Solubility enhancement of nimodipine using mixed hydrotropic solid dispersion technique

Naz Jamal Ibrahim1* Shahla Sadeq Smail1 Nozad Rashid Hussein1 Tara Abdulrahman Abdullah1

Abstract

Background and objective: Low aqueous solubility of active pharmaceutical ingredients has an effect on both formulation development and bioavailability. Nimodipine is an antihypertensive agent with low oral bioavailability, which might be attributed to the extremely poor water solubility. This study aimed to increase the solubility of nimodipine in water using hydrotropes and solid dispersion technology to increase dissolution rate compared to the marketed drug product.

Methods: Solubility of nimodipine was determined separately in sodium acetate, sodium citrate, sodium benzoate, and niacinamide solutions at a concentration of 10, 20, 30, and 40% w/v using distilled water as a solvent. The highest solubility was obtained in 40% sodium benzoate solution. Mixed concentrations of hydrotropic agents were used in ratio 1:3 (niacinamide: sodium benzoate). Fourier-transform infrared spectroscopy was used to exclude any drug-hydrotropes interaction. The dissolution rate of nimodipine from solid dispersion and physical mixture were studied using USP type II dissolution test apparatus in acetate buffer (pH 4.5) as a dissolution media.

Results: Hydrotropic solid dispersion of nimodipine with a blend (30% sodium benzoate and 10% niacinamide) increased the dissolution rate of the drug by 1.5 folds compared to the marketed conventional nimodipine tablet. Fourier-transform infrared analysis did not show any physicochemical interaction between drug and carriers in solid dispersion formulation.

Conclusion: The hydrotrop is a novel and safe compound. It is a successful way to enhance the solubility of poorly aqueous soluble drugs. Immediate dissolution of practically insoluble drug nimodipine in dissolution media indicates that it has a great potential to solubilize the drug in biological fluids. Thus, a considerable improvement in bioavailability and onset of action of the drug can be predictable. Adding of a hydrotropic agent with nimodipine in solid dispersion increased the dissolution rate of the drug compared to the marketed conventional nimodipine tablet.

Keywords: Hydrotropes; Nimodipine; Solubility enhancement; Solid dispersion.

Introduction

More than 40% of new chemical entities being generated are not adequately soluble in water. Hence, various techniques have been employed to enhance the bioavailability of poorly water-soluble drugs to improve their clinical efficacy after oral administration.1,2 From the pharmacological point of view, this exerts strong limits to the performance of a drug by necessitating administering a much higher dose than strictly required from the pharmacological point of view. This may induce side-effects or create problems related to the cost of treatment.3 For better oral bioavailability, the drug must be soluble in gastrointestinal fluids and should possess permeability properties to diffuse easily through the GIT membrane and reach the bloodstream.4,5 Numerous strategies are available to enhance the solubility and dissolution profile of sparingly soluble drugs to

1 Department of Pharmaceutical Sciences, College of Pharmacy, Hawler Medical University, Erbil, Iraq.
* Correspondence: naz.ibrahim@hmu.edu.krd
Methods

Design, setting, and time of the study

The experimental research was carried out in the College of Pharmacy, Hawler Medical University, from February 1st, 2018, to May 31st, 2018.

Materials

An analytically pure sample of nimodipine was purchased from Sigma Aldrich. Sodium acetate, sodium citrate, sodium benzoate, and niacinamide were obtained from rishi chemicals. All other chemicals and solvents were of analytical grade, and
freshly prepared distilled water was used throughout this study.

