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Research paper

Surface composition and contact angle relationships for differently prepared solid dispersions

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ABSTRACT

Solid dispersions are promising drug delivery forms which offer the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution behavior and the bioavailability of the drug. One important aspect and a prerequisite in understanding the drug dissolution mechanism from solid dispersions is a better analytical monitoring of the solid dispersion surface properties, such as powder surface composition and water adsorption properties. In this paper, we have considered chemical and structural surface analysis data for solid dispersions processed by spray drying or roto-evaporation and compared these data with information obtained by contact angle measurements. Firstly, we establish the usefulness and suitability of X-ray photoelectron spectroscopy (XPS) for determination of surface chemical composition and scanning electron microscopy (SEM) for determining the structure of solid dispersions composed of different types of carriers, drugs and drug concentrations. Secondly, we measure contact angles of solid dispersions to describe wettability, to finally establish a link between the surface chemical composition, the powder structure and the wetting behavior. These experimental methods offer a rapid screening tool for the selection of carrier, drug concentration and/or process in early development. In addition, they provide a useful tool for investigating structural aspects of solid dispersions which have intrinsic relevance for drug dissolution and stability.

1. Introduction

Enhancement of the bioavailability of poorly water soluble drugs has been one of the main targets of drug development during the last decade and will continue in the upcoming years. Several techniques have been developed concerning enhancement of the dissolution rate of these drugs, including particle size reduction [1], salt formation [2] and preparation of solid dispersions [3].

Solid dispersions can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties [4]. During the solid dispersion preparation, the aim is to disperse the drug homogenously within the carrier matrix and to encapsulate the hydrophobic drug to ensure complete wetting, fast carrier dissolution and improved drug stability [4,5]. Solid dispersions of different characters exist. In this study, we are using amorphous carriers to originate amorphous solid dispersions. These can be classified as solid amorphous solutions, solid amorphous suspensions and a mixture of both [4]. As the drug concentration is increased, the characteristics of the solid dispersions tend to shift towards solid suspensions.

Despite the intense research on solid dispersions, only a very limited number of commercial products have been developed. One of the primary reasons is the poor predictability of solid dispersion behavior due to a lack of a basic understanding of their material properties. The rate at which a solid oral drug delivery system dissolves depends on many parameters, and occurs in a series of steps: wetting, solvent penetration, disintegration, swelling (if applicable) and dissolution of components. Each of these areas is complex, and their respective roles in the dissolution process need to be considered separately. In this work, we have focused on the relationship between surface properties and wetting. The powder surface composition is expected to play an important role in the wetting process, as it influences the overall hydrophobicity of the powder. In particular, high surface coverage of hydrophobic drug is assumed to give poor wetting properties with large contact angles. The amount of drug at the powder surface is further believed to significantly influence dissolution and physical drug stability. The importance of contact angles and wettability on dissolution rate is discussed in several studies [6–8]. In one recent study by Chokshi et al. [9], it was reported that the contact angles of solid dispersions correlate to improved intrinsic dissolution data for a poorly water soluble drug. In another study, Buckton [10]

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describes the Noyes–Whitney model which infers a direct proportionality between the dissolution rate of drug and the effective surface area of a powder (determined partly by wettability). There are some reports in the literature which describe structure–activity relationships of powders which refer to solubility and wettability [11]. They claim that the structure of molecules is linked to both wettability and solubility, but the mechanism by which the structure affects wettability and solubility is different. This relates to the fact that wetting is a reflection of the functional groups that are present at the surface of the solid, but solubility relates to the structure of the entire molecules respectively powder. It follows that it should be possible to alter the structure of a powder to independently manipulate wettability and solubility. However, what is lacking so far is a more detailed description of the solid dispersion structure including aspects such as drug distribution, surface properties, wetting and its impact on the molecular disintegration during dissolution.

There are several ways to prepare solid dispersions, such as melting or solvent methods [3,14]. The latter method consists of the solubilization of the drug and carrier in a volatile solvent which is later evaporated. In this study, we have compared solid dispersions prepared by two solvent methods; rotary evaporation, which is a slow drying technique, in combination with milling, and spray drying, which is a fast drying technique that directly produces a powder. The properties of the prepared solid dispersions may depend greatly on the preparation technique. The possibility to alter the structure of a powder to manipulate wettability is presumably relevant for drying processes, which have a significant impact on the surface composition of powders, in particular when one or more surface-active components are present.

It has been shown for water-based solutions that the surface of a spray-dried powder is dominated by surface-active species in the formulation [15–18]. This effect on the surface composition is due to adsorption of the surface-active substance to the air/liquid interface of the spray droplet before it turns into a dry particle. If none of the materials is surface-active, the less soluble material dominates the surface. The fact that most solid dispersion of poorly soluble drugs is prepared form non-aqueous solvents does not change the mechanism in principle: the substance with the strongest affinity for liquid/air interface will tend to dominate the surface of the powder. Thus, in the case of solid dispersion preparation processes the migration of the hydrophobic drug towards the particle surface would render the powder surface hydrophobic with a large contact angle between the powder surface and the penetrating surface. In this case, retardation or inhibition of the drug dissolution could be expected. In order to improve the wetting, surfactants are frequently incorporated into the formulation to decrease contact angles and promote a better powder wetting. The competitive adsorption process between the components with different surface affinities might be different for slow and fast drying techniques, which might lead to differences in the surface properties related solely to the drying technique. These differences in enrichment or depletion at the powder particle surface relative to the bulk composition may have consequences for the wetting, dissolution and bioavailability for the final formulation.

