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Surface analysis of powder binary mixtures with ATR FTIR spectroscopy

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Abstract

Attenuated Total Reflectance Fourier Transform Infra Red spectroscopy (ATR FTIR) has been used for surface analysis of powder mixtures. The appearance of one component on the surface of the mixture in greater amounts than that expected from the mass or volume ratio was quantified. Coloured mixtures containing methyl orange were analysed. They contained proportions of components from 0% to 100% in steps of 10%. Mixtures of non-sieved powders of methyl orange and Povidone were dark red when containing only 20% of methyl orange, indicating that particles of methyl orange were present on the surface of the mixture in higher amounts than expected from the mass ratios. Mixtures of methyl orange and Mg stearate, on the other hand, were a light colour, showing the presence of more Mg stearate on the surface than expected. Visual observations correlated with semiquantitative surface concentration determination by ATR FTIR spectroscopy using specific peaks of each component. Quantitative determination of components on the surface of the mixture, using the Beer Lambert law, was possible when characteristic peaks for the first component did not overlap with those of the other component. A non-linear correlation between peak height and concentration of a component in a mixture was explained by distribution of the particle size of components. With a small component, the larger number of particles in the same volume allowed them to surround the larger particles of the second component. These conclusions were confirmed by preparing mixtures with non-coloured components (Povidone-Eudragit®, NaCl-Povidone, NaCl-Eudragit®). Results again correlated with the ATR FTIR spectroscopy measurements. It was additionally shown that a small proportion of finer particles can drastically influence the surface of powder mixtures, due to their large contribution to the specific surface area. ATR FTIR is thus demonstrated to be a useful method for studying surfaces of powder mixtures also in terms of process analytical technology (PAT).

Keywords: IR spectroscopy; ATR FTIR; Powder; Binary mixtures

1. Introduction

Infrared (IR) spectroscopy finds wide applications in solving many important problems in pharmacy. It is used for verifying drug identity and purity, in structural investigations, in solving crystalline structures (polymorphs, pseudopolymorphs), in investigating interactions between drugs and excipients and for measurements of concentration (Kalinkova, 1999). Fourier Transform-Near Infrared spectroscopy (FT-NIR) is a basic tool that can be used to help understanding and controlling pharmaceutical processes within Process Analytical Technology (PAT). Also other IR techniques could be helpful in understanding and controlling manufacturing processes (Diffuse Reflectance Fourier Transform-DRIFT-IR or Raman spectroscopy (Pöllänen et al., 2005; Johanson et al., 2005). Attenuated total reflectance (ATR) IR spectroscopy can be applied for solid-state characterization (Compton and Compton, 1993). An advantage of this technique is that it requires very little sample preparation – the sample is simply placed in contact with the ATR crystal. ATR does not sample the bulk of a material, since IR radiation penetrates only a few micrometers or tenths of micrometers, making it an excellent technique for surface studies (Bugay, 2001). Advantages of this system are also a high chemical specificity, which allows the analyses of many different materials, and a relatively high spatial resolution with possibility of accurate quantification (van der Weerd et al., 2004). The system can reach a nominal

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spatial resolution of 13–18 μm without the use of a microscope (Chan and Kazarian, 2003). Also Raman spectroscopy could be used for surface analysis of the samples. With other vibrational spectroscopy techniques, Diffuse Reflectance (DR) and NIR, bulk of the material is analysed or quantified (for example in the mixture of the components or in the pharmaceutical product).

Higuchi et al. (1969) suggested the use of ATR for analyzing polymorphs and ATR has been used for qualitative identification of pharmaceutical solids (Kang et al., 1974). Hartauer and Guillory (1989) reported the quantitative analysis of sulfamethoxazole and trimethoprim in pharmaceutical formulations by circle-cell ATR. ATR FTIR was first applied to the quantification of polymorphs by Salari and Young (1998), and developed for this purpose by using a peak ratio plot based on second derivative spectra (Helmy et al., 2003).

In this study we investigated the application of ATR FTIR spectroscopy to analysis of powder mixture surfaces. Mixing powders is an essential operation in pharmacy. However, lubricants for example, present in the vast majority of tableted products, can lead to undesirable properties, such as decreasing tablet strength and slowing dissolution (Alpar et al., 1996; Jarosz and Parrott, 1984). Both effects are related to the mixing efficiency since, when the lubricant (normally Mg stearate) has coated the powder surface, the interfacial properties of the original materials are replaced by those of the lubricant (Buckton, 1995). Coating drug particles with excipients is sometimes desirable to prevent adhesion and loss of the drug onto vessel and other surfaces.