**Methods**

**Equilibrium solubility study of the drug in different hydrotropic agents:**
Solubility studies were performed according to Higuchi and Connors. First of all, the solubility of nimodipine was determined in purified water. Then, the solubility of the drug was investigated individually in four types of solution, which were prepared from hydrotropic agents, sodium acetate, sodium benzoate, sodium citrate, and niacinamide in a concentration of 10%, 20%, 30%, and 40% using purified water as a solvent. For determining solubility, accurately measured 5ml of a particular blend of the hydrotropic agent was taken in a 10 ml volumetric flask, and an excess amount of drug was added and mechanically shaken for up to 12 hours to obtain a saturated solution. The solution was allowed to equilibrate for 24 h, then passed through Whatman filter paper no.41. The filtrates were diluted and the drug quantified using spectrophotometer at 355nm against the blank. Absorbance was extrapolated on the calibration curve to determine the unknown concentration, and the solubility of each sample was calculated. Each experiment was performed in triplicate, and solubility enhancement ratios were calculated from equation 1.

**Preparation of hydrotropic solid dispersions of the drug by solvent evaporation method (HSDs):**
For the preparation of HSDs containing nimodipine and hydrotropic blend (sodium benzoate and niacinamide), nimodipine (0.428g), sodium benzoate (1.928 g), and niacinamide (0.642 g) were weighed. The minimum possible amount of distilled water at 80ºC was used to dissolve the hydrotropic blend in a beaker. Then, nimodipine was added to the same beaker (at 40ºC). Stirring of the mixture was started, using a magnetic stirrer and maintaining the temperature at 30 to 40ºC. Nimodipine was completely solubilized. After evaporation of a large quantity of water, a semisolid mass was formed in the beaker. Semisolid mass was spread on several watch glasses in a thin layer for quick drying and kept in the oven at 40ºC for complete drying. The powder of solid dispersion was triturated with mortar and pestle, then sifted through sieve number 100. The prepared HSDs were stored in an air-tight glass container for further investigation.

**Physical mixture of drug (PM):**
For the preparation of PM, nimodipine (0.428g), sodium benzoate (1.928 g), and niacinamide (0.642 g) were accurately weighed and mixed intensely for 10 minutes using glass pestle and mortar with intensive trituration. Then, powder mass was sifted through sieve number 100.
After this, the physical powder was stored in air-tight glass bottles for further investigation.

**Evaluation parameters of solid dispersion:**

**Fourier-transform infrared study:**

Fourier-transform infrared study (FTIR) of pure nimodipine, its solid dispersion with hydrotropic agents was recorded over a range 4000-400 cm\(^{-1}\) to study main peaks using FTIR.

**Angle of Repose:**

Powder flowability of the physical mixture and solid dispersion was conducted using angle of repose method. Powders were poured separately through a funnel that was affixed at a distance 10 cm above the bench until a maximum cone height (h) of the powder was obtained. Radius of the heap (r) was measured, then the angle of repose calculated using the following equation:

\[
\tan \theta = \frac{h}{r} \quad \text{Eq2}
\]

Where, (\(\theta\)) is the angle of repose, (h) is height of pile, (r) is radius of the base pile

**Determination of dissolution rate:**

The dissolution profile of nimodipine from solid dispersion and physical mixture were studied in acetate buffer (pH4.5) using USP II dissolution rate test apparatus (Serwell Electronics) employing a paddle stirrer. Dissolution fluid 900 ml was placed in a dissolution jar, and a sample of solid dispersions equivalent to 30 mg of nimodipine was tied in a muslin cloth to the dissolution medium. The paddle was adjusted to rotate at a speed of 75 rpm, and the temperature was kept at 37 ± 0.5°C throughout the experiment. Sample of dissolution medium 10ml was taken periodically at times 5, 10, 15, 20, 25, and 30 minutes interval; then, the drug quantified at the absorbance 355 nm. The drawn sample volume was replaced with a fresh dissolution medium. The soluble percent of nimodipine at various times was calculated and plotted against time.\(^{22,23}\)

**Statistical analysis**

All experiments were carried out in triplicate. The values were represented as means ± standard deviation. Independent two sample t-test with the aid of the statistical package for the social sciences (version 18) were used to compare the dissolution release profile of prepared hydrotropic solid dispersion of the drug with the marketed drug product. The variation was considered statistically significant when the calculated \(P\) values were less than 0.05.