In general, wettability is a measure of the ability of a bulk powder to imbibe a liquid under the influence of capillary forces, and it depends on particle size, density and porosity of the powder bed. The rate of ingress of water into a powder bed can be described by Washburn's equation [12,13], but, the wetting properties of powders are not straight forward to determine, and several attempts have been presented in the literature. In food industry, the most common procedure is to observe the time for a powder to sink from the surface into the liquid. In the pharmaceutical area, no pharmacopeia methods exist for describing the wettability of dispersed drug delivery forms such as solid dispersions, although this value has a significant impact on the method development of release studies. Several approaches have been reported which describe powder wettability by using the Wilhelmy plate technique [19] to determine an apparent contact angle of water insoluble powders by gluing the powder onto the Wilhelmy plate and measuring the contact angle. The difficulty here is to determine the actual perimeter of the powder covered plate, which is essential for the determination of the contact angle. Further, the influence of the glue on the powder is not clear. Lippold et al. [20] have tried to measure contact angles on different crystal faces, which is interesting since different crystallization protocols can give rise to different crystal habits, with relative differences between the sizes of the different crystal faces. This is thus a way to influence the wetting properties of a crystalline powder. However, this method is not applicable for small crystals or amorphous materials. Buckton et al. [21] used compressed tablets of pure drug powders to determine the contact angle of these powders. A similar method is used in this paper for analysis of the wetting properties of solid dispersions.

To correlate the observed wetting behaviors with surface chemical composition data, obtained by X-ray photoelectron spectroscopy (XPS) measurements, the Young–Laplace equation is suitable:

$$\gamma_s = \gamma_{sl} + \gamma_l \cos\theta \quad (1)$$

where γ_s, γ_l and γ_{sl} are the solid–vapor surface tension, the liquid–vapor surface tension and the solid–liquid surface tension, respectively. The suggestion is that the amount of drug on the surface would correlate to the contact angle with water via the surface energy of the powder compact, γ_s. The negative aspect of this is that according to Eq. (1) we ignore effects due to the γ_{sl} term, and also any effects due to the physical surface structure (roughness, pores, etc.). None the less this exercise can be seen as a step towards correlating surface chemical composition, itself determined by the drug and excipient components present and the production method used, to wetting properties.

The aim of this work is to establish a link between solid dispersion surface properties, i.e., chemical surface composition and wettability. In addition, we study the impact of formulation variables such as type of carrier, drug concentration and the preparation process on the encapsulation efficiency of the drug inside the powder bed. To this end, we consider chemical and structural surface analysis data for different processed solid dispersions composed of different types of carriers, drugs and drug concentrations and compare these data with information obtained by contact angle measurements with the view to assess relationships between them. Firstly, we establish the usefulness and suitability of experimental methods for the determination of surface chemical composition and structure of solid dispersions, secondly we measure contact angle of solid dispersion to describe wettability, and finally we attempt to establish a link between the surface chemical composition, the powder structure and the wetting behavior.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) (Dow Chemical, USA), polyvinyl pyrrolidone (PVP K30) (BASF, Germany) and hypromellose phthalate (HP50) (Shin-Etsu Chemical, Japan) have been used as carriers in combination with drug A and drug N (obtained from Novartis Pharma AG) to generate amorphous solid dispersions. Both the drug candidates represent a class of drugs which have increased industrial importance and which are frequently developed by the solid dispersion concept (for physical–chemical properties see Table 1). Poloxamer F68 (Uniqema Germany) was used as a surface-active

Table 1
Physical–chemical properties of drug A and drug N used in this work

Drug	Log P	Solubility in water	Solubility in ethanol
N	⩾4.35	0.09 mg/l	32 g/l
A	⩾4.39	2.4 mg/l	>100 g/l

agent. Ethanol (Alco Suisse, Switzerland) and acetone (Shell, the Netherlands) were used in preparation of the solid dispersions. For the contact angle measurements, purified water (Millipore) was used.

2.2. Methods

2.2.1. Roto-evaporation

First, the drug substance (and the Poloxamer F68 when used) was dissolved in a mixture of ethanol and acetone (50:50). Subsequently, the polymer was dispersed in the drug substance containing solution, and was allowed to swell for at least 1 h, resulting in a swollen suspension with a solvent/polymer ratio of 10:1. The solvent used (technical grade) contains traces of water which induce enhanced swelling of the carrier and ability for drug encapsulation. The swollen suspension was dried in a rotary evaporator at about 40 °C until a highly viscous state was reached. The highly viscous material was then dried under vacuum in a tray dryer (Binder, Germany at 40 °C/30 mbar) overnight (12 h) to remove residual solvent. Finally, the solid dispersion was hand milled and passed through a 500 μm mesh to get a particle size distribution suitable for direct compression into tablets. All solid dispersions were amorphous (verified by differential scanning calorimetry, DSC, and X-ray diffraction, XRD, experiments, not shown here).

