Preliminary Investigation of Improved Solubility of Nifedipine by Co Processing with Vinylcaprolactam/ Vinylacetate/PEG_{6000} copolymer Through Spray Dried Solid Dispersions

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Summary: Poorly soluble drug nifedipine was co-processed through spray-drying with poly (vinyl caprolactam-co-vinyl acetate-co-ethylene glycol) (PVCVAEG). The obtained particles were characterized by X-ray diffraction (XRD), differential scanning calorimetry (DSC), infra-red spectroscopy (IR), optical and electronic microscopy. Dissolution kinetics was evaluated and compared to unprocessed and processed samples. Spray-drying produced smooth spherical particles. Crystallinity of the co-processed nifedipine and polymeric solubilizer was reduced as showed by XRD and DSC. No specific interaction between nifedipine and the polymeric solubilizer could be observed by IR or DSC. Dissolution kinetics of the co-processed samples was improved as compared to original nifedipine crystals and to spray-dried plain nifedipine particles. Solubility parameters showed that nifedipine had strong probabilities of being miscible and to dissolve in the polymeric carrier. Results point to the formation of solid dispersion-like systems which explain the improved solubility profiles.

Keywords: drug solubility; nifedipine; polymeric solubilizer; solid dispersion; spray drying

Introduction

Different strategies have been proposed to help improve the bioavailability of poorly soluble drugs. These approaches can be classified in the following three categories. First of all physical methods such as size reduction in order to increase specific area of drug particles are well known.[1] Chemical methods such as salt or pro-drug synthesis in which the new chemical entity has better solubility profiles but the same pharmacological activity once absorbed in the blood stream have been proposed.[2,3] Finally, formulation methods: where the drug is formulated with solubilizing excipients in order to increase the solubility profile is another strategy.[4] One can also use a combination of these methods in tandem with processing techniques in order to obtain co-processed products which have a better solubility profile than the original drug.[5–7]

A commonly used strategy within the last category is the formulation and processing of solid dispersions in which drug is molecularly or near molecularly dispersed in an inert partially hydrophilic carrier.[8] The amorphous state of the drug contributes to its better solubility as compared to if it were in a crystalline state. Solid dispersions can be of different types such as eutectic mixtures or solid solutions. These solid dispersions can be obtained by

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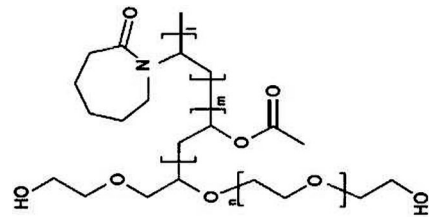

Figure 1.
Chemical structure of PVCVAEG.

different processing techniques such as solvent evaporation, melt processing, spray and freeze drying. Lately, poly (vinyl caprolactam-co-vinyl acetate-co-ethylene glycol) (PVCVAEG) (Figure 1) new polymeric solubilizer has been commercialized (Soluplus BASF) for processing solid dispersions by hot melt extrusion.[9]

The amphiphilic nature of PVCVAEG makes it miscible with hydrophobic drugs due to its vinyl acetate and vinyl caprolactam blocks while keeping its aqueous solubility due to its EG blocks. In an aqueous medium it forms micelles capable of trapping hydrophobic drugs in its hydrophobic core thus improving the drugs solubility. In this study we report the co-processing of nifedipine (NIF) a poorly soluble drug, with PVCVAEG by spray-drying in an attempt to diversify easy process ability methods of this polymer in producing solid dispersions for achieving improved dissolution profiles of a poorly soluble drug.