**Results**

**Equilibrium solubility study of drug in different hydrotropic agents:**

The solubility of nimodipine in purified water was 0.0024 g/100ml, and its solubility in four different hydrotropes solution (niacinamide, sodium acetate, sodium benzoate, and sodium citrate) was determined. The results are summarized in Table 1.

| Hydrotropic agent used | Concentration of Hydrotropic agent % (w/v) | 10% | 20% | 30% | 40% | SER* |
|------------------------|------------------------------------------|-----|-----|-----|-----|------|
| Niacinamide (Ni)       |                                          | 0.0953±0.0040 | 0.1153±0.0032 | 0.4243±0.0030 | 0.6643±0.0045 | 276.66 |
| Sodium acetate (A)     |                                          | 0.0136±0.0020 | 0.075±0.0043 | 0.1426±0.0030 | 0.236±0.0030 | 98.33 |
| Sodium benzoate (B)    |                                          | 0.1316±0.0030 | 0.5933±0.0028 | 0.6936±0.0030 | 0.8096±0.0025 | 337.08 |
| Sodium citrate (C)     |                                          | 0.0143±0.0030 | 0.032±0.0026 | 0.0633±0.0035 | 0.1243±0.0041 | 51.66 |

*solubility enhancement ratio
Equilibrium solubility study of drug in mixed hydrotropic agents:

Tables 2 shows the solubility profile of nimodipine in the blended of two hydrotropic agents (niacinamide and sodium benzoate) in various ratios. Solubility enhancement ratio of hydrotropic agents individually and in mixed form was calculated, and the results were compared, as shown in Figure 1.

Evaluation parameters of solid dispersion:

Fourier-transform infrared study:

The FTIR spectra of pure nimodipine and its solid dispersion with blend of two hydrotropic agents (sodium benzoate and niacinamide) are shown in Figure 2.

Table 2: Solubility of nimodipine in mixed hydrotropic agents.

| Combination | Total concentration (% w/v) | Ni concentration (% w/v) | B concentration (% w/v) | Solubility (% w/v) | SER* |
|-------------|-----------------------------|--------------------------|-------------------------|-------------------|------|
| Ni + B      | 40                          | 30                       | 10                      | 1.1256±0.0011     | 468.75 |
| Ni + B      | 40                          | 20                       | 20                      | 1.3083±0.0030     | 545.41 |
| Ni + B      | 40                          | 10                       | 30                      | 1.5856±0.0042     | 659.58 |

*Solubility enhancement ratio

Figure 1: Solubility enhancement ratio of hydrotropic agents.

Figure 2: FTIR spectrum of (a) pure nimodipine, (b) nimodipine, and blend of hydrotropic agents (sodium benzoate and niacinamide).
Angle of Repose: The powder flowability of the physical mixture of nimodipine and hydrotropic agents was 33.56°± 0.523, while for solid dispersion of nimodipine with hydrotropic agents was 29.03°± 0.040.

Dissolution rate studies: In-vitro release profile of nimodipine from hydrotropic solid dispersion (HSDs), physical mixture (PM), and marketed conventional nimodipine tablets was studied. The results are shown in Figures 3 and 4.

Figure 3: In vitro drug release for solid dispersion, physical mixture, and conventional tablet of nimodipine.

Figure 4: Comparison in the release profile of nimodipine from marketed tablets (a) with PM and (b) with HSDs at different time intervals.
Discussion

Equilibrium solubility study of drug in different hydrotropic agents:
Nimodipine is insoluble in water, and it is used as a model drug in this study. Hydrotropic solubilization phenomena has been used to improve the solubility of nimodipine without the aid of organic solvent. Finding the exact hydrotropic agent for a poorly soluble drug requires screening of a large number of hydrotropic agents. However, significant solubility enhancement of drug can be easily achieved by selecting the correct hydrotropic agent or mixed hydrotropic agents. Sodium salicylate, sodium benzoate, urea, nicotinamide, niacinamide, sodium citrate, and sodium acetate are the most common examples of hydrotropic agents utilized to increase the water solubility of drug. As evident from Table 1, there is a remarkable increase in the aqueous solubility of nimodipine in the presence of a high concentration of hydrotropes. The highest solubility enhancement ratio (337.08) was attained in 40% sodium benzoate solution. The mechanism by which it improves solubility is more closely related to complexation involving a weak van der Waals interaction such as ($\pi - \pi$) or attractive dipole-dipole interaction.