The process of powder mixing has been described in several ways. A *perfect mixture* is one in which any group of particles, taken from any position within a mixture, will contain the same proportions of each particle as the mixture as a whole. With powders this is virtually unattainable. All that is possible to achieve is the maximum degree of randomness for the mixture, that is, a mixture in which the probability of finding a particle of a given component is the same at all positions in the mixture (Davies, 2001). In the absence of segregation, mixing of micronized particles with larger, carrier particles can cause adsorption of small particles onto larger ones to form an ordered mixture (Twitchell, 2002). In reality, a mix will most probably behave somewhere between the different possibilities described. The final organization of the mixture depends on gravity and surface forces. There have been attempts to utilize spreading coefficient to probe the mixing performance of powders. Solubility parameters (Rowe, 1989) and surface free energy parameters based on wettability were used for this purpose (Ahfat et al., 1997; Barra et al., 1998). The latter authors confirmed that surface energy and particle size play a major role in the organization of a binary powder mixture.

Organization of the mixture is most often observed by scanning electron or optical microscopy. An alternative method is diffuse reflectance spectroscopy, using a chromatometer as an indicator of the organization of powder mixtures (Barra et al., 2000).

We have used ATR FTIR spectroscopy, in combination with visual observation and optical microscopy, to study the organization of powder mixtures. The aim was also to explain the results of ATR FTIR analysis using particle size analysis.

2. Materials and methods

2.1. Materials

Methyl orange (Acros Organics, USA), Povidone F90 (BASF, Germany), Mg stearate (Sigma–Aldrich, Germany), NaCl (obtained from Lex d.o.o., Slovenia), Eudragit® RL100 (Röhm Pharma Polymers, Germany) and stearic acid (Sigma–Aldrich, Germany) were used for powder mixtures preparations. Ethanol (obtained from Pharmachem d.o.o., Slovenia) and ethyl acetate (Sigma–Aldrich, Germany) were used for powders particle size determination.

2.2. Preparation of binary mixtures

Each component was weighed separately to an accuracy of 0.1 mg and mixed with a second component in a Manual Mini Inversina mixer (LAVAL LAB, Canada) for 20 min to prepare a set of mixtures containing from 10 w/w% to 90 w/w% of each component, in steps of 10% or 20%. A 4 g of each mixture was prepared in glass vial with a volume of 10 ml. Sets of mixtures containing methyl orange were prepared using mass proportions of the components. All other sets of mixtures were prepared using volume proportions of the components. Apparent volume after tapping was measured for every mixture component according to European Pharmacopoeia (2005) after 2500 taps. Apparent density of powders was calculated from these measurements and used for calculation of components masses needed for each set of mixtures.

2.3. Attenuated total reflectance (ATR) Fourier transform infrared spectroscopy

A Nicolet Nexus FTIR Spectrometer (Nicolet Instrument Co., Madison, USA) equipped with a DTGS (Deuterated Triglycine Sulphate) detector was employed for all experiments. A diamond ATR accessory (DuraSample IR – Technologies Danbury, USA) was employed for ATR FTIR experiments. Each mixture was sampled 20 times and their IR spectra averaged. The same pressure was used for all measurements. Each spectrum comprises 32 co-added scans measured at a spectral resolution of 4 cm^{-1} in the 4000–600 cm^{-1} range with an aperture of 36. Spectral data were acquired with Omnic E.S.P. software version 5.2 (Nicolet instrument Co.). Baseline and ATR corrections were used for processing the spectra before quantitative analysis.

2.4. Optical microscopy

An optical stereo microscope Olympus SZX12 with digital image capture was used for observing mixtures.

2.5. Particle size analysis

Particle size distributions of the powder samples were determined by laser light scattering (Mastersizer S, Malvern, UK) with a 300RF lens with QS small volume sample dispersion unit for measuring liquid dispersion.

3. Results and discussion

Barra et al. (1998) stated that a simple and important question – what is the organization of a mixture prepared simply from two powders? – is still unanswered. To begin to answer this question we need methods to quantify the proportions of components at the surface of the mixture, since these influence the interfacial interactions. One of the possibilities is visual observation, especially when one of the components is coloured (Ahfat et al., 1997). Methyl orange, as a red coloured component, in combination with white Mg stearate powder, was found to form light red mixtures. Mixtures containing up to 60–70% of Mg stearate remained only lightly coloured. This implies that, if both components of similar particle size, Mg stearate covered agglomerates of the coloured component. A second explanation, however, could be the larger number of small Mg stearate particles in the same volume compared to large methyl orange particles.

