Improving the solubility of nevirapine using A hydrotropy and mixed hydrotropy based solid dispersion approach

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Abstract

Background. Nevirapine, an antiviral drug, is a potent reverse transcriptase inhibitor (NNRTI). It is used in combination with nucleoside analogues for treatment of HIV type-1 (HIV-1) infection and AIDS. Nevirapine is a BCS class II drug which shows dissolution rate limited absorption.

Objectives. The aim of the present research was to provide a fast dissolving solid dispersion of nevirapine.

Material and methods. The solubility of nevirapine was initially determined individually in four hydrotropic agents – namely urea, lactose, citric acid and mannitol – at a concentration of 10, 20, 30 and 40% w/v solutions using purified water as a solvent. The highest solubility was obtained in the 40% citric acid solution. Then different combinations of 2 and 3 hydrotropic agents in different ratios were used to determine solubility, so that the total concentration of hydrotropic agents was always 40%.

Results. The highest solubility was obtained in a solution of lactose and citric acid at the optimum ratio of 15:25. This optimized combination was utilized in preparing solid dispersions by a common solvent technique using distilled water as a solvent. The solid dispersions were evaluated for XRD, DSC and FTIR to show no drug-hydrotrope interaction.

Conclusions. It was concluded that the concept of mixed hydrotropic solid dispersion is a safe, novel and cost-effective technique for enhancing the bioavailability of poorly water-soluble drugs by dissolving the drug in a nonionized form. The enhancement in solubility of nevirapine using hydrotropy is a clear indication of its potential to be used in the future for other poorly water-soluble drugs in which low bioavailability is a major concern.

Key words: nevirapine, solid dispersion, mixed hydrotropy

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One of the important phenomena in pharmaceutical formulation is “solubility”, which plays very effective and significant role in the formulation of various dosage forms.^{1,2} The solubility of a compound in a particular solvent is defined as the concentration of a solute in a saturated solution at a certain temperature.^{3,4} The solubility of a drug molecule may be a critical factor determining its usefulness since the solubility dictates the amount of compound that will dissolve and therefore the amount available for absorption. If a compound has low water solubility, it may be subject to dissolution rate limited absorption within the gastrointestinal residence time.^{5,6} The term “hydrotrope” was introduced by Neuberg in 1916. A hydrotropic agent is a compound that solubilizes hydrophobic compounds in aqueous solutions. Hydrotropy is a molecular phenomenon whereby the adding of a large amount of a second solute (hydrotrope) results to an increase in the aqueous solubility of poorly soluble solutes.^{7,8} Hydrotropes possess a hydrophobic as well as a hydrophilic group. The hydrophobic part is too small to cause spontaneous self-aggregation. The efficiency of a hydrotropic agent depends on the balance between hydrophobic and hydrophilic parts of the hydrotrope. Finding the right hydrotropic agent for a certain poorly soluble drug necessitates a screening of numerous hydrotropic agents based on the balance between hydrophobic and hydrophilic parts. The presence of a large hydrophobic part leads to better hydrotropic efficiency.⁹ The enhancement of aqueous solubility by a hydrotropic agent is based on 1) molecular self-association of the hydrotropic agent and 2) the association of hydrotrope molecules with the solute.¹⁰ Mixed hydrotropic solubilization has great potential to improve the solubility of poorly water soluble molecules.^{11–13}

Nevirapine (NVP), an antiviral drug, is a potent reverse transcriptase inhibitor (NNRTI). It is used in combination with nucleoside analogues for the treatment of HIV type-1 (HIV-1) infection and AIDS. It is a BCS class II drug with high permeability and low solubility (aqueous solubility 0.09941 mg/mL).^{14,15} The solubility of NVP was increased by using a mixed hydrotropic solid dispersion technique. Here, two or more hydrotropic blends were used, which gives a synergistic solubility enhancement effect on poorly water soluble drugs. The individual concentrations of hydrotropic agents are reduced, thus minimizing the probability of their toxicity.^{16,17}

The aim of this research was to enhance the solubility of NVP in water by making use of hydrotropes and their combination blends to prepare its solid dispersion.

Material and methods

Material

The NVP was gifted by Wockhardt Ltd., Aurangabad, India. Urea, sodium benzoate, citric acid, lactose and mannitol were purchased from Loba Chem Pvt. Ltd., Mumbai, India. All reagents were of analytical grade and used as received.

