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Effect of crystal habit on the dissolution behaviour of simvastatin crystals and its relationship to crystallization solvent properties

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Simvastatin crystals, having same crystal structure but different types of habits and hence different intrinsic dissolution rate, were prepared by recrystallization from solvents selected according to their polarity index. Scanning electron microscopy, laser diffraction, image analysis, X-ray powder diffractometry, Fourier transform infrared spectroscopy and differential scanning calorimetry were used to investigate the physicochemical characteristics of the prepared crystals. The isolated crystals exhibited different crystal habits but possessed the same internal crystal structure. In this study the comparative intrinsic dissolution behaviour of the simvastatin crystals with different types of habits was studied and explained by surface energy and correlated to different solvent systems that were used for crystallization. In our work we diminished the influence of all other physical parameters that could influence the dissolution rate, e.g. particle size, specific surface area and polymorphism in order to focus the study onto the impact of crystal shape itself on the dissolution rate of simvastatin crystals. Rod shaped crystals isolated from more hydrophilic solvent mixture dissolved faster than plate-like crystals obtained from solvent mixture with lower polarity index. We correlated this fact to the different growth rate of the individual faces which resulted in different relative size of the individual crystal faces exposed to the dissolution medium as well as the chemical nature of those faces which in turn influenced the wettability and subsequent dissolution of the active pharmaceutical ingredient.

1. Introduction

The increasing prevalence of poorly soluble active pharmaceutical ingredients requires a thorough research of the parameters influencing the pharmacokinetic parameters of the chosen active pharmaceutical ingredient when developing a new pharmaceutical product; particularly for active ingredients delivered by the oral route of administration.

There are numerous ways described in the literature by which one can enhance the bioavailability of active ingredients expressing low aqueous solubility. The success of these approaches is not always guaranteed since it is dependent on the physical and chemical nature of the molecules being formulated.

These approaches include particle size reduction techniques such as micronization (Fu et al. 2015; Han et al. 2011) or nanomilling (Sarnes et al. 2013), self-dispersing and self-emulsifying formulations (Čerpnjak et al. 2015; Pouton 1997), solid solutions and dispersions (Leuner 2000), ionic inclusion and lipid-based complexation (Serajuddin 1999), formation of salts, polymorph screening, cocrystals (Sugandha et.al 2014) and formation of prodrugs (Stegemann et al. 2007). Crystal engineering (Blagden et al. 2007; Yadav et al. 2009; Derle et al. 2010) is one of the possibilities which offer a number of routes for the solubility and/or dissolution rate improvement, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. This article covers the concept and theory of crystal engineering and discusses the relations between polarity of the crystallization solvents, crystal habit and the intrinsic dissolution rate of the active ingredient isolated from such media.

Various authors (Chow 1995; Keraliya et al. 2010; Khan and Jiabi 1998; Stegemann et al. 2007) have proven that the changes in the intrinsic dissolution rate of different active ingredients could be linked to crystal habit and crystal imperfections. Most authors have described the variability of crystal habits as a result of different internal structure of the isolated crystals. In our present work research was focused on simvastatin, a model poorly water soluble active pharmaceutical ingredient, prone to exhibit different crystal habits without changing its internal structure (same polymorphic form). The crystal habit in terms of morphology significantly influences particle orientation, thus modifies the flowability, packing, compaction, syringability, suspension stability, and dissolution characteristics of active ingredient in the form of powder (Maghsoodi 2015).

In order to elucidate the influence of crystal habit of simvastatin crystals on the dissolution rate, wettability determination of the isolated crystals was performed and correlated to the crystallization solvent properties.

2. Investigations, results and discussion

2.1. X-Ray powder diffraction

To obtain information on the physicochemical characteristics of the prepared crystals, X-ray powder diffraction measurements were conducted. As it is known form the literature, simvastatin does not exhibit polymorphism above room temperature (Hušak et al. 2010). The crystal structure of simvastatin is known and was characterized by J. Čejka et.al. (2003).

As can be seen from the recorded X-ray powder diffractograms (Fig.1), both recrystallized samples have the same crystal structure and degree of crystallinity which is also comparable to the starting material, i.e. "untreated simvastatin". These results prove that recrystallization procedure does not induce any polymorphic changes of the isolated product.

