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Research paper

Can compression induce demixing in amorphous solid dispersions? A case study of naproxen–PVP K25

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ABSTRACT

The aim of this work is to investigate the effect of compression on miscibility of naproxen (NAP)–PVP K25 solid dispersions. Solid dispersions with diverse drug/polymer compositions were compressed at various forces for uniform dwell time. Miscibility assessments were performed using mDSC, and the effect of compression on the specific interactions of NAP and PVP K25 was investigated by FTIR. The 20% (w/w) naproxen containing solid dispersion showed a single T_g before and after compression. FTIR analysis showed the unchanged profile of this system upon compression. On the other hand, the miscibility in the compositions with 30% and 40% (w/w) naproxen is markedly affected by compression. Compression pressures from beyond 565.05 MPa induced apparent amorphous–amorphous phase separation as indicated by two characteristic T_gs in DSC and altered IR spectral profile. The highly ductile nature of PVP promotes plastic deformation upon compression induced by the rotation of the PVP backbone with the transition of dihedral angles from low to high energy state. Segmental rotation can also be an outcome of plastic deformation that often leads to increase in structural temperature. This can have influence on miscibility resulting from weakening and/or disruption of intermolecular hydrogen bonding between drug and polymer upon compression.

1. Introduction

Improving bioavailability of poorly water soluble drugs is an utterly critical challenge for pharmaceutical formulators. Solid dispersions are considered as one of the multifarious options to improve bioavailability of poorly water soluble drugs [1]. However, they have often displayed chemical and physical stability problems. Phase transformation from amorphous to crystalline or/and to amorphous phase separated systems can be induced by unfavorable storage conditions such as elevated temperature and humidity. In this study, we report for the first time that compression results in amorphous–amorphous phase separation in solid dispersions. This observation can open the avenue to use compression as a stress condition to assess the physical stability of solid dispersions and also to include quality control measures during tabletting to examine the induction of inhomogeneity in the system that can spontaneously crystallize with time.

Compression is an important stage of tablet manufacturing, and understanding its consequences such as segmental dynamics, structural, and thermodynamic changes in solid dispersions has a vital role on the quality of the final product. A ductile material such as PVP exhibits comparatively high plastic deformation upon compression and is also often used as a carrier in solid dispersions [2]. Due to its high deformability, solid dispersion can be formulated as a tablet easily if they have acceptable bulk properties [2,3]. However, there is a limited understanding on the impact of compression on structural stability of pharmaceutical solid dispersions. Miscibility, specific and non-specific interactions between drug and polymer are essential measures of physical stability [4]. Compression might result in a disparity in chain conformation and structural behavior of the components of a glass solution, predominantly the polymer that precludes the attainment of physical stability which is commonly reported for uni-axial and multi-axial deformation of polymers and their blends [5].

Deformation of polymers namely creeping and compression might result in chain elongation, chain scissions, weakening of hydrogen bondings, chain conformation change, and aging reversal as depicted in Fig. 1 [5–8]. These changes in structural behavior induce crystallization of glassy solids. Deformation beyond strain hardening (fragmentation) induces crystallization of poly(ether ether ketone) films, and it is also a common phenomenon in rubber materials like synthetic polyisoprene [9,10]. Glassy poly(tetramethylene naphthalate) has been found to show a reversible phase transition or crystalline modifications induced upon an application of a tensile force [11]. Plastic deformation can also trigger structural relaxation of polymer glasses, but the mechanism is not yet fully

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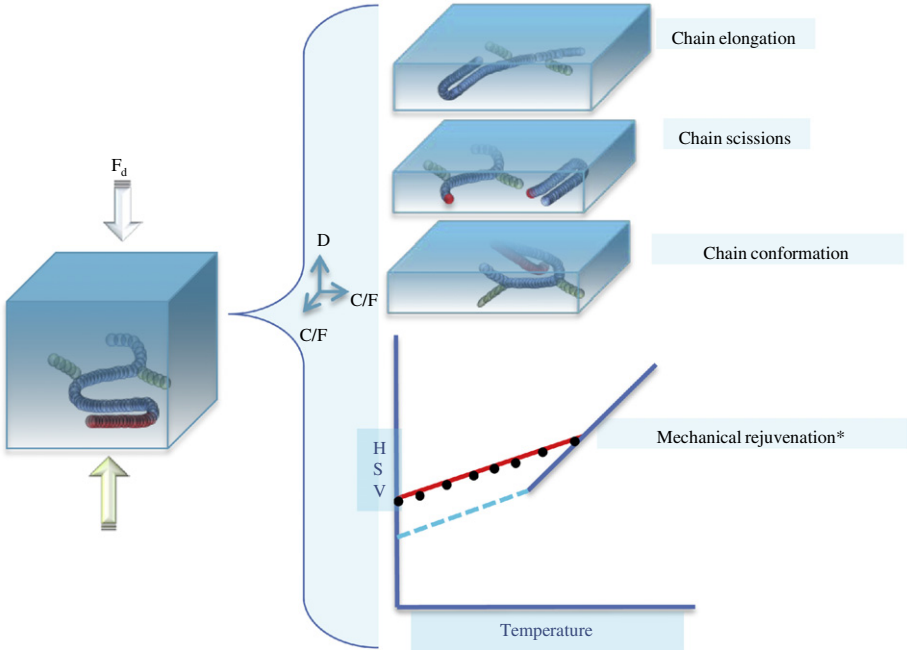