Methods

Determination of solubility

The saturation solubility of NVP was determined with distilled water. An excess amount of NVP was added to each medium and kept in an incubator shaker at 200 rpm for 24 h. The temperature was maintained at 37°C. After 24 h the mixture was centrifuged at 2000 rpm for 10 min. The supernatants were diluted using distilled water. The absorbance of samples was measured at 282 nm for distilled water using a UV spectrophotometer (JASCO V-630, Tsukuba, Japan).^{18,19}

NVP-hydrotropic agent interference study

UV spectrophotometric study

Interference of the hydrotropic agents was estimated using the UV spectrophotometric method. Briefly, the absorbance of NVP standard solutions were determined in distilled water alone and in the presence of the hydrotropic blend, respectively (Table 1). The absorbance was recorded against respective blank medium at appropriate wavelengths. A UV-visible spectrophotometer (JASCO V-630) with 1 cm matched silica cells was employed for spectrophotometric estimations.²⁰

Fourier-transform infrared spectroscopy (FTIR)

The FTIR spectral data of NVP, physical mixtures of NVP and individual hydrotropes and NVP with two

Table 1. Results of drug-hydrotrope interference study by UV spectrophotometric method

Drug	Solvent system	Drug conc. [$\mu\text{g/mL}$]	Hydrotrope conc. [$\mu\text{g/mL}$]	Wavelength [nm]	Absorbance against blank
NVP	dist. water + P	50	1000	282	0.233
NVP	dist. water + Q	50	1000	282	0.256
NVP	dist. water + R	50	1000	282	0.223
NVP	dist. water + S	50	1000	282	0.219
NVP	dist. water	50	1000	282	0.201

P – lactose; Q – urea; R – citric acid; S – mannitol.

hydrotropes were taken for the determination of possible molecular interaction between the drug and excipients by the KBr disc method using an FTIR spectrophotometer (Shimadzu Affinity-1, Kyoto, Japan). The samples were scanned over a range 4000–400 cm^{-1} .²¹

Equilibrium solubility studies in different hydrotropic agents

Initially the equilibrium solubility studies were carried out in different hydrotropic agents. The aqueous hydrotropic solutions of lactose (P), urea (Q), citric acid (R) and mannitol (S) were prepared individually at a concentration of 10, 20, 30 and 40% w/v. Accurately measured 10 mL of a particular blend of hydrotropic agent was taken in a 10 mL vial, and an excess amount of NVP was added and mechanically shaken until a saturated solution was formed. The vial was shaken on a mechanical shaker for 12 h and the solution was allowed to equilibrate for 24 h to achieve equilibrium solubility. The resultant solution was centrifuged at 2000 rpm for 10 min in an ultracentrifuge and further filtered through Whatman grade 41 filters. An aliquot was diluted with distilled water and analyzed using a UV spectrophotometer at 282 nm.^{22,23} Enhancement ratios in solubility were calculated by the following formula:

$$\text{enhancement ratio} = \frac{\text{solubility of drug in hydrotropic solution}}{\text{solubility of drug in water}}.$$

Similarly, the equilibrium solubility studies were carried out in different blends of hydrotropic agents. Here, the combinations of 2–3 hydrotropic agents were taken at a 1:1 ratio and dissolved in water to get a clear solution. An excess amount of NVP was added to the hydrotropic solution. The saturated solution was mechanically shaken and aqueous solubility was determined. Further, the ratio of the mixed hydrotropic agent was optimized to achieve the highest aqueous solubility of NVP.

Formulation of hydrotropic solid dispersions of NVP

For the preparation of the hydrotropic solid dispersion (1:4 ratio), accurately weighed 1.5 g lactose and 2.5 g of citric acid were taken in a 100 mL beaker and mixed properly. A sufficient quantity of freshly prepared demineralized water (5 mL) was added to dissolve the hydrotropic mixture. Dissolution of the hydrotropic mixture was facilitated by the agitation of a Teflon coated magnetic rice bead on a high speed magnetic stirrer. After complete dissolution of the hydrotropic mixture, 1 g of NVP was dissolved in the above solution and the temperature was maintained at $57 \pm 2^\circ\text{C}$ to evaporate the water. As evaporation proceeded, the speed of the rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of the

solid dispersion (wet). The wet solid dispersion was kept in a hot air dry oven maintained at $50 \pm 2^\circ\text{C}$ to remove the remaining moisture. After a complete drying, the solid dispersion was crushed using a clean and dry glass mortar and pestle, passed through a #60 sieve and finally stored in an airtight glass bottle.^{24–26}