Experimental Part

2% w/v solutions were prepared by dissolving different ratios (1:1 and 0:1) of PVCVAEG and NIF in absolute ethanol. Spray drying was done using a Büchi Mini-Spray Dryer B-290 (Buchi, Switzerland) Solution and compressed air flow rates were fixed at 0.34 and 357 L/h, respectively. Particles were collected by a cyclone and then further dried for 24 h at 30 °C in a thermo stated desiccators. The final yields were between 50 and 80% of solid feed. Physical mixture of spray dried NIF and original PVCVAEG were obtained by blending the two components in a 1:1 ratio in a mortar with a pestle. Scanning electron microphotographs were obtained from metalized samples using a Hitachi 4800 S microscope (Hitachi, Japan). Simulated dissolution studies were done according to the European Pharmacopeia 2007 in a gastric simulated media pH 1,2. Samples were analyzed every 20 minutes using a continuous flow-through system attached to an 8 cell UV/VIS (Specord 250, Germany) spectrophotometer. X-ray diffraction patterns of pure ingredients, physical mixtures and spray dried powders were performed using a X-ray diffractometer (D8 advance, Bruker, USA) with a Ni filtered CuKα anticathode as the source of radiation ($\lambda = 1{,}5405$ Å). Samples were mounted on glass frames and scanned three times from 2° to 30° (2θ), with a step size of 0,02° (2θ).

Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectras of Soluplus®, NIF, physical blendings and spray dried powders were recorded over the range 4000–600 cm^{-1} using a Perkin–Elmer Spectrum 100 FTIR spectrometer Perkin Elmer, USA). Differential scanning calorimetry analyses (DSC) were performed with a thermoregulated DSC 6000 (Perkin Elmer, USA). One heating ramp was performed from 30 to 200 °C at 10 °C/min.

Results and Discussion

Particle Size and Morphology

Figure 2 shows that both particle size and morphology are affected by the spray-drying process. Spray drying processing reduces the size of original nifedipine particle by a factor of nearly 10 times. A much more spherical morphology can also be noticed for the spray dried particles. Spray drying is a process known for size reduction and this characteristic can be controlled by setting particular processing parameters such as air and liquid flow rates.[10]

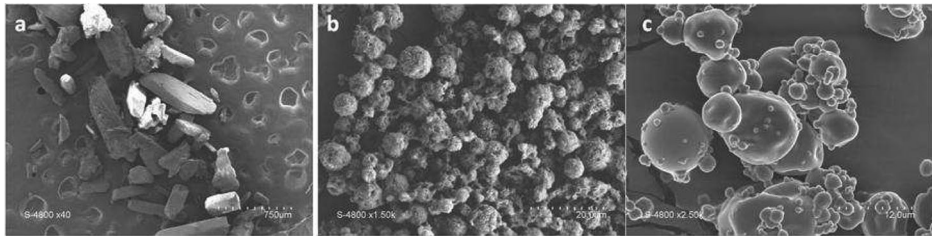

Figure 2.
Scanning electronic microscopy of a) original NIF particles b) spray dried NIF particles and c) co- spray dried NIF/PVCVAEG particles.

Dissolution Test

Figure 3 shows the dissolution profiles of the different tested formulations. Dissolution profiles showed a very prominent increase in dissolution rate for co-processed NIF and PVCVAEG as compared to simple spray dried (SD) NIF, physical mixtures (PM) and original NIF particles. These results rule out two important factors contributing to the better dissolution of the co spray dried NIF PVCVAEG particles. First of all, increased dissolution is not due simply to size reduction of the particles from the processing technique. Even though the size reduction does have a positive impact on increasing dissolution when compared to original NIF particles, the SD NIF profile is still slower than the co spray-dried NIF PVCVAEG. Secondly, the tensioactive properties of PVCVAEG is not sufficient to explain the increase in dissolution profile since the PM profile is not as fast as the co processed particles.

DSC

Observing differences in thermal transition temperatures is a useful tool to investigate structural morphology as well as potential drug polymer interactions [11]. In Figure 4, pure original NIF particles show a distinctive endothermic peak at around 176 °C, distinctive of the nifedipine melting temperature. The spray-dried NIF particles show two main differences. First of all the melting enthalpy of fusion is a lot smaller for the spray dried particles. This can be attributed to a decrease in crystallinity due to the spray-drying process which does not