Since the dissolution experiments and drop shape analysis were performed on compressed samples, we have also confirmed that the physical state in terms of crystal form and degree of crystallinity did not change during compression. Solid state properties of the particles after maximum compression force (2.5 T for contact

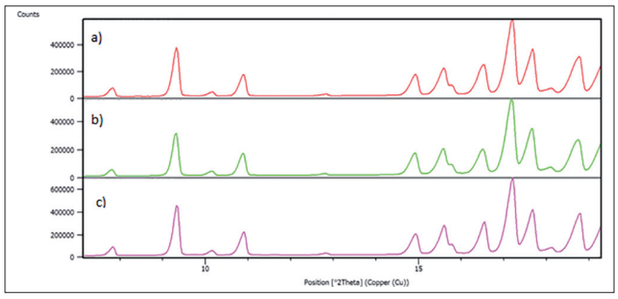


Fig. 1: X-ray powder diffraction patterns of isolated crystals: a) Untreated material, b) SAMPLE 1, crystals isolated from hydrophilic solvent mixture, c) SAMPLE 2, crystals isolated from hydrophobic solvent mixture

angle measurement) did not change, so the observed changes in the dissolution rate and surface properties are not attributed to amorphisation induced by mechanical stress.
The same crystal structure of the untreated simvastatin and both isolated samples was also confirmed by comparative analysis performed by Fourier Transform Infra-red (FT-IR) spectroscopy (data not shown).

2.2. Thermal analysis

2.2.1. Differential scanning calorimetry (DSC)

DSC measurements demonstrate only slight differences in the melting behaviour of the crystalline samples (melting peak between 139-140 °C), Fig. 2.
The melting temperature and the enthalpy of the sample crystallized form hydrophilic solvent mixture are higher than those of the sample crystallized from more hydrophobic solvent mixture (Table 1). The crystals isolated from more hydrophobic solvents melt at lower temperature. We have not attributed this fact to the residual solvents detected in the samples and confirmed with consequent TG-MS coupled analysis. An additional experiment was performed in order to confirm this thesis. Thermal behaviour of the crystals isolated from hydrophobic solvent mixture and additionally dried (SAMPLE 2-DRIED) was determined. The residual heptane content was 0,7 %. Melting peak and enthalpy of this sample were higher in comparison to the initial sample (SAMPLE-2) (Table 1). Different content of residual heptane could have influenced the intrinsic dissolution rate and was taken into account when interpreting the intrinsic dissolution data (see section 3.4).

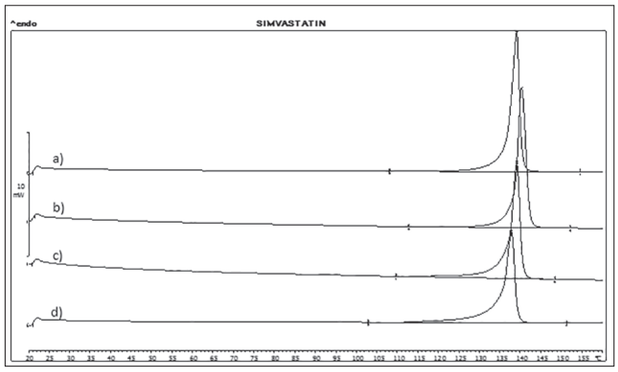


Fig. 2: Thermal behaviour of the isolated simvastatin crystals: a) untreated material; b) SAMPLE 1, crystals isolated from hydrophilic solvent mixture; c) SAMPLE 2-DRIED, crystals isolated from hydrophobic solvent mixture and additionally dried; d) SAMPLE 2, crystals isolated from hydrophobic solvent mixture

2.2.2. Thermogravimetry (TGA) coupled with Mass Spectrometry (MS) detection

Samples isolated form hydrophobic solvent mixture had higher values of residual heptane on the other hand in the samples crystallized from hydrophilic solvent mixture and in the untreated material low concentrations of residual solvents were detected (Table 1).
Results from IR spectroscopy, X-ray powder diffraction analysis and DSC analysis taken together show that the polymorphic form was not altered during recrystallization of simvastatin under various conditions, all three samples exhibit the same polymorphic form, which is unchanged in respect to untreated material for both recrystallization procedures.