In contrast, methyl orange–Povidone mixtures remained dark red up to 90% of Povidone content, showing that more methyl orange occupied the surface area than Povidone. These two examples show that the concentration of each component on the surface deviates from the actual mass concentration. This result can be influenced by different parameters that will be discussed later.

An attempt was made to establish correlations between visual observation and quantitative measurements of the surface composition of mixtures, using ATR FTIR. For this purpose components with appropriate ATR spectra were chosen such that overlapping of specific peaks belonging to the each component, and used for concentration determination, could be neglected. In general ATR spectrum of powders comprehend sharper peaks than for example DR or NIR spectra of the same sample. ATR spectra of all three components forming two coloured series of binary mixtures are shown in Fig. 1. For the first set of mixtures, the peak height in the region 2945–2880 cm^{-1} was used to quantify Mg stearate and in the region 1010–1050 cm^{-1} for methyl orange. For the second set of mixtures, the peak heights for methyl orange and Povidone in the regions 1100–1140 and 1640–1690 cm^{-1} were used, respectively.

The Beer-Lambert law, which states that absorbance increases linearly with concentration, was used for quantitative analysis of mixture surfaces by measuring absorbance peak heights.

It is not always possible to find an absorbance peak for one component at a wavelength at which there is no absorbance by the second component. The contribution of a second component to the absorbance at the peak max of the first component should, however, be as low as possible. For example, in the Mg stearate–methyl orange mixture, the contribution of methyl orange to the Mg stearate peak is approximately 7% and, for the methyl orange peak, the contribution of Mg stearate is approximately 3%. This is one of the reasons why this method must be considered semiquantitative. For the confirmation of used experimentation concept, ATR analysis of every mixture from a series should lead to the same conclusion about the proportion of components on the mixture surface. In the analysis of Mg stearate–methyl orange mixtures, a positive deviation from linearity for Mg stearate is observed and a negative deviation for methyl orange (Fig. 2). Similar deviations are seen for methyl orange and Povidone mixtures (Fig. 3). Correct measures of concentrations of components are required for quantitative conclusions about their distribution on the surface. Theoretically the sum of the two components at the surface mixture should be 100% for every mixture. In practice the calculated values ranged from 90% to 110%, underlining the semiquantitative nature of this type of ATR FTIR analysis.

ATR FTIR analysis results of both coloured series of mixtures correlate with those from visual observation. The results can be explained on the basis of particle size distribution and specific surface area calculated from laser diffraction measurements (Table 1). The average diameter of Mg stearate and methyl orange are 8.3 and 157.8 μm, respectively and the relative specific surface areas (S.S.A.), calculated from particle size analysis, are in accordance.

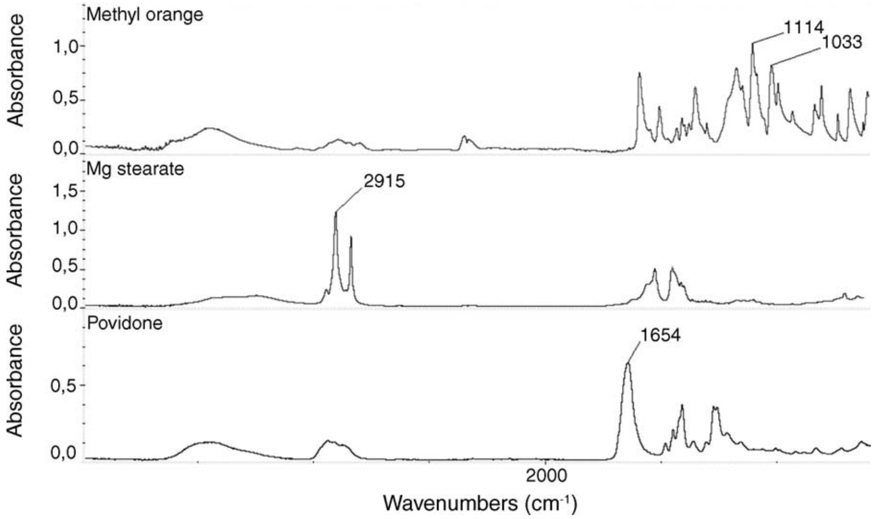

Fig. 1. ATR FTIR spectra of methyl orange, Mg stearate and Povidone showing wavenumbers used for quantitative measurements.

