Towards Nanosized Particles in Pharmaceutical Industry

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ABSTRACT

Two drug substances have been used as model compounds to investigate the possibility of enhancing the performance of poorly water-soluble drug formulations using spray drying of nanodispersions. The active pharmaceutical ingredient (API) is present as nanosized solid in an aqueous solution. Different carrier materials have been added to generate dispersions of API in hydrophilic polymer poly(vinyl-pyrrolidone)-K30 (PVP), lactose and mannitol. The dispersions were spray-dried to investigated the influence of wettability on the API-in-carrier-embedding. In-vitro dissolution results reveal an improved dissolution rate of the spray-dried substance in water when compared to physical mixtures for all carriers.

Spray-drying of nanodispersions are therefore an alternative manufacturing process that can be used in the production of poorly soluble and poorly bioavailable drugs

Keywords: Spray drying, nanodispersion, dissolution rate, wettability.

1 INTRODUCTION

The pharmaceutical industry faces the problem of an increasing number of drug substances which are either poorly water-soluble or show pH-dependency of solubility. This poor aqueous solubility of drugs is generally accompanied by poor bioavailability and represents a major problem in drug formulation, especially in the case of drugs that are poorly soluble both in water and in lipid-based formulations. The utilization of suspensions containing the drug substance as nanosized solids is expected to solve some of the associated problems as nanoparticles potentially show increased dissolution rates and solubilities. These improvements result in enhanced bioavailability, reduced dosing volume and improved stability, if properly formulated and potentially reduce food effects [1].

Spray-dried nanodispersions are seen as an alternative manufacturing process that can be used in the production of poorly soluble and low bioavailability drugs.

2 MATERIALS

The general aim of the work is to increase the bioavailability of poorly water soluble drugs, to decrease the required dose, and/or to improve other qualities such as food effects. Specific goal is the spray-drying of two aqueous dispersions containing nanoparticles of two different drug substances using different carrier materials. The dispersions containing the active pharmaceutical ingredient (API) as nanoparticles were provided with a fixed composition consisting of water as solvent, API and additives. Different carrier materials have been added to give a drug product to carrier ratio of 1:1 resulting in the composition of the dispersions shown in Table 1.

API type	Water	API conc.	Additives	Carrier
Substance A	89.3	5	0.7	5
Substance B	95.7	2	0.3	2

Table 1: Composition of feed dispersion in (wt.%)

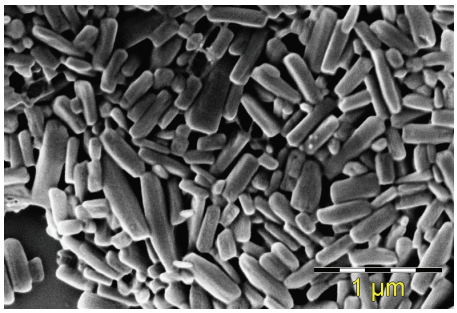
2.1 Characterization: particle size and shape

The quality of the dispersion before adding the carrier has been characterized using different analytical techniques. In particular, photon correlated spectroscopy (PCS) (Nanophox, Sympatec), ultrasonic spectroscopy (USS) (DT1200, Quantachrome), and sedimentation centrifuge (SC) (LUMiSizer, LUM) were used to measure particle size distributions (PSDs). Scanning electron microscopy (SEM) was used to characterize particle shape. The average particle size x_{50} is shown in Table 2 and SEM pictures of the dispersions A and B are provided in Figure 1. The deviating value for solution B with USS is due to the low weight proportion of drug pro which should be at least 5 wt.%.

