Design of new drug forms by cryo-nanotechnologies

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Abstract. A detailed study of processes occurring on annealing of frozen solutions of selected APIs in mixed organic-aqueous solvents allowed us to optimize the ratio of components and the experimental conditions for preparing novel forms of the APIs with improved properties.

1. Introduction

Currently, about 40% of industrially produced pharmaceuticals are poorly water soluble [1], what restricts their usage as orally administered drugs because of poor wetting properties and solubility in liquors of the digestive tract. Development, preparation and introduction of novel drug forms are time- and money-consuming, therefore the search for various approaches to optimizing already known and widely used medicines is highly topical. Improvement of bioavailability of drugs through enhancement of their dissolution kinetics is the task of paramount importance and urgency for pharmaceutical science. Besides, the interest of pharmaceutical companies in developing the technologies of producing micro- and nanoparticles of desirable size is related, among other reasons, to the growing popularity of inhalation therapy [2]. However, scarce solubility of pharmaceutical ingredients in water limits severely the application of spray-drying or freeze-drying due to the necessity of evaporating large volumes of solvents during the process, or of removing a large amount of ice by sublimation. This results in a substantial increase in the duration of an experiment and a large energy consumption for the preparation of even relatively small amounts of a drug. At the same time, it is known that the solubility of APIs can be considerably increased, if water is mixed with an organic liquid having a low boiling point. Many of such systems are characterized by formation of clathrate
hydrates at low temperatures, which are stable up to fairly high temperatures, thus making it possible in a certain concentration range to carry out drying at essentially higher temperatures under the conditions which exclude the appearance of liquid phases in the system. Fast cooling giving amorphous phases is followed by solvent removal by sublimation, and since no liquid phases are present, fine particles are formed, which do not grow.

Paracetamol is a wide-spread analgetic drug, exhibiting antiinflammatory and antipyretic effect, and it is also a common model object in many studies on key problems of pharmaceutical science [3-9]. For example, in our recent work [10] we have demonstrated the possibility to use the acetone-water mixture for preparing ultrafine powders of the monoclinic paracetamol suitable for direct compression. At the same time, the tetrahydrofuran (hereafter THF) - water system received much more attention of researchers focused on enhancement of solubility of poorly water soluble APIs (e.g., danazol) [11], what is related, among other things, to the fact that the clathrate hydrate in this system is crystallized on cooling of homogeneous aqueous solutions [12]. However, up to the moment, the search for appropriate solvents and their mixtures lacked systematic approach; little attention was paid to the processes occurring on rapid cooling of solutions and on their freeze-drying. As a result of wrong choices of the ratio of components in the mixed solvents, the consumption of energy needed to maintain low temperature during a prolonged drying was very high [11]. Therefore, our primary task was to demonstrate (with paracetamol example), how a detailed study and understanding of the processes occurring in a chosen mixture of solvents on cooling and subsequent freeze-drying allows one to make an optimum choice of the ratio of components in the mixture, to achieve substantial energy saving and to develop novel APIs with improved properties.

2. Experimental

Tetrahydrofuran (THF) and 1,4-dioxane (purified from peroxides and double distilled), chromatographically pure acetone and distilled water were used as solvents. Ultrafine powders of APIs were obtained by spray freeze-drying of their solutions in the organic volatile liquid - water mixtures.

Bruker D8 Advance equipped with a low-temperature TTK 450 Anton Paar chamber permitting to work under vacuum down to 10^-3 torr was used for X-ray powder diffraction experiments aimed at optimizing drying conditions. The samples were carefully but gently ground in a mortar at the liquid nitrogen temperature and placed onto a holder, which was preliminary cooled down to liquid nitrogen temperature. If a diffraction pattern was measured at low pressure, the sample was kept in the chamber for 5 minutes prior to the start of data collection for an equilibration. Diffraction patterns were measured in the -140 - +20ºC temperature range (2θ scans in the 5-55 degrees range, at a 0.02 degrees step, about 8 minutes per pattern).

Scanning electron microscopy (SEM) analysis was carried out with TM-1000 (Hitachi) to obtain a visual image and to evaluate particle size, shape, and surface. The specimens were mounted on a metal stub with double sided adhesive tape and coated under vacuum with platinum.