Evaluation of hydrotropic solid dispersion containing NVP

Micromeritic properties of solid dispersions

The prepared hydrotropic solid dispersion was characterized for various micromeritic properties such as bulk density, tapped density, compressibility index, Hausner ratio and angle of repose.^{27,28}

For the determination of density, the solid dispersion sample (1 g) was taken into a 10 mL graduated measuring cylinder and the initial volume was noted down. The graduated measuring cylinder was tapped 50 times using USP bulk density apparatus (ETD 1020, Electrolab, Mumbai, India). The bulk density and tapped density were determined using the following formula:

$$\text{bulk density (g/cm}^{-3}\text{)} = \frac{\text{weight of the solid dispersion}}{\text{initial volume}},$$

$$\text{tapped density (g/cm}^{-3}\text{)} = \frac{\text{weight of the solid dispersion}}{\text{volume after tapping}}.$$

The compressibility index was determined by the following formula:

$$\text{compressibility index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100.$$

The Hausner ratio was determined by the following formula:

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}.$$

For the determination of angle of repose, the solid dispersion was poured through a funnel. The funnel was fixed at a position in such a way that its lower tip was at a height of 2 cm above the surface. The sample was poured till the tip of the particle pile surface touched the funnel. The $\tan^{-1}$ of the ratio of the height of the pile and radius of its base gave the angle of repose. The angle of repose was determined by the following formula:

$$\tan^{-1} = \frac{h}{r}.$$

X-ray powder diffraction analysis

The X-ray diffraction pattern of pure NVP and a physical mixture of the drug and hydrotropic agents (lactose + citric acid) was recorded by X-ray powder diffractometer (Philips 1710). The X-ray diffraction patterns were recorded using Cu-K α radiation ($\lambda = 1.5405980\text{\AA}$), a current of 30 mA and a voltage of 40 kV. The samples were analyzed, over 10–89 2 theta, range with a scan step size of 0.02 and 0.50 s per step.^{29,30}

Differential scanning calorimetry analysis

In order to determine the physical state of the NVP, the differential scanning calorimetry (DSC) thermograms of pure NVP and physical mixture of the drug and hydrotropic agents (lactose + citric acid) was recorded using a differential scanning calorimeter (DSC 4000, PerkinElmer, Waltham, Massachusetts, USA). The instrument was calibrated using indium (156°C), tin (232°C) and zinc (419.5°C) as internal standards. An empty aluminum pan was used as a reference. Each sample was accurately weighed into an aluminum pan and sealed. The probes were heated from 30 to 300°C at a rate of 10 K/min under a nitrogen atmosphere.^{31,32}

Results and discussion

Determination of solubility

The solubility of NVP as observed in distilled water was 0.0994 ± 0.056 mg/mL. The results indicate poor solubility of NVP in distilled water.

NVP hydrotropic agent interference study

Ultraviolet spectrophotometric study

To examine the interference of a hydrotropic agent, the UV absorbance spectrum of NVP was recorded in distilled water alone and in the presence of the hydrotropic blend solutions. The results indicated no change in the wavelength of maximum absorbance (λ_{max}) of NVP in distilled water. Hence, it was concluded that there was no drug-hydrotrope interference.

Fourier-transform infrared study

Fourier-transform infrared study was employed to examine the possible interactions of NVP and the hydrotropes. The FTIR spectrum of NVP showed characteristic peaks at 3400 cm^{-1} of N–H (secondary amine) stretch, 3190 cm^{-1} of C–H (aromatic) stretch, 3062 cm^{-1} of C–H (aliphatic) stretch, 1647 cm^{-1} of C=O cm^{-1} (ketone) stretch, 1587–1417 cm^{-1} of C=C stretch and 1296 cm^{-1} of C=O (ketone) bending. All peaks are within the reported range, indicating the purity of NVP.^{33,34} All the major peaks of NVP are also present in the FTIR spectrum of the hydrotropic physical mixture. Hence, there were no drug-excipient interactions (Fig. 1).