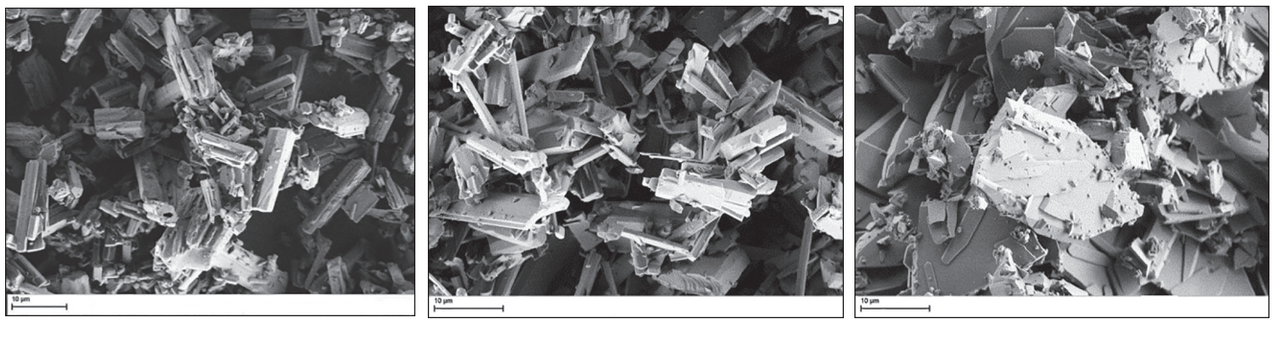
2.3 Morphology of the crystals

Figure 3 shows the scanning electron micrographs (SEM) of untreated and recrystallized simvastatin crystals isolated from different solvents. It can be seen that the crystals of untreated simvastatin have a rod-like morphology (Fig. 3a). Similar morphology was observed also for crystals isolated form hydro-

Table 1: Thermal values

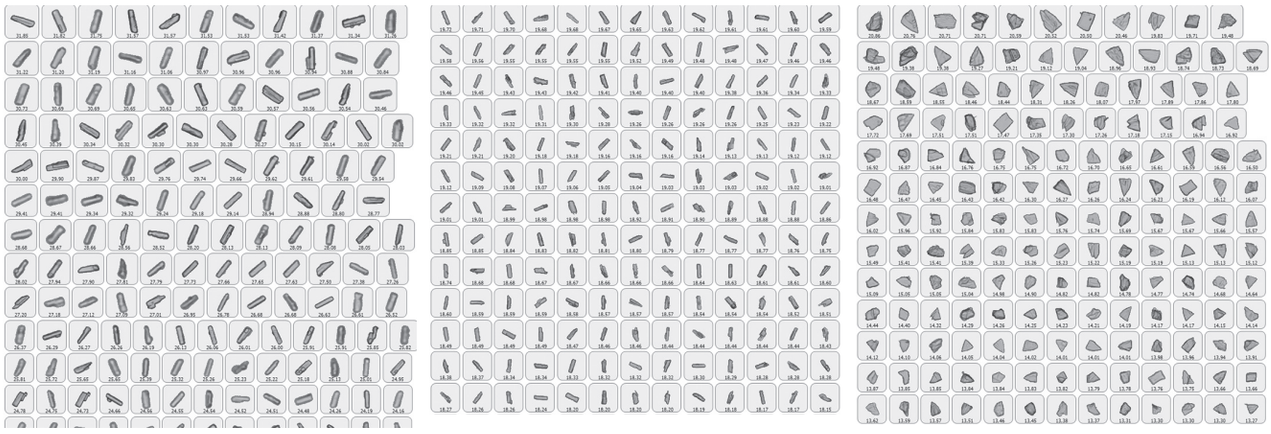
	*Tmelt *(°C)*	*Tmax (°C)*	*ΔHmelt (J/g)*	*LOM (w/w%)*	*MS detected solvent***
Untreated	136,47	139,17	63,54	0,2	Isopropyl acetate
Sample 1	138,37	140,33	67,13	0,1	Acetone
Sample 2-dried	136,84	139,17	62,93	0,7	Heptane
Sample 2	135,13	137,83	60,42	1,1	Heptane