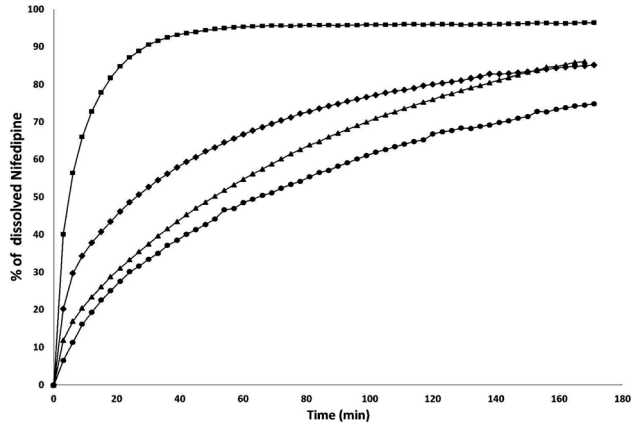

Figure 3.
In-vitro dissolution of co- spray dried NIF/PVCVAEG particles (■), physical mix of PVCVAEG and spray dried NIF (◆), spray dried NIF (▲) and original NIF particles (●).

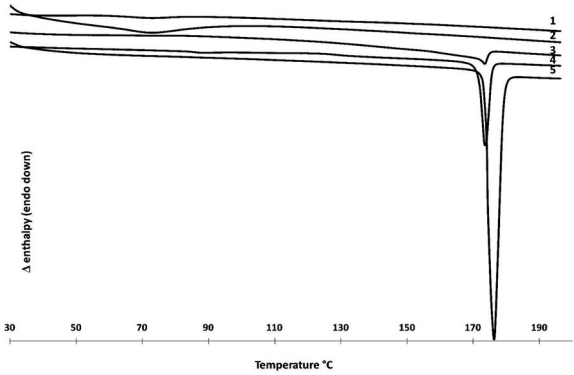

Figure 4.
DSC thermogram of co- spray dried NIF/PVCVAEG (1), PVCVAEG (2), physical mix of PVCVAEG and spray dried NIF (3), spray dried NIF (4) and original NIF (5) particles.

allow optimal crystallization upon rapid drying. The melting temperature drops by 3 °C to 173 °C. Once again this translates a non optimal crystallization process. The physical mixture of PVCVAEG and NIF shows a very small endothermic melting peak at 172 °C. The important flattening of the melting peak can be associated to two phenomena. First of all, the high concentration of the polymer in the physical mix naturally reduces the melting peak of NIF, however when measuring the difference of enthalpy related to the weight of NIF in the sample, it is clear that a reduction of cristallinity occurs. This phenomenon is thought to be due to the solubilization or interaction of NIF with the polymer as the temperature increases during the initial heating ramp. Indeed, after NIF crystal can start to dissolve in the polymer during the heating ramp, especially past the Tg of the polymer.

XRD

Figure 5 shows the X-ray diffractograms of the different samples. The original NIF particles show many characteristic intense diffraction peaks at 4,1°; 6,0°; 8.2°, 9,9°, 12,3°; 13,1°; 18,4°; 21,2°; 24.3° and 26,5° for 2θ. distinctive of diffracted x-rays from crystalline lamellas. The SD NIF and the PM sample also show distinctive peaks

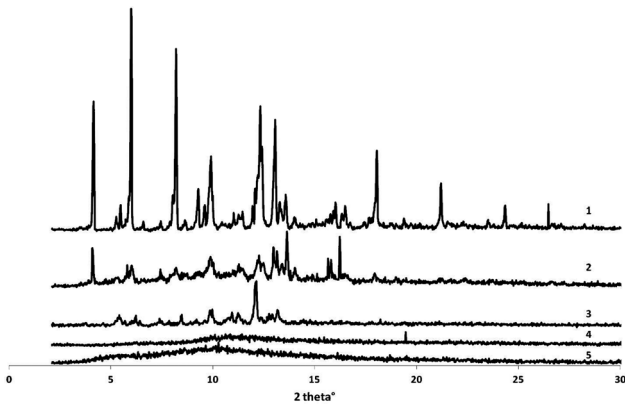

Figure 5.
XRD difractogram of original NIF (1), spray dried NIF (2), physical mix of PVCVAEG and spray dried NIF (3), co- spray dried NIF/PVCVAEG (4) and PVCVAEG (5) particles.