2.2.2. Spray drying and fluidized spray drying

The feeds for formulations 1, 2, 4, 6, 7, 10 and 11 were prepared by first dissolving the drug substance in a mixture of ethanol and acetone (50:50). Subsequently, the polymer was added and dispersed (and allowed to for at least 1 h), resulting in a solvent/polymer ratio of 4:1 (formulations 1 and 2), 5:1 (formulation 4) and 9:1 (formulations 6, 7, 10 and 11). The feeds for formulations 8 and 9 were prepared by first dissolving the drug substance in a mixture of ethanol, acetone and water (40:40:20). Subsequently, the polymer was dissolved in the drug substance containing solution resulting in a solution with a solvent/polymer ratio of 9:1.

The feeds were atomized in a spray dryer (Niro IFD-0.8, SD and FSD modus) with a two-fluid nozzle (Schlick Modell 0/2). In the spray drying (SD) mode, the atomized feeds were dried by a nitrogen gas stream in the drying tower. The particles/granules were separated by a cyclone and could be compressed into tablets without further processing. In the fluidized spray drying (FSD) mode, the atomized suspensions and solutions were just partly dried by the nitrogen gas stream and then completely dried in the fluid bed attached to the tower. The product was taken out by a sluice and compressed into tablets without further processing. All solid dispersions were amorphous (verified by DSC and XRD experiments, not shown here).

2.2.3. Preparation of compacts

Powder compacts for the wetting studies were produced by pressing 120 mg of powder for 1 min in a manually operated hydraulic press (Spectac, England). The operating pressure used was 74 MPa. The tablets were stored at room temperature in a desiccator before use.

2.2.4. X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS), also known as electron spectroscopy for chemical analysis (ESCA), was used to probe the elemental composition of the powder surfaces with an analysis depth of less than 100 Å. The ESCA measurements were performed with an AXIS HS photoelectron spectrometer (Kratos Analytical, UK). The instrument uses a monochromatic Al Kα X-ray source. The pressure in the vacuum chamber during analysis was less than $10^{-}7$ torr. In the present investigation, a take-off angle of the photoelectrons perpendicular to the sample holder was used throughout. The area analyzed consisted of a region ≈1 mm^2. Three measurements were made for each sample, and the standard deviation was typically 0.3–1.0 atom% (average 0.4 atom%). The data for the atomic surface composition were converted into molecular surface composition under certain assumptions. Assuming that all molecular species at the surface are present in "patches" with a depth of at least the depth of analysis (≈5 nm for these powders), the surface can be regarded as a linear combination of the different molecular species. By analyzing the pure components, in addition to the samples, one can estimate the relative surface coverage of the different molecular species by solving a system of linear equations; using the least squares method to allow for over-determined systems (as described in detail by Faldt et al. [22]),

$$C \cdot \gamma = c \Rightarrow \gamma = (C^T C)^{-1} C^T c \quad (2)$$

where C is a matrix containing the elemental compositions of the molecular species (atom%), c is the vector containing the elemental surface composition (atom%), and γ is the surface coverage of the different molecular species (area%). The result is the relative surface composition of the sample, with a typical standard deviation of approximately 2% units.

2.2.5. Contact angle

The contact angle measurements on the powder compacts were performed on a Dynamic Absorption Tester (DAT Fibro 1122, Fibro Systems AB), with a timing accuracy of 1 ms. The liquid is contained in a syringe from which a predefined volume in pumped and impacted onto the substrate, followed by image capture and analysis, giving parameters such as drop volume, base diameter and contact angle as a function of time. The wettability of the compact is assessed through an evaluation of the equilibrium contact angle. In an attempt to decouple the spreading and absorption processes and their effects on the contact angle evolution, and "replace" the surface with an ideal nonporous substrate, the equilibrium contact angle of the compacts was determined by first identifying the stage where the drop diameter remains constant and the contact angle decreases steadily with time. The contact angle evolution was then fitted with a linear function in this region. The value for the extrapolated linear function at $t = 0$ was taken to mimic the value of a contact angle that would have been observed if the substrate would not have been porous, and spreading to the equilibrium value had occurred instantaneously on contact with the substrate without pinning due to surface roughness or chemical heterogeneity effects. At least two measurements per sample were performed to ensure reproducibility. All the measurements were performed at 23.0 ± 0.1 °C and RH 45%.

2.2.6. Scanning electron microscopy (SEM)

An XL30 ESEM (Philips) scanning electron microscope was employed in high vacuum mode for characterization of the powder structure. Using a secondary electron detector SEM images with contrast primarily from sample topography were obtained. Before analysis, the samples were gold coated (180 s, 40 mA) using a Balzers SCD050 coater.

3. Results and discussion

Two different solid dispersion preparation techniques (spray drying and roto-evaporation) have been used and compared in this

paper with respect to their effects on drug encapsulation and wetting properties. We introduce analytical methods which allow quantification of the amount of drug on the powder surface and study its impact on the powder wettability by determining contact angles.

3.1. X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS) was used to quantify the amount of drug on the powder surfaces of twelve different solid dispersions (see Table 2). The results for the relative surface composition of the component materials, together with theoretical values, are shown in Table 3. When comparing theoretical and experimental XPS data, we find that the carbon content is consistently higher in the measured values compared to the theoretical value. This is usually attributed to adventitious carbon, i.e., contaminants adsorbed on the powder surface from the surroundings. The oxygen/nitrogen ratio for PVP and drug N is close to the theoretical ratio, and for drug A this ratio is slightly reduced. In this case, orientation effect of the molecule at the surface may play a role as the signal intensity decreases exponentially with the distance from the surface. The relative surface compositions of the solid dispersions are shown in Table 4.