	PCS x_{50} (nm)	USS x_{50}(nm)	SC x_{50}(nm)
Dispersion A	278	263	215
Dispersion B	280	540	215

Table 2: Average particle size x_{50} of dispersion before adding carrier measured with different methods

a)



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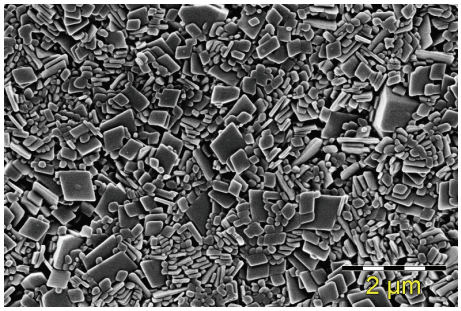

Figure 1: SEM micrographs of dispersion A (a) and B (b)

SPRAY DRYING RE-DISPERSIBLE, EMBEDDED NAOPARTICLE DISPERSION

2.1 Wetting angle and embedding efficiency

Spray drying of API particles embedded in carrier substance hydrophilic matrices are known to produce directly compressible powder mixtures with superior physico-chemical properties (flowability, hygroscopicity and compactability) compared to their physical mixtures or the individual carrier substances [2]. During spray-drying no chemical changes occur and the improved compression properties are attributed to the physical properties of the API-carrier compound particles [3].

The influence of wettability on the API-in-carrier-embedding was investigated in this work in order to find a fast method to screen possible carriers and therefore reduce the number of experiments. Embedding of the API particles is expected to be superior if the carrier solution wets the API surfaces well. Impact of the quality of embedding on dissolution rates are investigated in section 3.

The physical value describing the wetting properties of a API powder is the contact angle (θ) between liquid and powder. The contact angles for different carrier solutions with pure substances A and B have been determined with a tensiometer (K100MK2, Krüss), using the Washburn method. The powder to be measured is filled and tapped into a glass tube fitted with a filter base, which is then suspended from the balance. A vessel containing the carrier solution is raised until the liquid contacts the liquid. The speed at which the liquid rises though the bulk powder is measured by recording the increase in weight as a function of time, which corresponds to the contact angle between solid and liquid, is calculated by the Washburn equation [4].

Several aqueous solutions with addition of different carriers/additives to dispersion A have been investigated and are listed in Table 3. The Washburn method cannot give an exact measure for wetting angles larger than 90°. Hence, solely the information that the liquid is not wetting the drug substance A is given, which is indicated by θ ≥ 90°. Density was measured with a vibrating tube density meter (KEM DA-100M, Mettler Toledo), viscosity with a rotational torque viscosimeter (Visco Tester 7L, Haake).

Liquid phase + carrier (wt.%)	Density (kg/m^3)	Viscosity (mPa·s)	θ (°)
Dest. water (DW)	997	1.00	≥ 90
DW + 1 wt.% PVP K30	999	1.30	87.6
DW + 0.4 wt.% SLS	998	1.10	89.9
DW + 5 wt.% Lactose	1018	1.10	≥ 90

Table 3: Density, viscosity of liquid phase including different carriers/additives and contact angle of liquid with substance A

Based on the results obtained with the spray drying of dispersion A, PVP K30, Lactose and Mannitol have been selected as carrier substances for the spray-drying experiments with substance B. Density, viscosity and the corresponding contact angles were measured as before, with results shown in Table 4.

Liquid phase + carrier (wt.%)	Density (kg/m^3)	Viscosity (mPa·s)	θ (°)
DW + 2 wt.% PVP K30	1002	1.60	89.4
DW + 2 wt.% Lactose	1005	1.10	89.96
DW + 2 wt.% Mannitol	1004	1.05	≥ 90

Table 4: Density, viscosity of liquid phase including different carriers/additives and contact angle of liquid with substance B

The spray drying (SD) experiments were carried out on a Büchi laboratory scale spray drier (B290, Büchi). The drug-to-carrier ratio investigated was 1:1. Inlet temperatures were 140°C in all experiments, nitrogen atomization gas flow rate was 600 L/h, atomization pressure was 4.5 bar, and the aspirator was operated at 100% (approx. 12 kg nitrogen drying gas per hour). Typical experimental yields were between 60 and 70 wt.%.