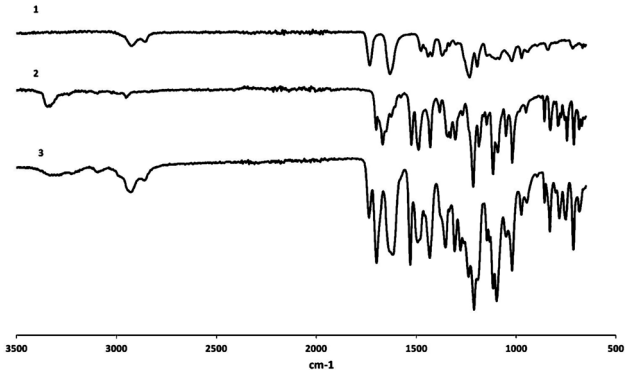

Figure 6.
FTIR spectra of PVCVAEG (1), original NIF (2) and co- spray dried NIF/PVCVAEG (3) particles.

characteristic of crystalline material. However in both samples the peak intensity is significantly diminished. Regarding the PM samples this can be explained by simple sample dilution with an amorphous polymer. The decrease in the diffraction pattern of the spray dried sample is explained, on the other hand, by the process itself. Regarding the co-spray dried PVCVAEG and NIF, the diffractogram is clearly distinctive of an amorphous material. The same is true for the original polymeric carrier known to be amorphous. This data confirms the DSC data in which the co-processed NIF and PVCVAEG do not show any fusion of crystalline material. However, further investigations would be useful to determine miscibility or phase separation with the two components such as described in literature.[12]

FTIR

For crystalline NIF the amine and carbonyl groups were observed at 3321 and 1676 cm-1 respectively. Regarding PVCVAEG, a strong stretching vibration peak at 1732 cm-1 can be attributed to the acetate from the vinyl acetate moiety. Equally the peak at 1632 cm-1, is characteristic the amide function of the caprolactam moiety. When focusing on the spectra of the coprocessed particles no particular shift in the vibration peaks can be observed. There is however a decrease in certain peak intensities of the NIF functions thus suggesting a loss of particular interaction between the NIF molecules themselves.

Conclusion

PVCVAEG has been explicitly developed and is extensively studied as an excipient in hot melt extrusion for solid dispersions. In this study preliminary results show that we can propose an alternative processing technique for this excipient by spray drying. All characterization techniques pointed to the formation of solid dispersion like systems in which the drug is amorphously distributed in a polymeric carrier. All though abundant literature is available concerning these systems we think that further investigation would be appropriate to clarify specific interaction between the polymer and the drug and more specifically the structural morphology of the produced particles.

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[1] G. Liversidge, K. C. Cundy, *Int. J. Pharm.*, **1995**, *125*, 91.
[2] S. Li, S. Wong, S. Sethia, H. Almoazen, Y. M. Joshi, A. T. M. Serajuddin, *Pharm. Res.* **2005**, *22*, 628.

[3] Heimbach, D. M. Oh, L. Y. Li, M. Forsberg, J. Savolainen, J. Leppaenen, Y. Matsunaga, G. Flynn, D. Fleisher, *Pharm. Res.*, **2003**, *20*, 848.
[4] M. E. Brewster, T. Loftsson, *Adv. Drug. Deliv. Rev.* **2007**, *59*, 645–666.
[5] S. Wikarsa, D. Durand, J. L. Delarbre, G. Baylac, B. Bataille, *Drug Dev. Ind. Pharm.*, **2008**, *34*, 485.
[6] M. K. Gupta, A. Vanwer, R. H. Bogner, *J. Pharm. Sci.* **2003**, *92*, 536–551.
[7] D. Bahl, R. H. Bogner, *Pharm. Res.* **2006**, *23*, 2317–2325.
[8] A. T. M. Serajuddin, *J. Pharm. Sci.* **1999**, *88*, 1058–1066.
[9] H. Hardung, D. Djuric, S. Ali, *Drug Deliv. Technol.* **2010**, *10*, 20.
[10] K. Alexander, C. Judson King, *Dry. Technol.*, **1985**, *3*, 321–348.
[11] R. Nair, N. Nyamweya, S. Gonen, L. J. Martìnez-Miranda, S. W. Hoag, *Int. J. Pharm.* **2001**, *225*, 83–96.
[12] A. C. Rumondor, I. Ivanisevic, S. Bates, D. E. Alonzo, L. S. Taylor, *Pharm Res.* **2009**, *26*, 2523–2534.

