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Research paper

Nanocrystals: Comparison of the size reduction effectiveness of a novel combinative method with conventional top-down approaches

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ABSTRACT

Nanosizing is a non-specific approach to improve the oral bioavailability of poorly soluble drugs. The decreased particle size of these compounds results in an increase in surface area. The outcome is an increased rate of dissolution, which can lead to a better oral absorption. Standard approaches are bottom-up and top-down techniques. Combinative technologies are relatively new approaches, and they can be described as a combination of a bottom-up process followed by a top-down step. The work presented in this paper can be described as a combination of a non-aqueous freeze drying step (bottom-up), followed by wet ball milling or high pressure homogenization (top-down) to produce fine drug nanocrystals. The crystal habit of the model drug glibenclamide was modified by freeze drying from dimethyl sulfoxide (DMSO)/tert-butanol (TBA) solvent mixtures using different ratios. The resulting drug powders were characterized by scanning electron microscopy (SEM) as well as by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). It was shown that the combinative approach can significantly improve the particle size reduction effectiveness of both top-down methods over conventional approaches. Drug lyophilization using DMSO:TBA in 25:75 and 10:90 v/v ratios resulted in a highly porous and breakable material. The milling time to achieve nanosuspensions was reduced from 24 h with the jet-milled glibenclamide to only 1 h with the modified starting material. The number of homogenization cycles was decreased from 20 with unmodified API to only 5 with the modified drug. The smallest particle size, achieved on modified samples, was 160 nm by wet ball milling after 24 h and 355 nm by high pressure homogenization after 20 homogenization cycles at 1500 bar.

1. Introduction

Nowadays, many pharmaceutical companies are faced with an increasing number of poorly soluble new chemical entities (NCEs) in their development pipelines [1–3]. These drug candidates require the use of relatively new drug delivery systems and formulation approaches, the so-called enabling technologies, in order to address the low solubility in aqueous media and the related bioavailability problems [4]. Moreover, these drugs have disadvantages in their performance, that is, food effects, erratic absorption, and a non-linear pharmacokinetic profile [5,6]. A practical and well-established method to enhance the absorption of these active pharmaceutical ingredients (APIs) is particle size reduction, especially for those molecules having a dissolution rate limited bioavailability. Particle size reduction can be regarded as a non-specific formulation approach to enhance the bioavailability of poorly soluble compounds because it can be applied for almost every poorly soluble compound independently from its solid state or other physico-chemical properties [7].

By reducing the particle size of the drugs, one can achieve a significant increase in surface area. According to the Noyes–Whitney equation, an increase in surface area results in faster rates of dissolution [8]. Simultaneously, according to the Ostwald–Freundlich equation, the saturation concentration at the surface of small particles, especially in the lower nanometer range, is higher than the saturation concentration at the surface of large particles [9]. Oftentimes drug products containing nanosized APIs possess also reduced or even eliminated food effects [5].

Drug nanocrystals can be produced by employing various particle size reduction technologies. Depending on the production method, they can be classified as bottom-up and top-down. In bottom-up technologies, one starts with an organic drug solution, which is admixed to a miscible non-solvent. The drug nanocrystals are formed by precipitation. This is a traditional method, known as via humida paratum (v.h.p.). Problems associated with this method are the presence of solvent residuals and crystal growth after precipitation [7,10].

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Top-down processes are by far the most important industrial relevant particle size reduction technologies. Typical top-down processes are high pressure homogenization and wet ball milling. Using these technologies, one starts with a micronized drug powder, which is suspended into an aqueous/non-aqueous dispersion medium containing surfactants or polymeric stabilizers [11]. Micronized API is recommended in order to shorten the required time for the diminution process and to prevent a clogging of the machines. Therefore, in general, jet-milled drug powders have to be used [7].

The suspension is then, for example, passed through a ball mill or a high pressure homogenizer [12–14]. The larger drug particles are broken down to very small drug nanocrystals. In contrast to the bottom-up technologies, almost any poorly soluble drug can be processed, also those being poorly soluble in aqueous and simultaneously in non-aqueous media [15].

However, depending on the physico-chemical properties of the drug and the processing parameters, different durations of the particle size reduction processes are needed in order to obtain a nanosuspension. From industrial and economical point of view, it is highly desirable to minimize the milling times or the number of homogenization cycles [7].