In order to convert the data from atomic surface composition into molecular surface composition, we assumed that the ratio of elements found in the solid dispersions was a linear combination of the ratio of the elements present in the component material (as described in Section 2). The results are shown as "drug concentration on surface" in Table 2. The surface composition data were analyzed with a view to find a relationship between formulation and processing on one hand and surface composition on the other. The bulk concentration of drug (measured in weight%) can be related to the surface concentration (calculated as surface coverage, area%) via the density. Since the material density of the carriers and the drugs is very similar, composition in area% corresponds to composition in weight%.

The variation in encapsulation efficiency, expressed as the surface excess of drug (with values below 1 indicating drug encapsulation in the matrix to some degree), is illustrated in Fig. 1. The same excipient can give rise to both high and low drug surface coverages, depending on the preparation method. A general trend is that drug N is present at the powder surface to a higher extent than drug A, which is consistent with a higher tendency of the more hydrophobic drug to accumulate at the air/liquid interface during the drying process. One can also observe that this migration process is dependent on the carrier. As an example, the presence of PVP as an excipient increased the surface concentration of drug N when combined with the spray drying method, compared to HPMC. This increase is not observed for PVP and drug A. This might be related to the physical–chemical properties (e.g., hydrophilicity) of the polymer which exhibits low surface activity and shows a relatively lower tendency to migrate

Table 3
Atomic concentrations (%) determined by ESCA and theoretical values for the excipients used for preparing the solid dispersions

	Atomic concentration				
Substance	C 1 s	O 1 s	N 1 s	F 1 s	Cl 2p
PVP	76.8 ± 0.7	11.3 ± 0.4	11.9 ± 0.3	–	–
Theory	*75.0*	*12.5*	*12.5*		
HPMC	65.4 ± 0.3	34.6 ± 0.3	–	–	–
Theory	[a]				
HP 50[b]	65.5 ± 0.3	33.0 ± 0.4		–	
Theory	[a]				
Drug A	78.3 ± 0.1	18.2 ± 0.2	2.1 ± 0.2	–	1.4 ± 0.1
Theory	*76.8*	*19.6*	*1.8*		*1.8*
Drug N	75.1	4.0	6.2	12.4	2.4
Theory	*72.1*	*4.7*	*7.0*	*14.0*	*2.3*
Poloxamer	71.9	28.1	–	–	–
Theory	66.6[a]	33.4			

Note: Mean value ± standard deviation.
$n = 3$ for all samples except for drug N and poloxamer where $n = 1$ due to sample degradation caused by the laser beam (seen by systematic changes in atomic composition).
[a] The theoretical values for HPMC and HP50 are not calculated because only the approximate substitution grades are known. The same is true for the polaxamer. The values given are based on approximate numbers which can explain the deviation from the experimental values.
[b] This sample had a relative % atomic concentration of Si (1.5 ± 0.1), most certainly originating from silicon oil used in the preparation process.

Table 4
Atomic concentrations (%) determined by ESCA for formulation 1–12 (see Table 2)

	Atomic concentration				
Formulation	C 1 s	O 1 s	N 1 s	F 1 s	Cl 2p
1	67.8 ± 0.2	25.8 ± 0.4	1.70 ± 0.2	4.3 ± 0.3	0.5 ± 0.1
2	75.6 ± 0.5	8.0 ± 0.1	9.6 ± 0.6	6.1 ± 0.1	0.7 ± 0.1
3	66.0 ± 0.3	29.6 ± 0.4	1.2 ± 0.3	2.9 ± 0.1	0.4 ± 0.0
4	76.4 ± 0.5	13.3 ± 0.1	9.7 ± 0.5	–	0.6 ± 0.1
5	66.6 ± 0.7	33.0 ± 0.7	–	–	0.4 ± 0.0
6	66.9 ± 0.6	33.1 ± 0.6	–	–	–
7	72.4 ± 0.4	25.5 ± 0.3	1.2 ± 0.2	–	–
8	67.9 ± 0.5	31.8 ± 0.4	0.3 ± 0.2	–	–
9	72.1 ± 0.3	26.0 ± 0.2	1.1 ± 0.3	–	0.9 ± 0.1
10	66.5 ± 0.4	33.6 ± 0.4	–	–	–
11	73.5 ± 0.4	24.1 ± 0.4	1.3 ± 0.1	–	1.1 ± 0.1
12	67.4 ± 0.9	32.0 ± 0.9	–	–	0.6 ± 0.1

Note: Mean value ± standard deviation ($n = 3$).

Table 2
Solid dispersions containing drug N and drug A prepared by roto-evaporation (RO), spray drying (SD) and fluidized spray drying (FSD)

Formulation	Drug	Drug conc. in bulk[b]	Carrier	Drying technology	Drug conc. at surface[b]	Surface excess of drug[a]	θ (deg)
1	N	20%	HPMC	SD	30%	1.5	39
2	N	20%	PVP	SD	47%	2.4	44
3	N	20%	HPMC	RO	16%	0.80	ND
4	A	20%	PVP	SD	25%	1.3	48
5	A	20%	HPMC	RO	9%	0.45	35
6	A	10%	HP 50	FSD	3%	0.30	ND[c]
7	A	50%	HP 50	FSD	52%	1.0	58
8	A	10%	HPMC	FSD	20%	2.0	80
9	A	50%	HPMC	FSD	54%	1.1	72
10	A	10%	HPMC swollen	FSD	9%	0.9	56
11	A	50%	HPMC swollen	FSD	65%	1.3	80
12	A	20%	HPMC/poloxamer (10%)	RO	13% drug % poloxamer	0.65	34

[a] Calculated as surface coverage/bulk concentration.
[b] Drug concentration in bulk (weight%), drug conc. at surface (atomic%).
[c] Not determined due to too rapid drop adsorption.