Figure 2 shows SEM micrographs of the spray dried powder of substance A manufactured with the different carriers. Carrier PVP (Fig. 2a) shows good embedding of the API. Individual particles cannot be distinguished on the surface of the spray-dried microparticles. For carriers lactose (Fig. 2b) and mannitol (Fig. 2c) the embedding is poor. Individual stick-like API nanoparticles are clearly recognizable on the surface of the microparticles.

SEM micrographs of the spray dried powder of substance B show similar behavior for the chosen carriers. Again carrier PVP (Fig. 3a) shows better embedding than mannitol (Fig. 3b) and lactose (Fig. 3b), where individual plate-like API particles can still be distinguished on the surface of the spray-dried microparticles.

a)

b)

c)

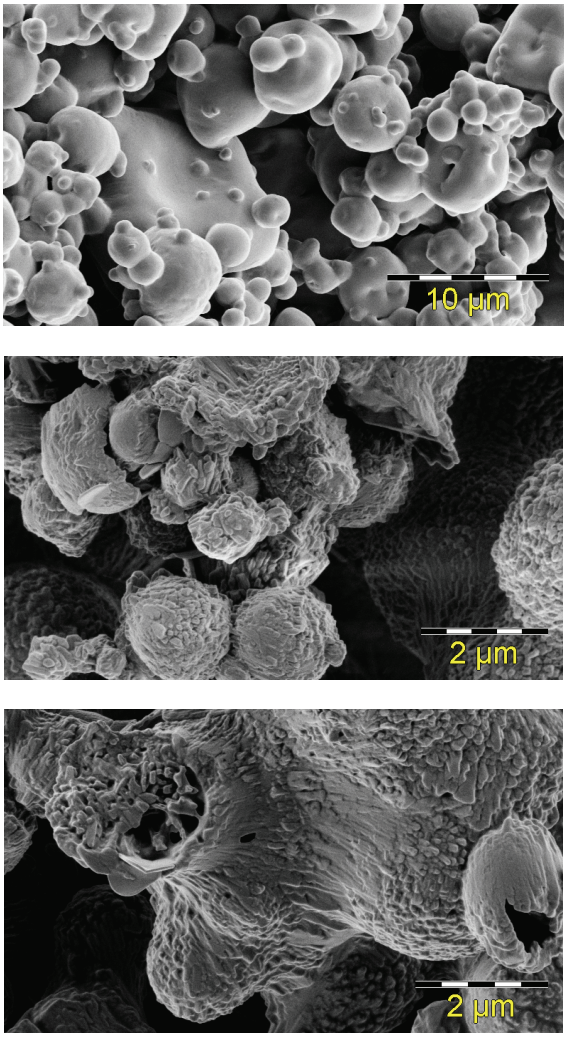

Figure 2: SEM micrographs of the spray dried microparticles of substance A with different carriers: a) PVP, b) lactose, and c) mannitol

Both substances showed the best API-in-carrier embedding for the carrier liquid with the lowest contact angle between solid and liquid. In both cases this was the case for carrier PVP. The two other carriers showed similar behavior for both drug substances. Because the measurement method for the contact angle can give no actual number for contact angles ≥ 90°, it is not possible to differentiate between these two carriers for both APIs.

2.2 Comparative analysis of dissolution performances

Dissolution rate (DR) measurements were performed to compare physical mixtures (PM) with the spray-dried product (SD). The goal of these tests was to determine the impact of formulation, particle size reduction (embedded nanoparticles), isolation by spray-drying and carriers in substance dissolution tests of nanodispersions A and B.

a)

b)

c)

