SHORT COMMUNICATIONS

NEVIRAPINE SOLID DISPERSION: DESIGN, DEVELOPMENT AND EVALUATION

ABSTRACT

The objective of the present investigation was to enhance the solubility and dissolution rate of BCS class II drug nevirapine through scalable and commercially feasible solid dispersion approach by using Soluplus® (BASF) as hydrophilic carrier. The solid dispersion produced by melting method (1:5 weight ratio) exhibited highest solubility ~ 15 folds greater than pure drug. The changes in DSC, PXRD, and SEM validated the formation of solid dispersion and transformation of drug from crystalline to amorphous form. Besides, selected solid dispersion had better flow properties and higher dissolution rate than nevirapine. Furthermore, the two dissolution profiles were different (f_2 value 33). Hence, preparation of nevirapine-soluplus® solid dispersion by melting method could be an appropriate pharmaco technical strategy to enhance the solubility and dissolution rate of nevirapine and probably other BCS class II drugs.

Keywords: Nevirapine, soluplus®, melting method, solid dipersion, dissolution

INTRODUCTION

Nevirapine is BCS class II drug with low solubility and high permeability, and used in the treatment of HIV infection and AIDS. Nevirapine has limited aqueous solubility of 0.1 mg mL^{-1}. The low solubility may affect its dissolution and thereby act as limiting step in the absorption[3]. Hence, there is need to prepare scalable new form of nevirapine possessing greater solubility and dissolution[1,2].

Several approaches have been reported to enhance the physicochemical properties of new drug molecules such as particle size reduction, salt formation, pharmaceutical cocrystal, prodrug formation, complexation with cyclodextrin, nanoemulsions, and solid dispersion[4]. However, solid dispersion has been documented as effective, scalable and commercial pharmaceutical method to improve the solubility and dissolution of active pharmaceutical ingredients (APIs) with insufficient water solubility[3]. In this method, drug under investigation is dispersed in hydrophilic matrix. This method results in increased wettability and porosity, decreased particle size, and formation of amorphous product with enhanced solubility and dissolution[4]. In previous studies, solid dispersion of nevirapine had been reported using PEG, plasdone S-60 as carriers which showed improved solubility and dissolution[5]. In this research, solid dispersion of nevirapine has been reported using soluplus® (BASF) as hydrophilic carrier to enhance the solubility and dissolution rate.

Preparation of solid dispersion

Solid dispersions were prepared in different weight ratios (1:1, 1:2, 1:3, 1:4, 1:5) of drug:carrier to optimize carrier by solvent evaporation and melting method. Physical mixture was prepared in glass mortar by simple mixing of drug with carrier for 10 min[6].

Characterization of solid dispersion

Saturation solubility was determined separately by adding excess quantity drug, physical mixture, and solid dispersions in 5 mL of double distilled water in vials. The vials were shaken for 6 h on rotary shaker, equilibrated for 24 h and analyzed by UV spectroscopy at 314 nm after suitable dilution. The selected solid dispersion was further confirmed by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM). In addition, solid dispersion was also subjected to micrometric evaluation and dissolution study. Dissolution experiment was conducted by using paddle type dissolution test apparatus (Lab India) at preset sink condition. Dissolution efficiency was calculated from the area under the dissolution curve. The dissolution profiles of drug and solid dispersion were compared by similarity factor (f_2)[7]. The one way ANOVA followed by Tukey's test was used to find statistical difference by using Graph Pad prism software (Version 5).

RESULTS AND DISCUSSION

The carrier and weight ratio used to prepare solid dispersion affects the solubility of the drug. The solubility of nevirapine in water obtained was 0.096 mg mL^{-1}. Moreover, solubility of physical mixture was closer to drug solubility (0.12 mg mL^{-1}), indicating no improvement in solubility due to physical mixture. Solid dispersion produced by melting and solvent evaporation method exhibited substantial increase in solubility than pure drug. However, solubility obtained with solid dispersion

produced by melting method was higher than solvent evaporation method (Table I). The highest solubility was obtained in 1:5 weight ratio of drug:carrier, validating the influence of carrier concentration on solubility. Solid dispersion prepared in 1:5 ratio by melting method had ~15 folds greater solubility (1.476±0.142 mg mL^{-1}) and was statistically different from pure drug and other solid dispersions ($P<0.05$). The solubility enhancement could be attributed to decreased particle size, amorphous product and augmented wettability owing to formation of solid dispersion. Hence, solid dispersion produced by melting method in 1:5 ratio (SD_m) was selected for further investigation. In addition, melting method is appropriate for scale up, simple and economic.