To overcome the limitations of the conventional particle size reduction technologies for poorly soluble drugs, new combinational methods have been developed for the production of ultrafine suspensions. Combinative technologies are a relatively new approach to improve the particle size reduction effectiveness. In general, they can be described as a combination of a bottom-up process followed by a top-down technology [16]. Examples from bottom-up technologies are spray drying and freeze drying. Spray drying has also been widely used as a technique to improve the dissolution rate of drugs. However, it is not always possible to find a suitable solvent for the spray drying process. Another limitation is that spray drying in general is not the first choice for thermolabile compounds because the spray drying process could lead to elevated temperatures [17]. An alternative bottom-up process is freeze drying. It can also be coupled with a top-down step to produce ultrafine drug nanoparticles, for example, high pressure homogenization (so-called H 96 process) [18]. The freeze drying process involves freezing a solution. The frozen solution is then exposed to a very low pressure, at which the ice formed is eliminated by sublimation. The majority of the pharmaceutical products using this technology are lyophilized from aqueous solutions. With the increasing problem of poorly water-soluble APIs, the freeze drying with organic solvents systems has become an interesting strategy for the formulation of problematic APIs. Lyophilization or freeze drying is a promising technique to produce pharmaceutical powders with enhanced dissolution rate, although the freeze drying process is relatively slow [19]. Therefore, freeze drying is regarded as costly unit operation. Consequently, the production costs for the combinative method will be also higher compared to particle size reduction alone. However, the significantly improved particle size reduction effectiveness, both in terms of process time and minimal achievable particle size, could justify its application especially in case of expensive, labile compounds.

First experiments have shown that the size of the drug nanocrystals obtained via a combinative process can be influenced by adjusting different process parameters of the bottom-up step, such as freezing rate, solvent composition, and drug concentration during the precipitation process. The freeze drying technology also modifies the structure of API powders, which is interesting when using a secondary top-down step to nanosize a suitable breakable material [18]. The work described here is a combination of a non-aqueous freeze drying step (bottom-up) followed by wet ball milling or high pressure homogenization (top-down) to produce fine drug nanocrystals. A schematic description of this novel combinative technology is given in Fig. 1.

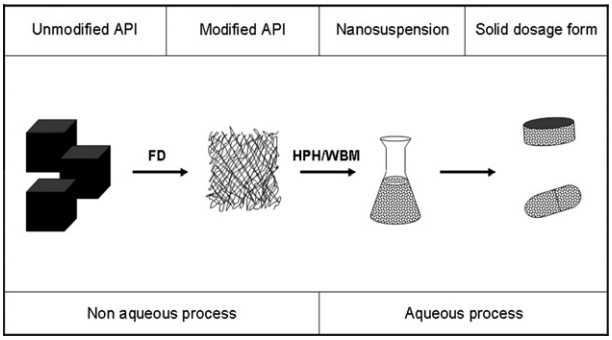

Fig. 1. Schematic description of the combinative H 96 technology for nanoparticle production. FD: freeze drying, HPH: high pressure homogenization, WBM: wet ball milling.

The investigation presented here is concentrated on the systematic research of parameters influencing the reduction effectiveness and on the comparison of two top-down technologies. A poorly water soluble (BCS class II) model compound (glibenclamide) [20] was used to determine the optimal process parameters for the development of a better and faster method for the particle size reduction of poorly soluble drugs. Glibenclamide is a sulfonylurea widely employed for the treatment of non-insulin dependent diabetes mellitus and belongs to the group of substituted arylsulfonylureas. Many members of this API class show polymorphism, and one of the forms is more soluble but less stable than the other ones [21]. The purpose of this research was also to investigate the thermal behavior of our model compound using thermoanalytical techniques like differential scanning calorimetry.

2. Materials and methods

2.1. Materials

The model compound glibenclamide and docusate sodium salt (DSS) were purchased from Sigma Aldrich, Germany, the organic solvents dimethyl sulfoxide (DMSO), tert-butanol (TBA), 1,4-Dioxan and acetonitrile, were purchased from Merck KGaA, Germany. Liquid nitrogen was used as cryogenic liquid. Demineralized water was supplied by a Millipore MilliQ-Plus system, and yttria stabilized zirconium oxide (YSZ) beads (0.2 mm), purchased from Hosokawa Alpine, Germany, were used as grinding media. The HPLC grade solvents were acetonitrile and HCl, both purchased from Merck KGaA, Germany.

2.2. Methods

2.2.1. Solubility screening and saturation solubility determination

An appropriate amount of API (5 or 10 mg depending on the expected solubility) was dissolved in a beaker by continuously adding the solvents. The solubility screening was conducted in DMSO, TBA, dioxan, and acetonitrile. The solvents were added with a pipette in aliquots of 0.1 ml or 0.5 ml applying magnetic stirring until complete dissolution of the drug. The solubility was calculated in mg/ml. Once an approximated solubility was found, the saturation solubility was determined. An amount of glibenclamide, above the solubility founded at the screening, was dissolved in 1 ml of each solvent on vials. The vials were shaken for 72 h at 30 °C on an Innova 4230 refrigerated incubator shaker (New Brunswick Scientific, USA). The supernatants were then centrifuged for 3 h at 17,000 rpm (19,386 G) on a Biofuge 22R centrifuge (Heraeus Sepatech, Germany) in order to ensure a complete separation of drug particles. Then, 500 μl from each solution was separated from