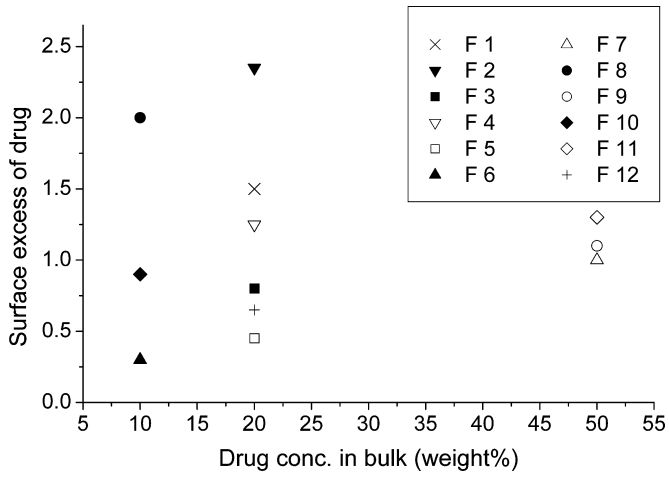

Fig. 1. The surface excess of drug in relation to the bulk concentration in formulations 1–12 (F1–F12).

to the air/liquid interface when competing with drug N than with drug A during the drying process. Further, the swollen HPMC (prepared from suspensions) encapsulates the drug more efficiently than does the dissolved HPMC (prepared from solutions), although the effect of the two different solvent systems must be considered as well. In the latter case, water is added to the system which significantly increases the surface tension of the liquid phase and also influences the drying kinetics.

Three other trends were found, involving roto-evaporation and spray drying as processing techniques and HP50 as excipient. Evidently, HP50 as an excipient provided rather good encapsulation of the drug. This is illustrated by comparing formulations 6 and 8, where, by using the same preparation technology but different carriers the drug surface coverage is seven times lower in the case of HP50 compared to HPMC, indicating a much better encapsulation capacity for HP50. This may be due to the hydrophobic carrier of this latter excipient. The spray drying methods led, in all cases, to an enrichment of the drug on the surface, although the level varies considerably with the choice of excipient. In contrast, the roto-evaporation technique consistently produced fairly well encapsulated drug, regardless of excipient and drug used. This slow drying technique seems to promote drug encapsulation, compared to fast preparation methods where process kinetics are assumed to be very fast, such as spray drying and fluidized spray drying. These results are in line with earlier experiences (results not shown), which have shown strong indications that solid dispersion powders prepared by the slow methods show improved bioavailability compared to products prepared by the fast methods. It is not clear how the encapsulation in roto-evaporation occurs, as a large solid mass of solid dispersion is obtained which is further processed by milling. In theory, this would result in a surface composition close to the bulk composition, although this was not the case here.

In formulation 12, 10% of a surface-active agent (Poloxamer F68) was included with the aim to improve the wetting properties. The presence of poloxamer slightly increases the surface concentration of drug (F5 compared to F12). This may depend on a higher affinity of the drug for the interface or improved transport of drug to the interface during drying due to drug–surfactant interactions. However, the surface coverage of surfactant was less than the bulk concentration, showing that the surfactant did not adsorb to the gas/liquid interface.

This study indicates that to achieve a good drug encapsulation, the combination of excipient with emphasis on the physical properties and processing technique must be selected for the drug in question.

3.2. Contact angle

In order to correlate the surface drug concentration to wettability, a series of contact angle measurements were performed using the observation of sessile drop relaxation. Since the measurements on uncompacted powder showed poor reproducibility due to the rough surface and high porosity, the wetting properties of the powders were obtained by measuring the dynamic contact angle of minimally compressed compacts of the powders. Possible complications that can arise as a result of pressing include changes in the chemical composition of the powders [21] and effects on drop absorption and spreading, which vary due to the surface roughness and pore structure [23]. In order to ensure that such effects did not have an overbearing influence on the wetting measurements, we compared the surface chemical composition of the powder and tablets of formulations 2 and 3 (Fig. 2). As these initial investigations showed that the surface composition of the compressed powders was very similar to that of the original powder, tablets could be used to represent the powders. The effect of tablet structure on the wetting process was investigated by studying the dynamic contact angle evolution of water on tablets of a placebo powder (HPMC) which had been pressed at different set pressures (Fig. 3A). The results indicate that the effect of tabletting pressure and consequently tablet roughness and pore structure is minimal

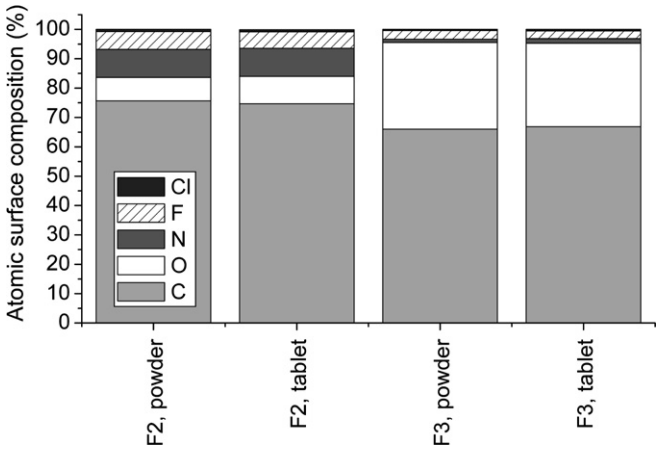

Fig. 2. Comparison of atomic surface composition of powder and pressed tablets for formulations 2 and 3 (F2 and F3). Average values from three measurements.