Table I: Solubility data of solid dispersions

Drug: Carrier ratio	Solubility (mg mL^{-1})	
	Melting method	Solvent evaporation method
1:1	0.146±0.056	0.114±0.026
1:2	0.387±0.078	0.197±0.058
1:3	0.656±0.167	0.376±0.097
1:4	0.984±0.202	0.425±0.113
1:5	1.476±0.142	0.453±0.132

Solubility is expressed as mean±standard deviation; n=3

DSC study showed that peaks corresponding to melting of drug (245 °C) and carrier (74.45 °C) disappeared, and less intense peak showing decreased crystallinity observed in solid dispersion. This indicates the transformation of drug into amorphous form which may lead to greater solubility and dissolution because low energy is needed break crystal lattice. The nevirapine showed sharp and prominent diffraction peaks at 2θ values of 9.4, 14.9, 19.2 and 24.5°, indicating crystalline nature. The absence of sharp peaks in PXRD pattern shows amorphous nature of Soluplus®. In addition, characteristic peaks were disappeared in SD_m and diffuse pattern was observed.

The homogeneous mixed mass was observed in SEM for SD_m showing the loss of crystalline nature of drug and the formation of solid dispersion in which nevirapine is present in amorphous form possessing decreased particle size and increased surface area. The lower value of angle of repose, Carr's index and Hausner's ratio for SDm showed improved flow ability than pure drug.

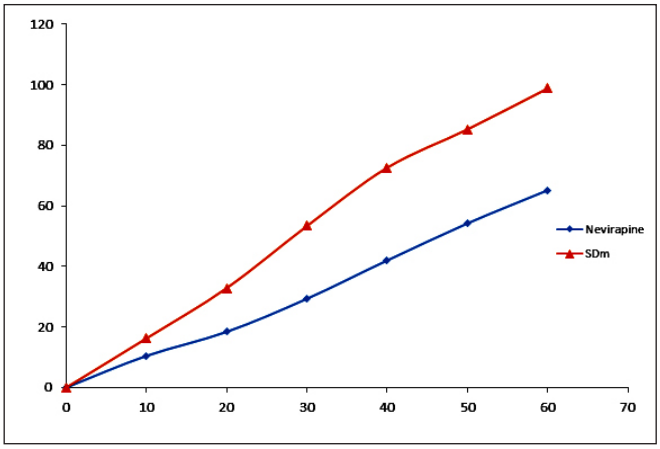

Fig. 1: Dissolution profiles of nevirapine and its solid dispersion

Dissolution is a significant property related to bioavailability and performance of drug *in vivo*[8]. The dissolution profile of nevirapine and SD_m is presented in Fig. 1. The nevirapine had slow and incomplete dissolution after 60 min (65.16±6.78 %) owing to less water solubility and poor wetting. On the other hand, dissolution of nevirapine from SDm (98.78±7.89 %) was significantly greater ($P<0.05$) than nevirapine alone. Moreover, drug release from SD_m was nearly complete. This may be due to reduced particle size and increased surface area. The calculated dissolution efficiency for SD_m was 73.46 %, which was substantially greater than pure nevirapine (23.65 %). The difference factor (f_2 value) for SD_m and nevirapine was 33, indicating different dissolution profiles.

The solid dispersion of nevirapine using Soluplus® as a carrier by scalable melting method has been demonstrated. The solubility and dissolution of nevirapine solid dispersion was significantly improved than pure drug. Therefore, this technique can be used to prepare pharmaceutical formulation of nevirapine having better biopharmaceutical properties.

REFERENCES

1. Panzade P.S., Priyanka S. and Pavan R.: Nevirapine Pharmaceutical Cocrystal: Design, Development and Formulation. **Drug Deliv. Lett**., 2019, 9(3), 240-247.
2. Costa R. N., Reviglio A. L., Siedler S., Cardoso S. G., Garro Linck Y. and Monti G.A. *et al.*: New multicomponent forms of the antiretroviral Nevirapine with improved dissolution performance. **Cryst. Growth Des**., 2019, 20(2), 688-698.
3. Raju A., Reddy A. J., Satheesh J. and Jithan A.V.: Preparation and characterization of nevirapine oral nanosuspensions. **Indian J. Pharm. Sci**., 2014, 76(1), 62-71.

4. Teixeira C. C., Mendonça L. M., Bergamaschi M. M., Queiroz R. H., Souza G. E. and Antunes L. M. *et al.*: Microparticles containing curcumin solid dispersion: stability, bioavailability and anti-inflammatory activity. **AAPS PharmSciTech.,** 2016, 17(2), 252-261.
5. Huang Y. and Dai W.G.: Fundamental aspects of solid dispersion technology for poorly soluble drugs. **Acta Pharm. Sin. B**., 2014, 4(1), 18-25.
6. Chaudhari S. P. and Dugar R. P.: Application of surfactants in solid dispersion technology for improving solubility of poorly water soluble drugs. **J. Drug Deliv. Sci. Technol**., 2017, 41, 68-77.
7. Vo C. L., Park C. and Lee B. J.: Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. **Eur. J. Pharm. Biopharm**., 2013, 5, 799–813.
8. Tambe A. and Pandita N.: Enhanced solubility and drug release profile of boswellic acid using a poloxamer-based solid dispersion technique. **J. Drug Delivery Sci. Technol.,** 2018, 44, 172–180.

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