Equilibrium solubility studies in different hydrotropic agents

The equilibrium solubility of NVP in the presence of different hydrotropic agents was investigated as shown in Table 2. All hydrotropes, viz. lactose, urea, citric acid and mannitol, are able to enhance the solubility of NVP. The highest solubility was obtained in the 40% citric acid solution. Then, in order to decrease the concentration of citric acid, different combinations of the above-mentioned four hydrotropic agents in different ratios were tried to determine the enhancement in solubility, so that the total concentration of hydrotropic agents was always 40% w/v. All the hydrotrope blends were also found to increase the solubility of NVP (Table 3). The blend P + R (lactose: citric acid) at a ratio of 5 : 35 gave the highest solubility enhancement, but the concentration of citric acid in this blend is not within the inactive ingredients guidelines (IIG) limit for a single tablet (500 mg/tablet),^{17,35} so the ratio of 15 : 25 was chosen, and therefore, this optimized combination of hydrotropes was selected for the preparation of solid dispersion (Table 4).

Micromeritic properties of solid dispersions

The closeness of values of tapping density and bulk density indicates the free-flowing property (Table 5). The difference in bulk density and tapped density was only 0.092, indicating that the change in volume is very small even after 50 tappings, which confirms the small particle size

Table 2. Equilibrium solubility* of NVP in different hydrotropic agents. The data presents mean $\pm$ SD, n = 3

Hydrotropic Agents	Concentration (w/v)				Solubility enhancement ratio
	10%	20%	30%	40%	
Lactose (P)	1.07 $\pm$ 0.121*	1.09 $\pm$ 0.101	1.09 $\pm$ 0.111	1.13 $\pm$ 0.126	11.36 $\pm$ 1.62
Urea (Q)	1.39 $\pm$ 0.152	1.80 $\pm$ 0.094	2.34 $\pm$ 0.121	2.74 $\pm$ 0.125	27.16 $\pm$ 3.54
Citric acid (R)	2.57 $\pm$ 0.180	3.80 $\pm$ 0.122	4.70 $\pm$ 0.054	4.18 $\pm$ 0.123	42.04 $\pm$ 1.92
Mannitol (S)	0.94 $\pm$ 0.051	0.96 $\pm$ 0.161	0.99 $\pm$ 0.154	1.01 $\pm$ 0.122	10.15 $\pm$ 2.34

* Solubility in mg/mL; P – lactose; Q – urea; R – citric acid; S – mannitol.

Fig. 1. UV spectra of pure NVP in (A) distilled water, (B) 0.1N HCl, (C) NVP hydrotropic solid dispersion (lactose-citric acid) in distilled water and (D) NVP hydrotropic solid dispersion (lactose-citric acid) in 0.1N HCl

range and reproducibility in drug content.^{27,36} It is frequently experienced that particle size and shape influences flowability. The fine particles (< 100 mm) tend to be more cohesive and therefore less free-flowing, whereas larger, denser particles tend to be free-flowing. The rougher and more irregular the surface of the particles, the higher the angle of repose will be.²² In the present study, the angle of repose was 33°, indicating good flowability of particles. A high compressibility index is indicative of the tendency

to form bridges between the particles. The smaller the compressibility index, the better the flow properties will be. For example, a value of 5–15 indicates excellent flow, 12–18 good, 19–21 fair, 22–35 poor, 36–40 very poor and > 40 extremely poor.²² The results show that the solid dispersion powder had a compressibility index of 11.429, indicating excellent flow property. Hausner ratio is related to inter-particle friction. It is also an indirect measure of bulk density, size and shape, surface area, moisture content and

Table 3. Results of equilibrium solubility of NVP in 1:1 mixed hydrotropic blends. The data presents mean $\pm$ SD, $n = 3$

Combinations	Total conc. [% w/v]	Individual conc. [% w/v]	Solubility [mg/mL]	Solubility enhancement ratio
P + Q	40.00	20.00	2.950 $\pm$ 0.101	29.67 $\pm$ 2.51
P + R	40.00	20.00	6.372 $\pm$ 0.212	64.07 $\pm$ 1.64
P + S	40.00	20.00	3.083 $\pm$ 0.052	31.01 $\pm$ 2.09
Q + R	40.00	20.00	2.640 $\pm$ 0.184	26.55 $\pm$ 1.54
Q + S	40.00	20.00	2.907 $\pm$ 0.152	29.04 $\pm$ 2.18
R + S	40.00	20.00	2.945 $\pm$ 0.098	29.62 $\pm$ 1.72
P + Q + R	40.00	13.33	1.1967 $\pm$ 0.954	12.03 $\pm$ 1.08
P + Q + S	40.00	13.33	1.4551 $\pm$ 0.574	14.63 $\pm$ 0.81
P + R + S	40.00	13.33	1.4776 $\pm$ 0.854	14.86 $\pm$ 1.25
Q + R + S	40.00	13.33	1.9677 $\pm$ 0.799	19.79 $\pm$ 2.04

P – lactose; Q – urea; R – citric acid; S – mannitol.