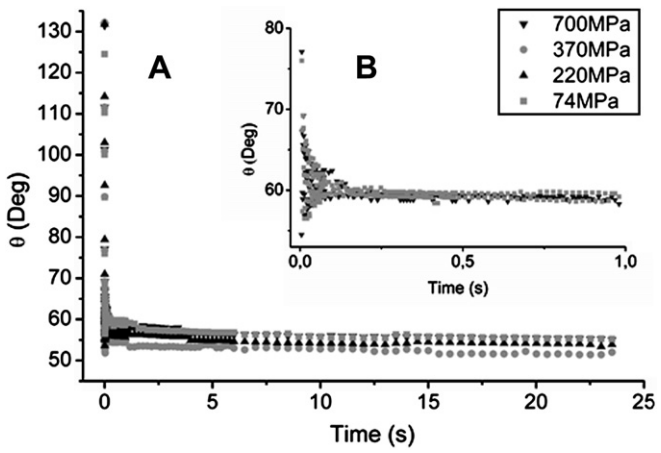

Fig. 3. (A) Dynamic contact angle measurements on tablets of spray-dried HPMC (placebo), produced with compaction pressures ranging from 74 to 700 MPa. (B) Enlargement of the initial second of the contact angle experiments for the highest and the lowest tabletting pressure.

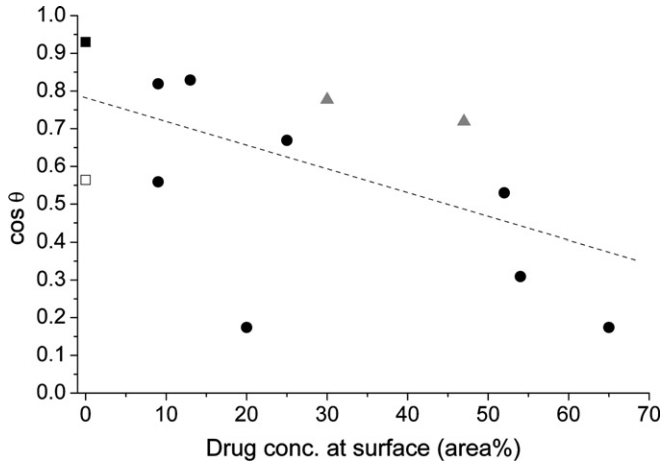

Fig. 4. Relationship between contact angle and drug surface concentration for formulations containing drug N ▲ drug A ●. The contact angles for pure HPMC and PVP are represented as □ and ■, respectively. A linear fit for the solid dispersions is shown as a dashed line, intended as a guide for the eye, to indicate the relationship between the contact angle and the surface composition.

within the range studied. Fig. 3B, showing an enlargement of the initial critical second of the experiments on tablets prepared by the lowest and the highest tabletting pressure, illustrates the controlled measurement procedure using a high-time resolution. In the following experiments, the lowest pressure setting was used to minimize any impact of the pressing on the results, and to ensure that the most open pore structure possible was obtained so that capillary effects on liquid absorption interfere as little as possible with the contact angle determination. The influence on the physical surface structure (roughness, pore size distribution) remains to be determined, but analyzing wetting properties through contact angle determinations on powder compacts appears to give the relevant data. This procedure was followed for all twelve solid dispersions and the results are presented in Table 2.

3.3. Relationships between surface composition and contact angle

As can be seen in Table 2, powders with HPMC as excipient display contact angles from 35° to 80°, indicating that the drug surface coverage indeed has a strong influence on the contact angle. For PVP, on the other hand, the influence of the surface composi-