** T melt is determined as the extrapolated value of the T_{onset}; **detected solvent released from samples during thermogravimetric analysis coupled with mass spectrometry; LOM= Loss of mass during TGA*



a) **b)** **c)**

Fig. 3: Scanning electron pictures of isolated simvastatin crystals: a) Untreated material, b) SAMPLE 1, crystals isolated from hydrophilic solvent mixture, c) SAMPLE 2-dried, crystals isolated from hydrophobic solvent mixture



a) b) c)

Fig. 4: Microscopic pictures of a part of the particles on which Image analysis was performed: a) Untreated material, b) SAMPLE 1, crystals isolated from hydrophilic solvent mixture, c) SAMPLE 2-dried, crystals isolated from hydrophobic solvent mixture

Table 2: Single crystal and bulk physico-chemical parameters

Mean values	Width	Length	AR	CED	Intensity	D10	D50	D90	D[4,3]	SSA	CA
	Image analysis – number distribution					*Laser diffraction – volume distribution*					
Untreated	8,1	26,0	0,320	14,4	142	1,6	7,4	24,8	10,8	2,3 ± 0,01	44±2
Sample 1	15,5	43,0	0,365	26,0	143	5,6	16,2	37,6	19,5	2,0 ± 0,01	52±2
Sample 2	10,1	15,7	0,670	11,7	156	3,5	15,4	47,1	21,1	2,1 ± 0,02	61±3

AR = Aspect ratio, SSA = Specific surface area, CED = Circular equivalent diameter, CA = Contact angle

philic solvent mixture (Fig. 3b) whereas crystals isolated from hydrophobic solvent mixture are plate-like (Fig. 3c), no morphology change was observed after additional drying of the crystals. Similar conclusions were described also in the case of tolbutamide when studying the influence of crystallization conditions on crystal habit of the formed crystals (*Keraliya et al. 2010*). In order to thoroughly determine the difference in the crystal habit of the isolated crystals we have additionally determined the average length, width and aspect ratio of the isolated crystals (Fig. 4). The results (Table 2) confirmed the above mentioned differences regarding crystal shape. The untreated simvastatin aspect ratio and that of the crystals isolated from hydrophilic solvent mixture were similar and characteristic for elongated shapes such as needles/rods whereas aspect ratio of crystals isolated from more hydrophobic solvent mixture was higher since the crystals had two faces that were of more similar size e.g. a plate like morphology (Table 2).

The analysis of particle size distribution samples using the light scattering method showed minor differences in the particle size distribution but although the method was carefully developed in order to determine the particle size of only the primary particles there could be some error since the method does not distinguish between formed agglomerates and primary particles (Eshel et al. 2004). We additionally analysed the same samples with image analysis to prove that the size factor did not influence the results of IDR analysis which could also happen according to the literature (Larsson 2010). Primary particles were found to be of the same size range. When interpreting and comparing the results of image analysis and laser light scattering method we have to take into account the difference in the third dimension of the particles. Third dimension of primary particles was determined with SEM analysis, which shows that crystals isolated from a hydrophobic solvent mixture are thinner. Third dimension of the particles is taken into account when determining the particle size using laser light scattering method, whereas when performing image analysis with an optical microscope the contribution of the third dimension does not influence the results, but can be seen through the intensity factor, which is defined according to the amount of light transmitted through a particle and is dependent on the particle thickness. Data showed that crystals isolated from a hydrophilic solvent mixture were of somewhat bigger size and exhibited the lowest specific surface area whereas crystals isolated from a more hydrophobic solvent mixture were still smaller in terms of the projected surface area in comparison to crystals isolated from hydrophilic solvent mixture and had a specific surface area similar to the latter. The untreated material had the smallest particle size and hence higher surface area.

The crystal habit is defined during the crystallisation process. Usually growth rate is not the same in all space directions consequently individual crystal faces differ in their size (Mersmann 2001; Myerson 2002). The formation of a new crystalline entity from a solution starts through the nucleation process and is followed by crystal growth which consists of a series of processes by which an atom or a molecule is incorporated onto the surface of a growing phase following desorption of the solute molecule from the growing surface, causing at the end an increase in size (Čejka, et al. 2010).