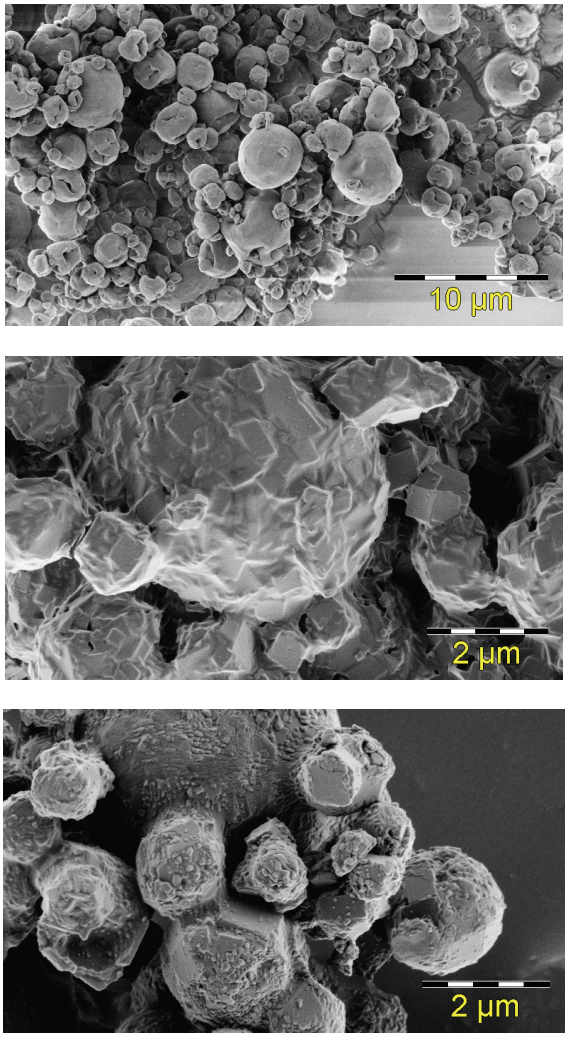

Figure 3: SEM micrographs of the spray dried microparticles of substance B with different carriers: a) PVP, b) lactose, and c) mannitol

In all dissolution measurements the spray dried drug product has been compared to a physical mixture with micronized API (not nanosized). In contradiction to the standard tabletting procedure, 120 mg of the formulation consisting of 46.73 wt.% API (m_A = 20 mg, m_B = 25 mg) mixed with Aerosil 200, Na-CMX-XL and lactose were filled in capsules instead of being pressed into pellets (Table 5).

API type	API	Aerosil	Na-CMX-XL	Lactose
Formulation A	20	2.07	10.34	54.09
Formulation B	25	2.4	12	62.8

Table 5: Formulation of capsules used for DR tests (in mg)

Dissolution rates of formulation A were determined in situ using a VK7030 UV-ATR fiber optic system (VARIAN). The dissolution rate of formulation B is determined by means of sampling from the dissolution

vessels and subsequent apply High Performance Liquid Chromatography (HPLC) (Technology 1200 Series, Agilent).

The test dissolution media initially consisted of 0.4 wt.% sodium dodecyl sulfate (SDS, CAS 151-21-3) in 1 L of distilled water, stirred at 50 ± 2 rpm at a temperature of 37 ± 0.5 °C. The pH was 1 for the physical mixture and 1 and 6.8 for the spray-dried product.

In Figure 4 the dissolution rate for substance A with SD-carrier lactose is shown for test media of pH 1 and pH 6.8. Unfortunately, advantages of particle size in the embedded structure compared to the physical mixture could not be shown. There is no significant influence of pH of the simulated test mediums and no influence of the carrier (not shown here).

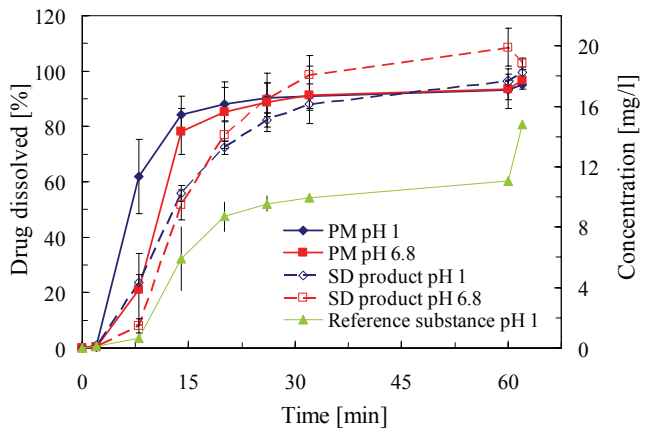

Figure 4: Dissolution rate substance A, pH 1 und pH 6.8 for carrier lactose, 0.4 % SDS

Dissolution rate tests for substance B (Figure 5) with SD-carrier mannitol also showed no advantages of the embedded nanoparticles, when compared to the physical mixture.