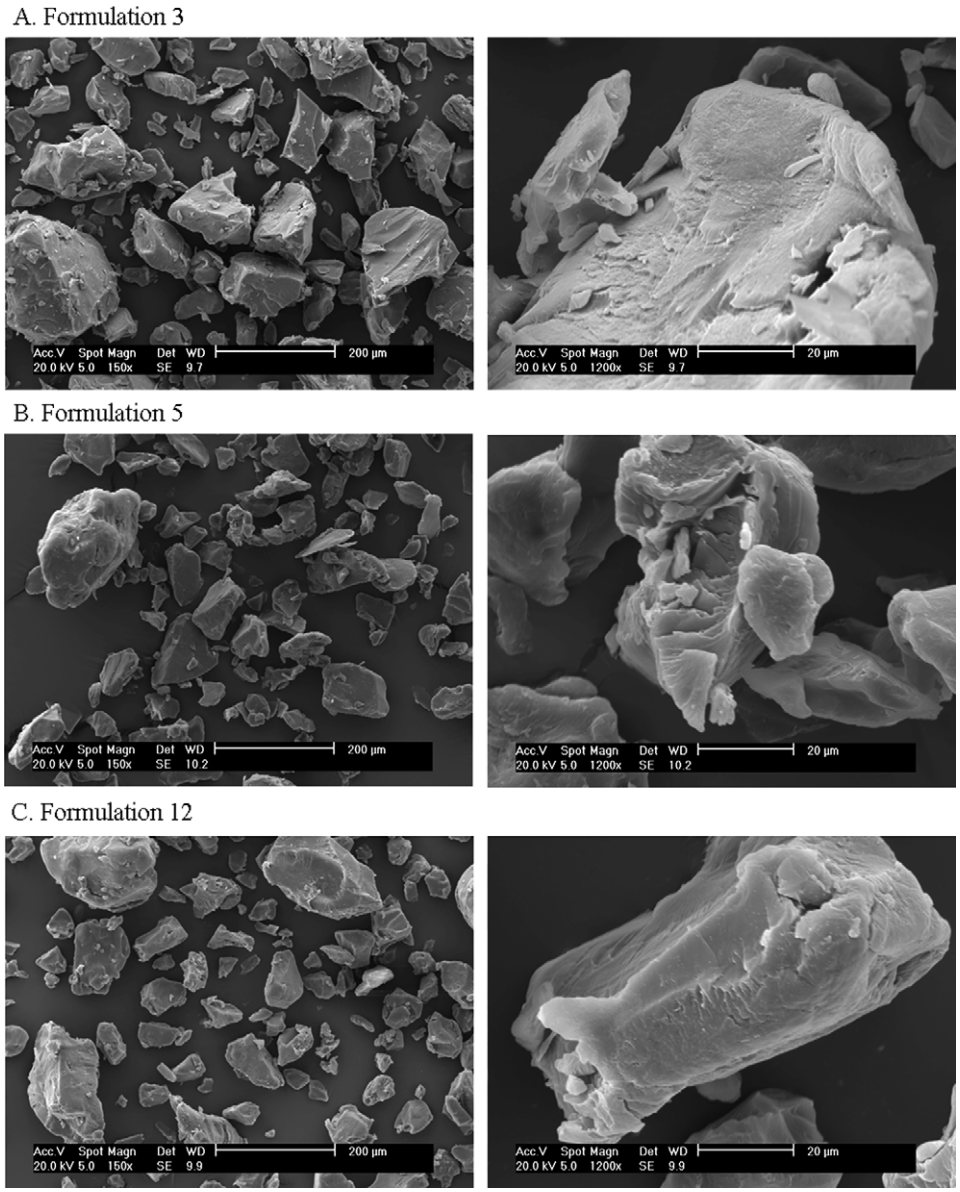

Fig. 5. Scanning electron microscopy images of roto-evaporated samples (formulation 3, 5 and 12). Two magnifications are shown for each sample, 150×and 1200×.

tion on the contact angle is not observed, the contact angle is roughly constant (44–48°) with respect to drug coverage (25–47%). Contact angles of around 30° have been observed for solid dispersions with the same drug content and PVP as excipient, but prepared by a solvent evaporation technique (roto-evaporation) [9], indicating the influence of the drying kinetics in combination with the selected carrier on the powder surface properties.

The fact that formulation 3 rapidly absorbed the entire water drop, together with the low contact angles for formulations 5 and 12, indicates a possible link between the roto-evaporation production method and low water contact angles. The addition of surfactant in formulation 12 did not change the contact angle, probably due to that the surfactant did not adsorb efficiently to the gas/liquid interface as discussed above.

The relationship between surface composition and contact angle of water is shown for the solid dispersions and placebo HPMC and PVP in Fig. 4. By plotting $\cos\theta$ versus surface composition a general trend is observed for increasing contact angles with increasing amounts of hydrophobic drug on the particle surface, although there is a significant scatter around this trend. This scatter is not unexpected as both the drug surface coverage and the properties of the excipients can be anticipated to influence the wetting properties. Because of the toxicity of drug A and drug N, we have chosen not to perform any experiments on the pure drugs. Both the drugs are very hydrophobic (see Table 1). This gives an indication of high contact angles (low $\cos\theta$). The results of the study indicated that the combination of XPS and contact angle measurements give useful information with respect to the wetting properties of solid dispersions.

3.4. Scanning electron microscopy

Further parameters that can influence the spreading rate and contact angle are powder particle size and pore size in tablets. The morphological differences between roto-evaporated and spray-dried powder are illustrated by scanning electron microscopy (SEM) images as shown in Figs. 5 and 6, respectively. It is clear that morphological differences are seen between the methods. However, the differences due to the choice of drug and excipient are small. Solid dispersions prepared by the roto-evaporation