Table 4. Equilibrium solubility of NVP in mixed hydrotropic blends at different ratios. The data presents mean $\pm$ SD, n = 3

Combinations	Total conc. [% w/v]	Ratio	Solubility [mg/mL]	Solubility enhancement ratio
P + R	40.00	05 : 35	10.654 $\pm$ 0.854	107.13 $\pm$ 7.64
P + R	40.00	10 : 30	10.022 $\pm$ 0.965	100.81 $\pm$ 5.34
P + R	40.00	15 : 25	10.174 $\pm$ 0.745	102.31 $\pm$ 5.64
P + R	40.00	20 : 20	07.761 $\pm$ 0.854	78.06 $\pm$ 8.24
P + R	40.00	25 : 15	05.777 $\pm$ 0.261	58.04 $\pm$ 3.51
P + R	40.00	30 : 10	05.258 $\pm$ 0.350	52.81 $\pm$ 5.34
P + R	40.00	35 : 05	02.101 $\pm$ 0.480	21.13 $\pm$ 3.64

P – lactose; Q – urea; R – citric acid; S – mannitol.

Fig. 2. Fourier transform-infrared spectra of (A) NVP, (B) nevirapine + urea, (C) nevirapine + lactose, (D) nevirapine + mannitol, (E) nevirapine + citric acid and (F) NVP + citric acid + lactose

Table 5. Micromeritic properties of NVP solid dispersions. The data presents mean $\pm$ SD, $n = 3$

Parameter	Result
Bulk density (g/cm ³)	0.714 $\pm$ 0.01
Tapped density (g/cm ³)	0.806 $\pm$ 0.03
Compressibility index	11.429 $\pm$ 2.31
Hausner ratio	1.12 $\pm$ 0.14
Angle of repose	33 $\pm$ 1°

cohesiveness of particles. A higher Hausner ratio and more fine particles indicate greater cohesion between particles while a low range indicates good flowability. The desirable value of Hausner ratio is < 1.25 for good flow of materials.²² In the present study, the Hausner ratio for the solid dispersion powder was found to be 1.12 indicating good flowability of particles. This result was also supported by an angle of repose study. These results indicate that the flow character of the solid dispersion is good and no aid is needed to increase the flow properties.

X-ray diffraction analysis of NVP

It is generally stated that if three consecutive relative intensity percentage values in an XRD pattern decrease, a decrease in crystallinity had occurred in the samples, therefore, these observations can be treated as confirmation of the reduction in crystallinity and thus phase transition.³⁷ As it is reported that an amorphous system is responsible for the enhancement in dissolution and bio-availability,³⁸ less intense peaks in the solid dispersion as

Fig. 3. X-ray powder diffraction spectra of (A) NVP and (B) NVP hydrotropic solid dispersion (lactose-citric acid) **Fig. 4.** Differential scanning calorimetry thermogram of (A) NVP and (B) NVP hydrotropic solid dispersion (lactose-citric acid)

compared to the NVP pure drug indicate an amorphous nature, explaining the higher solubility of SD as compared to NVP (Fig. 2). These observations were in accordance with the DSC studies (Fig. 3).

Differential scanning calorimetry analysis

The DSC thermogram of NVP is shown in Fig. 3a. The DSC thermogram of NVP shows an endothermic melting peak at 246.20°C, indicating its melting point (244–247°C). The DSC thermogram of NVP solid dispersion is shown in Fig. 3b. There was no shift in the NVP endothermic peak; hence there was no NVP and excipient (lactose-citric acid) interaction. The separate endothermic peak of lactose was found at 111.4°C due to its dehydration.³⁹

Conclusion

From the present research, we conclude that hydro-tropy is an effective, safe and novel method to increase the solubility of poorly water-soluble drugs. Quick dissolution of the practically insoluble drug NVP in aqueous dissolution media indicates its potential to solubilize the drug in biological fluids, and thus significant enhancements in the onset of the effect and bioavailability can be seen. Therefore, the concept of mixed hydro-tropy is an emerging field and greater importance must be given by the scientific community to explore its applicability and efficiency.

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