The specific surface area was determined by the BET method from N2-adsorption/desorption isotherm data using an ASAP-2400 instrument (Micromeritics, USA).

3. Results and discussion

The temperature regimes of drying were tuned on the basis of the X-ray diffraction study of the processes occurring on annealing of frozen solutions (prepared by spraying of the starting solution in a vessel with liquid nitrogen) and of the analysis of the phase diagram of the THF-water system, to guarantee that at every stage of drying only solid phases were present in the system. Paracetamol samples were obtained from the THF-water solutions as very light fluffy powders. Fig. 1 illustrates the difference in the volumes of the same amounts of ultrafine paracetamol obtained in this work and of the commercial sample as purchased. Specific surface area of the paracetamol samples measured by sorption/desorption of N2 was equal to 2.43±0.06 m²/g for our samples, and 0.13±0.01m²/g - for the commercial sample. According to SEM data, the samples of ultrafine paracetamol contain porous spherical agglomerates with typical sizes of 30-70 μm. These agglomerates are formed as the solvent
is removed from frozen droplets, which are produced by rapid cooling of the starting solution. It was noted that even on very slight mechanical impact (movement of the sample on tumbling of the vial; friction with a spatula) the agglomerates disintegrate into constituting planar particles with linear dimensions 2-4 μm and thickness about 100 nm (Fig. 2).

Fig. 1. A comparison of volumes of the same amounts (1.0 g) of ultrafine paracetamol obtained in this work (left) and of the commercial sample as purchased.

Fig. 2. Samples of the ultrafine paracetamol (a - d) obtained by spray freeze-drying of a frozen solution of paracetamol in the THF-water mixture. For a comparison: the commercial sample (e). The scale bar: a, e – 100 μm; b – 20 μm; c, d – 100 μm.

A study of the dissolution dynamics (Fig. 3) has shown that the samples of ultrafine paracetamol dissolve much faster at the initial minutes of dissolution as compared to the commercial sample, yielding the concentration in solution more than five times higher, than that achieved by dissolving a commercial sample during the same time. Besides, the dissolution of paracetamol samples prepared in
this work in both water and 0.1M HCl was complete already on the 2\textsuperscript{nd} minute, while the commercial samples could be dissolved in 20 minutes only.

![Dissolution profiles of paracetamol samples obtained in this work, and of the commercial samples (“raw material”) in different media (a: water; b: 0.1 M HCl).](image)

This approach to obtaining fine particles can be applied to practically any solid pharmaceutical. Another example is provided by ibuprofen, which is a very common analgetic and antiinflammatory drug, which shows a bad dissolution behavior because of its hydrophobic structure. A rapid drug release is preferable for analgesic drugs. Decreasing a particle size is a promising way to improve the bioavailability of the drug. According to SEM data (Fig. 4), ibuprofen samples prepared by our technique (from different mixtures of solvents) contain agglomerates with sizes 30-500 \( \mu \text{m} \) consisting of flat 1-10 \( \mu \text{m} \) particles with the thickness less than 300 nm (depending on the solvent mixture used). Specific surface area values of SFD ibuprofen obtained in this work and of the commercial sample are 2.58±0.11 and 0.05±0.01 m\(^2\)/g, respectively. The suggested technique of the micronization of ibuprofen makes it possible to prepare fast-dissolving suspensions, which meet the requirements to analgetic and antipyretic drugs for babies and infants.

![SEM images of the ibuprofen samples: obtained by spray freeze-drying (a), and commercial sample (b). The scale bar: a –50 \( \mu \text{m} \); b – 500 \( \mu \text{m} \).](image)

### 4. Conclusion

Two-component mixtures "volatile-liquid – water" giving clathrates at low temperatures can be used as solvents for APIs. Flash-cooling and subsequent evaporation of these solutions can give micronized samples with improved dissolution profile, compactability and other properties. If the ratio of the components is chosen correctly, the concentration of the initial solution and the evaporation
temperature can be high enough, to reduce energy consumption as the drying time significantly (this is of critical importance for technology), and to avoid the increase in the size of fine particles (since no liquid is present in the system at any stage anymore after cooling of the starting solution). The suggested technique based on freeze-drying of frozen solutions prepared from mixed water-organic solvents allows one to prepare a wide range of other APIs as ultrafine powders.

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