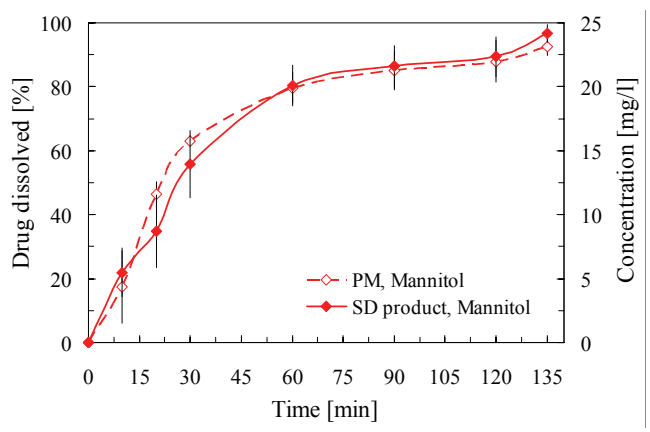

Figure 5: Dissolution rate substance B, 25 mg dose in 1L 0.4% SDS, pH 1 und pH 6.8 for carrier lactose

The reason for this lack of discrimination was found in the use of large amounts of SDS in the test medium. Its influence on measured dissolution rates was investigated performing experiments with SDS contents in the test medium of 0, 0.05, 0.1, and 0.2 wt.%. Only the case of 0% SDS in the test-medium is shown here for the different SD-carrier and substance B (Figure 6).

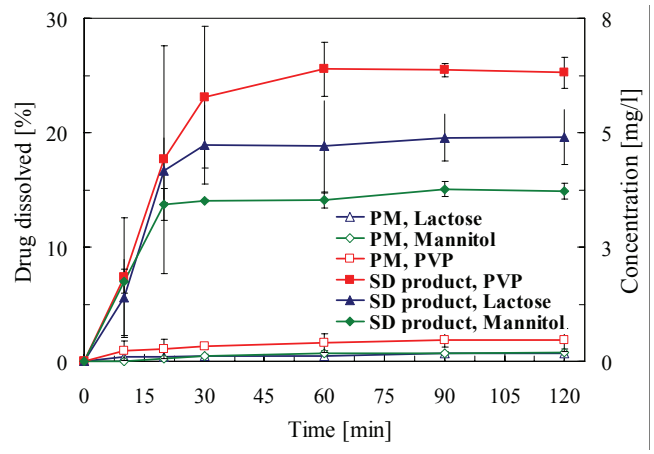

Figure 6: Dissolution rates for substance B, pH 6.8, 0 % SDS for different SD-carriers

The spray-dried product of substance B showed improved DR in water (pH 6.8) when compared to physical mixtures for all SD-carriers. The carrier PVP showed the best DR followed by lactose and mannitol. Discriminative power was lost when tests were performed in 0.4% SDS. These results demonstrate that the methods applied for in-vitro testing of quality parameters of a substance need to be checked and if needed adapted in order to show relevant effects.

The highest accomplished concentration can be associated with the quality of embedding of the API in the carrier and therefore with the wettability of API by the carrier shown earlier. Further experiments need to be performed to conclude on a direct influence between wettability and dissolution rate.

CONCLUSIONS

Conventional spray drying was successfully used to produce re-dispersible powders of dispersions containing API as nanoparticles. The spray-dried product showed improved DR in water (pH 6.8) when compared to physical mixtures. Discriminative power was lost when DR tests were performed adding 0.4% of SDS.

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