It is generally believed that the mechanical and other properties of the crystal entity are also connected to the properties of the growing phase and that crystal morphology provides the missing link between growth kinetics and physical properties of the formed particles (Gibbs 1961). It is known (Buckton 1995) that crystal growth is bound by those faces with the slowest growth rate and that close-packed planes frequently grow most slowly, so even when kinetic factors control the crystal habit there is usually a relation between the faces of a crystal and its molecular structure. Consequently the polarity of the solvent (hydrophilic vs. hydrophobic character) will have an impact on the growth rate of the particular crystal face. If the effect of the solvent character is maximized with respect to the other crystallization parameters (like non destructive stirring, supersaturation rate, etc.), crystal habit will considerably depend on the solvent used in crystallisation process (Brown et al. 2010). As described in the literature depending on the solvent used for crystallization, internalization of the functional groups of the solute that are less attracted to the liquid/solvent, takes place. Difference is mainly caused by the hydrogen bond interactions (Buckton 1995).

The mechanism of solvent affecting crystal growth and morphology was explained by Bennema et. al (2008). They proposed that favourable interactions between growing phase and solvent on specific faces lead to reduced interfacial tension, causing a concom-

itant faster surface growth. In contrast, preferential adsorption of the solvent at specific faces can inhibit their growth as removal of bound solvent acts as additional energy barrier for continued growth.

This fact was observed also during our research, namely crystals obtained from a more hydrophobic solvent mixture crystallized as plate-like particles, while crystals obtained from hydrophilic solvent were rod like. The aspect ratio of the formed crystals significantly differed as a consequence of different interaction between growing phase and solvent mixture properties.

We can conclude that polarity of the solvent and the interactions that lead to its preferential adsorption at selected faces of the solute are critical factors in determining the habit of a crystallizing solid as it was already described (Maghsoodi 2015) but was mainly focused and explained in connection to polymorphic transitions or different particle size and specific surface area.

Further we wanted to correlate the properties of different exposed crystal faces to the different dissolution behaviour through explanation of their ability to exhibit hydrophilic interactions with the aqueous dissolution media, since different crystal faces of a material may again exhibit different chemical properties, arising from the inherent crystal chemistry within the lattice and the molecular functional groups exposed at each crystal face (Ginde 2002). Grown crystal faces can vary considerably in their polarity (and therefore relative hydrophobicity) depending on the atoms/functional groups that emerge at the surface. The hydrophilic nature of the bulk samples was determined on the basis of sessile drop analysis.

2.4. Contact angle measurement

Precondition for the dissolution of solids is that the solvent i.e. the dissolution medium can sufficiently wet the surface. The Sessile Drop Technique is a method used for the characterization of solid surface energies and is a useful technique that helps us understand why a solid is more likely to dissolve faster in aqueous media e.g. physiological fluids or bio relevant media in which the dissolution of active substances is determined when developing a new solid dosage product. Water was used for the assessment of wettability of the samples. It can be seen from Table 2 that the water drop formed on compacted samples isolated from more hydrophilic solvent mixture exhibits a lower contact angle in comparison to the contact angle of a sample isolated from a more hydrophobic solvent mixture. The lowest values were nevertheless obtained in case of the untreated simvastatin crystals, which suggests that they are the most wettable when subjected to aqueous media and are therefore prone to have the fastest dissolution rate if no other physical or chemical influences are present e.g. polymorphism, different particle size and/or specific surface area.

Although the measurements were performed on bulk samples (compacted disks) the difference in results obtained from the samples isolated from solvents with different polarity indexes are mostly attributed to the most prominent faces because of the preference orientation of the crystals during preparation of discs. However, the difference in the morphology between both isolated crystal samples was in the ratio between their width and thickness, thus the probability for an individual particle to turn on the same face in case of rod like particles was lower than in case of plate like crystals. We can conclude that the most prominent face of plate like crystals isolated from hydrophobic mixture is of hydrophobic nature whereas in the rod-shaped sample this face is less prominent and thus the sample exhibits more hydrophilic properties.