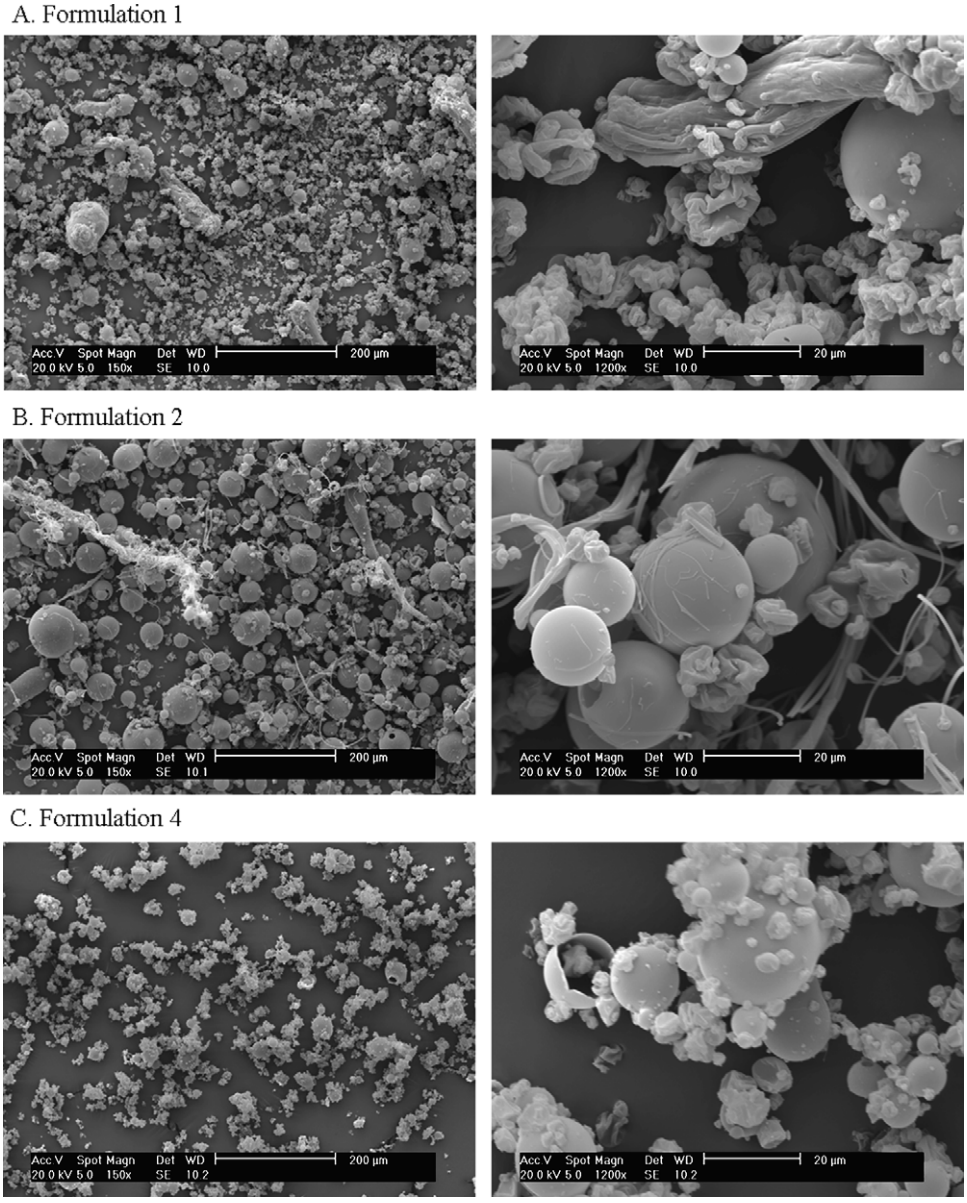

Fig. 6. Scanning electron microscopy images of spray-dried samples (formulation 1, 2 and 4). Two magnifications are shown for each sample, 150× and 1200×.

technique exhibit dense and compact structures with particles (some over 100 μm) having an irregular form and sharp edges. The initially obtained material from this processing technique is milled to obtain the particulate like material. Formulations 1, 2 and 4 in Fig. 6 show the typical morphological features of spray-dried materials as they are fine particles with smooth surfaces. Spherical particles are observed, some larger than 20 μm in size, together with a fine material.

As the morphological differences due to the choice of drug and excipient are less, it indicates that the differences in contact angle are primarily affected by the chemical surface composition. As the contact angles are measured on compressed tablets, the particle size does probably does not have the same influence as it would have had if measured on powder. The possible link between the roto-evaporation production method and low water contact angles mentioned above may not only be due to the surface composition, but also to be the particle size. Roto-evaporated particles are relatively larger than spray-dried, which may lead to a larger pore size and thereby an increased water penetration rate. This might affect the wetting as well as the dissolution.

4. Concluding remarks

In this paper, we have introduced analytical methods which enable quantification of the surface composition of solid dispersion powders and subsequent measurements of the contact angle. We have shown that a relationship exists between the amount of drug on the surface and its contact angle. The amount of drug which accumulates during the preparation process seems to depend on the excipient choice and processing method, in a manner that is not easy to predict. Using preparation techniques where process kinetics play a dominant role, the carrier properties seem to play a more prominent role compared to the techniques based on slow drying. In order to understand physical changes in the bulk as well as at the powder surface of a two-component system during powder dehydration, the specific phase diagrams of the two component systems (carrier and drug) have to be evaluated in order to follow or predict physical structural changes such as phase separation. However, a higher amount of hydrophobic drug at the surface is expected to influence the wetting negatively, and thus dissolution can be delayed.

From a structural point of view, we have established a relationship between process and formulation parameter with the surface properties of solid dispersions powders. In a second series of experiments, we plan to study the impact of surface properties on carrier swelling, drug diffusion and dissolution of solid dispersion tablets. A ^{1}H NMR microimaging method [24], described earlier by the authors, will be used for those studies. The combination of these analytical techniques is believed to give a better picture of the structural properties of solid dispersions and contribute to a better understanding of the release mechanism of this type of drug delivery forms.

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