape and uniform size i.e. below 100 nm and compatible with other excipients. Dissolution studies showed the maximum release of optimized Vilazodone nanoparticles (NP4) and optimized Vilazodone tablet formulation (F₂). This may be

due to the increased surface area due to decreased particle size and may due to micelle action of Soluplus. Also from *in vivo* study, it seems that VLZNP elicited significant antidepressant-like activity as compared to VLZ. Thus *in vitro* data supported by *in vivo* results. Evaporative precipitation into aqueous solution thus may be a useful approach to produce nanoparticles of poorly soluble drugs.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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