2.5. Intrinsic dissolution rate

Intrinsic dissolution profiles of simvastatin samples rather than classical dissolution method were determined to additionally exclude the influence of particle size and surface area on the dissolution behaviour.

Taking into account the Noyes–Whitney equation (1) we can explain the effect of solvent mixture properties on the dissolution rate of crystals obtained by crystallization from solvent mixtures of different polarity due to change in number, size, and wettability of crystal faces as a consequence of crystal habit modification (Hörter and Dressman 2001).

$$HR = \frac{dC}{dt} = A * \frac{D}{h} * (Cs - \frac{Cd}{V}) \quad (1)$$

where DR is the dissolution rate, A is the surface area available for dissolution, D is the diffusion coefficient of the active pharmaceutical ingredient, h is the thickness of the boundary layer adjacent to the dissolving surface, Cs is the saturated solubility of the active ingredient, Cd is the amount of active ingredient dissolved at time t and V is the volume of dissolution media.

The size of crystal faces and their individual chemical properties are the ones determining the surface area of the active ingredient available for dissolution and consequently regulate the dissolution rate.

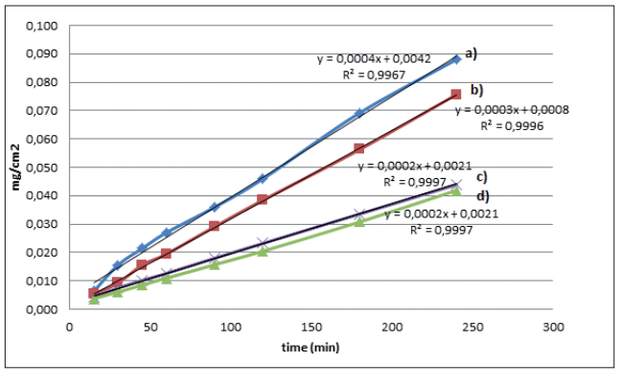


Fig. 5: intrinsic dissolution rate of raw material and crystals isolated from different solvent mixtures: a) untreated material; b) SAMPLE 1, crystals isolated from hydrophilic solvent mixture; c) SAMPLE 2, crystals isolated from hydrophobic solvent mixture; d) SAMPLE 2-DRIED, crystals isolated from hydrophobic solvent mixture and additionally dried

The results of comparative study of intrinsic dissolution rate are shown in Fig. 5. Recrystallization of simvastatin from various solvent mixtures resulted in significantly different intrinsic dissolution rates of the isolated crystals. Crystals obtained from more hydrophobic solvent mixture show the lowest intrinsic dissolution rate in comparison to the untreated simvastatin or the crystals isolated from more hydrophilic solvent mixture (p=0,003). The untreated simvastatin and the sample isolated from hydrophilic solvent mixture do not differ significantly (p=0,489). There is also no significant difference between the samples isolated form hydrophobic solvent mixture with different residual solvent content (p=0,702).

The results are concordant to the facts concluded during research of the surface properties. Since there was no significant difference regarding the specific surface area of both recrystallized samples the data suggest that the crystal face which grow larger in this case is of more hydrophobic nature, hence crystals dissolve slower in comparison to thicker crystals isolated from more hydrophilic solvent mixture. For the untreated material the final treatment is not known, therefore we cannot make the same anology regarding the influence of the used solvents. Particles of the untreated material are similar to those isolated from a more hydrophilic solvent mixture but are somewhat smaller and have higher specific surface area.

Both samples isolated from a more hydrophobic solvent mixture (SAMPLE 2-initial and dried) have similar dissolution rates. Therefore it can be concluded that the residual solvent did not influence the dissolution rate but rather the different crystal habit of samples obtained from a hydrophilic solvent mixture opposed to samples obtained from a hydrophobic solvent mixture by means of exhibition of more or less polar crystal faces and their contribution in the bulk.