Equilibrium solubility study of drug in mixed hydrotropic agents:
Mixed hydrotropic technique gives a miraculous synergistic enhancement effect on the solubility of poorly water-soluble drugs. It reduces the concentration of individual hydrotropic agent to minimize the side effect. It may reduce the high total concentration of hydrotropic agents required to produce an uncertain increase in solubility by employing a combination of agents in a lower concentration. Further, in order to decrease the concentration of sodium benzoate, different combinations of it with niacinamide in different ratios were tried to determine enhancement in the solubility. All blends were also found to increase the solubility of nimodipine, as shown in Table 2. The blend of sodium benzoate and niacinamide in the ratio of 3:1 gave the highest solubility enhancement of 659.58 (Figure 1) when compared with distilled water. Therefore, this adjusted combination of hydrotropes was chosen for the preparation of solid dispersion.

Preparation of hydro tropic solid dispersions of drug by solvent evaporation method:
Hydrotropic solid dispersions have been usually used to increase the dissolution rate, solubility, and gastrointestinal absorption of poor water-soluble drugs. Hence, hydrotropic solid dispersion of nimodipine was prepared using solvent evaporation method to further increase the solubility of drug.

Evaluation parameters of solid dispersion:
Fourier-transform infrared study:
The peak values of functional groups of FTIR of pure drug and combination of pure drug and hydrotropic agents were showing no shift, so it has been found that no incompatibility between the drug and polymer used.

Angle of Repose:
Hydrotropic solid dispersion of nimodipine shows good flowability due to the granulation size of the mixture. However, the flowability of the physical mixture was within the accepted range.

Dissolution rate studies:
The results of the dissolution rate study (Figure 3) showed that initial rates of dissolution of drug from HSDs were very quick as compared with the initial rate of dissolution from marketed conventional tablet ($P = 0.032$). PM also showed slightly better drug release profiles compared with drug release from marketed conventional tablets ($P = 0.095$). A significant increase in the release of drug after half an hour was evident from about 60% releases for the marketed tablet to above 80% releases for PM ($P = 0.04$) and 100% releases for HSDs ($P = 0.005$). Drug release profiles from HSDs were still better than the drug
release profiles from PM. The improved drug release rate could be attributed to the drug crystallinity reduction in the nimodipine solid dispersions prepared by niacinamide and sodium benzoate. The amorphous form of a drug has a higher thermodynamic activity than its crystalline form, resulting in the rapid dissolution of the drug. It is usually believed that a drug in a solid dispersion system commonly exists in an amorphous form.\(^\text{28}\) Furthermore, the reduced particle size and accordingly elevated surface area could elevate the dissolution rate of nimodipine in the solid dispersions.\(^\text{29,30}\) Plus, latter evidence, increasing drug wettability and solubility besides de-aggregation of the drug particles caused by the polymers could be the reasons for the enhanced rate of drug release from the solid dispersions.\(^\text{31}\)

**Conclusion**

This study has shown that hydrotropy is an effective way to enhance the solubility of poorly aqueous soluble drugs. Immediate dissolution of practically insoluble drug nimodipine in aqueous dissolution media indicates its great potential to solubilize the drug in biological fluids. Thus, appreciable enhancement in bioavailability and onset of action can be expected. Thus, the concept of mixed hydrotropy is an emerging field, which can serve as a milestone for solubility enhancement. Therefore, it deserves the urgent attention of the scientific community to assess its efficiency and applicability.

**Competing interests**

The authors declare no competing interests.

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