Fig. 1. Schematic presentation of the effect of deformation on a single glassy polymer (*C*/*F*, constraint or free; *D*, deformation; *H*, enthalpy; F_d, force of deformation; *S*, entropy; and *V*, free volume). *Mechanical rejuvenation of melt-quench glassy polymers: for freshly prepared samples (solid red line), after ageing (Aqua dashed line) and aged samples after compression (Black circular markers). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

understood, even its origin remains elusive [12]. Lee and Ediger reported that the relaxation times of lightly cross-linked poly(methyl methacrylate) (PMMA) undergoing creep are decreased significantly compared with the relaxation times of the material at rest [13]. The structural relaxation of amorphous sugar matrices was also accelerated to the level of a non-porous amorphous sugar matrix as the result of the compression [14]. Even the thermodynamics state of stretch and non-stretch glassy polymers is different. Internal energy is higher in the case of the stretched state [3,11]. Segmental motion in polymer glasses can be altered, and even liquid-like flow could be possible by plastic deformation. PMMA rejuvenates the energy lost due to aging upon compression due to increase in molecular mobility [13]. Moreover, phase separation can be induced by elements of deformation. Phase separation of polystyrene/poly (vinyl methyl ether) blends was induced under spatially and temporally periodic forcing conditions [15–17].

Structural and thermodynamics state changes induced by compression might diminish or improve miscibility between the components of a glass solution [18]. Hitherto, the effect of compression on the phase behavior of pharmaceutical solid dispersions especially amorphous–amorphous phase separations has never been reported. As solid dispersions of poorly soluble APIs are mostly targeted for the oral route of administration, formulating it in the form of tablet is the foremost preference. So, acquiring the in-depth understanding on the physical transformations that can occur in solid dispersions as the result of compression, an inevitable step of tabletting, can cast the refreshing direction to the research area of solid dispersions. Moreover, many outcome of compression would be directly associated with the change in physical structure of a solid dispersion that could potentially influence the physical stability, hence the claimed solubility advantage, of tablets prepared therefrom. It can also be used as a stress condition to assess the physical stability of solid dispersions. Taking the gap in the knowledge and the consequences of change in the physical structure of amorphous solid dispersions into consideration, this study was designed to have an assessment of physical change in solid dispersions induced by multi-axial compression process. On the basis of the drug/polymer ratio, such effect of compression was investigated on stable and metastable compositions of naproxen–PVP K25 solid dispersion. In this study, the effect of compression on various compositions of naproxen (NAP)–PVP K25 solid dispersions was investigated. The solid dispersions were prepared by spray drying and subjected to different compression forces for a uniform dwell time. Both compressed and uncompressed samples were analyzed by Modulated Differential Scanning Calorimetry (mDSC) and Infrared Spectroscopy (FTIR) to evaluate their miscibility and specific interactions, respectively.

2. Materials and methods

2.1. Materials

Naproxen was purchased from CERTA Ltd. (Brainl'Allend, Belgium). PVP K 25 (Mw = 25,000 Da) was a generous gift from BASF (Ludwigshafen, Germany). Methanol (HperSolv CHROMANORM) was purchased from VWR International (Leuven, Belgium). The solvent was HPLC grade and used without further purification.

2.2. Methods

2.2.1. Spray drying

Solid dispersions with 20%, 30%, and 40% w/w of naproxen in PVP K25 were prepared by spray-drying 6% w/v solutions of drug and polymer in methanol. Solutions were spray dried using a Buchi mini spray-dryer B191 (Buchi, Flawil, Switzerland), with 50 °C inlet temperature, 0.56 m^3/min drying air flow rate, 13.3 L/min nozzle air flow rate, and 8.11 ml/min feed rate using a peristaltic pump. The spray-dried samples were further dried to remove the residual solvent in a vacuum oven (0.2 bar) at 25 °C for one week before analysis.