Table 3: Properties of used solvents and their mixtures

SM	Composition			BP (°C)	MP (°C)	DC	μ (D)	ST (mN/m)		SAMPLE NAME
	Component	*Formula*	*m/m fraction*					*A**	*B**	(isolated crystals)
1	Water	H_2O	60 %	100	0	80,1	1,85	23,7		
	Acetone	CH_3COCH_3	40 %	56	-95	20,7	2,85	25,2	34,8	Sample 1
2	Ethanol	CH_3CH_2OH	5 %	78	-114	24,5	1,69	22,4		
	n-Heptane	$CH_3(CH_2)_5CH_3$	95 %	98	-91	1,9	0	20,1	19,8	Sample 2
3	i-propyl acetate	$CH_3COOCH(CH_3)_2$	100 %	89	-73	*	*	21,8		Untreated

SM = solvent mixture, BP = boiling point (McConville 2006)*, MP = melting point* (McConville 2006)*,, DC = Dielectric Constant* (McConville 2006)*, μ = dipole moment* (McConville 2006)*, ST = surface tension, A = surface tension of single component at 20 °C, B = surface tension of solvent mixture at 20 °C*
**not found in the literature*

As the influence of surface area in connection to particle size, polymorphism and amorphisation during compaction were excluded, the differences in intrinsic dissolution behaviour are attributed only to the differences in the crystal habit in terms of crystal shape and physicochemical properties of its crystal faces.
Although some differences were observed also in terms of particle size distribution and specific surface area which could also influence the dissolution rate, this was not the case in our study since larger particles with lower surface area dissolved faster than particles with higher surface area and smaller particle size. Moreover, the effect of particle size and specific surface area was diminished by choosing the IDR method for the research instead of performing the analysis on free flowing powder.

2.6. Conclusion

Isolated crystals showed significant changes in shape, wettability and consecutively dissolution rate but exhibited no differences in their internal structure.
Simvastatin crystals isolated from a more hydrophilic solvent mixture e.g acetone/water mixture dissolve faster than those crystallized from solvents with lower polarity such as ethanol/heptane solvent system. The grown simvastatin crystals differ in terms of shape as a consequence of different interactions of the solvent molecules and the solute. Hence, different growth rates of the individual faces reflect as the different crystal habit.
Selection of solvent enabled us to change the size and number of crystal faces exposed to the dissolution medium as well as the nature of those faces without changing the internal structure which in turn influenced the wettability and subsequent dissolution of the active ingredient. In continuation of our work we will focus on the explanation of the observed connection of the crystal habit and the dissolution behaviour on the molecular level on the basis of individual crystal face dissolution analysis.
Crystallization conditions and crystallization solvent have major effects on the crystal habit of simvastatin crystals. The present work proves that not only polymorphic transitions and changes of the physicochemical properties of the active pharmaceutical ingredient in terms of particle size and/or specific surface area can alter the dissolution rate. It is also possible to improve the dissolution rate by changing only the habit of the crystals itself. For optimizing the dissolution rate of the active ingredient by fine tuning of the crystallization process, the crystal habit has to be carefully selected in order to yield optimal physicochemical properties which would enable us to achieve proper in vivo performance of the final dosage form.

4. Experimental

4.1. Materials

Simvastatin (donated by Krka, Novo mesto, Slovenia) was used as a poorly soluble active ingredient. All solvents used, including ethanol (Riedel de Haën, Germany), acetone (Merck, Germany), n-heptane (Merck, Germany) were synthetical grade. The water employed for crystallization and surface characterization was organic-free, distilled water.

4.2. Methods

4.2.1. Characterization of starting material and isolated crystals

X-ray diffraction patterns of simvastatin crystals were obtained using the X-ray diffractometer Panalytical (X`Pert PRO MPD, Netherlands), at 45kV 40mA, over the range of 3 – 50° 2θ, using CuKα radiation wavelength 1,5405 Å.
The FTIR spectra were obtained on a Spectrum 100 FTIR Spectrophotometer (Perkin Elmer, USA). The KBr pellet technique was used to prepare the samples. The spectra were recorded in the spectral region from 4000 to 400 cm^{-1}.
DSC analyses were performed on differential scanning calorimeter DSC 1 (Mettler Toledo, USA). Samples for DSC measurement of about 3 mg were sealed into 40 μL aluminium pans and scanned between 20 °C and 160 °C at a heating rate of 10 K/min in nitrogen atmosphere (40 mL/min).
Thermogravimetric analysis was performed using analyser TGA/DSC 1 (Mettler Toledo, USA). Samples of about 10 mg were sealed into 70 μL aluminium pans and scanned between 20 °C and 200 °C at a heating rate of 10 K/min in nitrogen atmosphere (40 mL/min).
Determination of the crystal habit was performed using a Scanning electron microscope (ULTRA plus, Carl Zeiss, GER).
Particle size and morphological parameters were determined on Morphology G3 Particle Size and Shape Analyser and Mastersizer 2000 (both Malvern, UK).
Specific surface measurements were measured according to 6-point BET method using nitrogen gas as adsorbent on Tristar 3000 (Micromeritics, USA).
Surface tension was determined on Tensiometer Sigma 700 (KSV Instruments) and wettability experiments were performed using a Drop Shape Analysis System – DSA30 (Krüss, GER).
The contact angle of the isolated crystals was measured on the compacted disks, which were compressed with 2,5 bar pressure using an IR press. The drop volume was set to 2 μL and formed at 10 μL/min formation rate. The results were given as an average of 6 consecutive measurements of contact angles on 6 individual compressed disks of each sample (36 measurements/sample).
The Apparent intrinsic dissolution rates were determined with a stationary disk method on Varian VK 7010 (Agilent, USA). A 150 mg of the sample was compressed to form a non-disintegrating compact (8 mm in diameter) using 1 t compression force. The paddle rotation speed was adjusted to 50 rpm/min. Phosphate buffer (pH 6.8) at 37±0,5 °C with 0.1 % of sodium dodecyl sulphate (SDS) was used as the dissolution medium. The concentration of released active ingredient was determined by HPLC e2695 (Waters, USA) on samples of filtered dissolution medium (0.8 μm membrane filters) withdrawn from dissolution vessel at eight preselected time points (15, 30, 45, 60, 90, 120, 180, 240 min).

4.2.2. Crystallization – preparation of simvastatin crystals with different habits

Simvastatin crystals having same crystal structure but different crystal habits were prepared by recrystallization of the untreated simvastatin from solvents exhibiting different polarity and hydrophilicity.
Solvents can be broadly classified into two categories: polar and non-polar. Generally, the dielectric constant of the solvent provides a rough measure of a solvent's polarity. Solvents with a dielectric constant of less than 15 are generally considered to be nonpolar (Brown et al. 2010).
Ethanol, acetone, n-heptane and water were chosen because of their different physico-chemical properties as listed in Table 3. Using those solvent mixtures it was also possible to prepare larger crystals by only altering some of the crystallization process conditions. Untreated simvastatin was obtained by crystallization from isopropyl acetate.

Crystallization from hydrophilic solvent mixture (solvent mixture 1)

Untreated simvastatin (10 g) was dissolved in 30mL of acetone at room temperature. To the clear solution 30 mL of water (antisolvent) was added slowly during 30 min mixing at room temperature. Reaction mixture was stirred with overhead stirrer at 250 RPM. After addition of 17 ml of the antisolvent a two-phase system was formed resulting in emulsion of the oily solute in solvent mixture. After the whole amount of antisolvent was added, formation of the crystals from oily phase was observed resulted in thick suspension. Stirring was increased to 350 RPM. Obtained crystals were isolated by filtration and dried in a desiccator for 24 h and stored in appropriate

airtight container for further analytical evaluation. The process yielded 8.6 g (86 %) of dried simvastatin crystals.

Crystallization from hydrophobic solvent mixture (solvent mixture 2)

Simvastatin (5 g) was dissolved in 13 mL of absolute ethanol at 38 °C. Clear solution was added to cooled (15°C) heptane (65 mL) in reactor equipped with overhead stirrer in 10 min. When droplet contacted the antisolvent, nucleation of particles was observed followed by their dissolution. When the whole amount of simvastatin solution was added, some particles remained undissolved. Hazy solution was heated to 37 °C and concentrated by evaporation of the solvent mixture in nitrogen flow which led to crystallization. Crystallized material was isolated at room temperature and dried in a desiccator for 24 h. Additional 48 h drying in a desiccator was performed on part of the same sample in order to achieve lower residual solvent content. Initial sample and the additionally dried sample were individually stored in appropriate airtight container for further analytical evaluation. The process yielded 4.5 g (90 %) of initially dried simvastatin crystals.

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