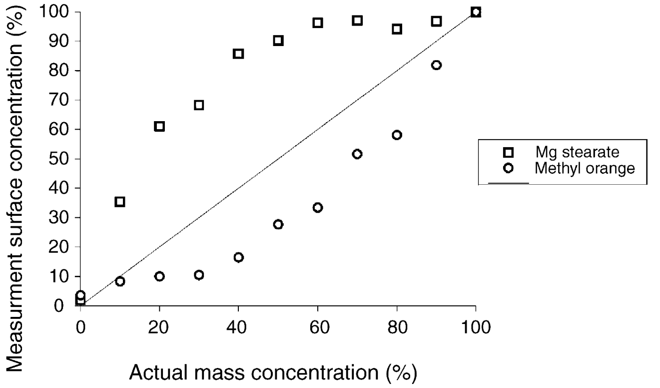

Fig. 2. Plot of surface concentration of Mg stearate and methyl orange on the surface, measured using ATR FTIR, against mass concentration of the component in the mixture.

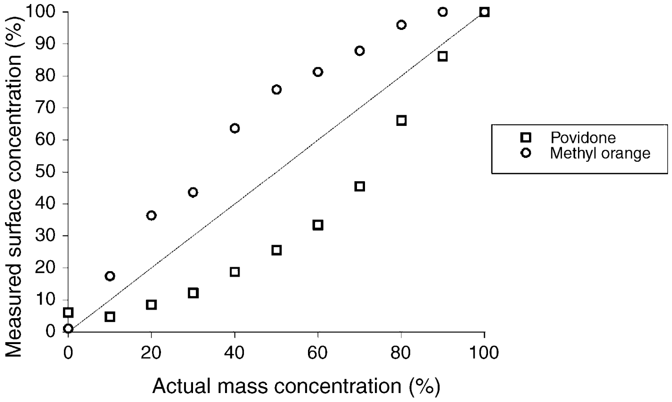

Fig. 3. Plot of measured concentration of Povidone and methyl orange on the surface, using ATR FTIR, against mass concentration of the component in the mixture.

The appearance of methyl orange on the surface of the mixture with Povidone in higher amounts than those expected on the basis of bulk concentrations cannot be explained by average particle size, since values for both component are similar (158 and 140 µm, respectively). Besides different average particle sizes, the particle size distributions also differ, because non-sieved powders were used for mixture preparation. The particle size at which 10% of the sample is below this size is lower for Methyl orange then for Povidone (Table 1), which is reflected also in the larger surface area (methyl orange 0.17 m^2/g, Povidone 0.08 m^2/g).

The optical microscope photographs of the mixtures of methyl orange with Povidone and Mg stearate in 1:1 mass proportions confirm the important contribution of the higher number of small size components on the mixture surfaces (Fig. 4).

Table 1
Particle size and specific surface area of non-sieved powders used for mixtures preparation

	(0 0 1) µm*	$\bar{x}$ (µm)	S.S.A. (m^2/g)
Mg stearate (ethanol)	1,1	8.3	174
Methyl orange (ethyl acetate)	10.3	157.8	0.17
Povidone (ethyl acetate)	57.9	139.6	0.08

* The particle size at which 10% of the sample is below this size, $\bar{x}$-volume mean diameter S.S.A.: specific surface area.

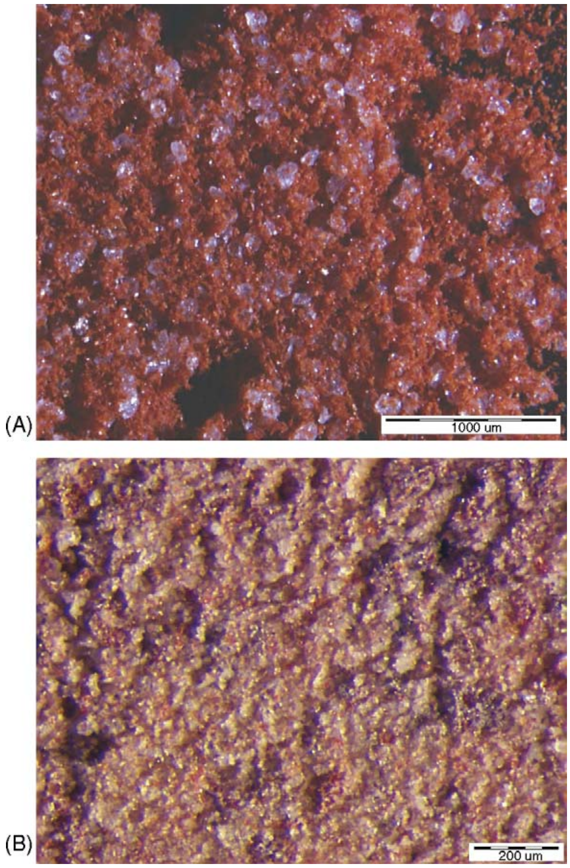

Fig. 4. Optical microscope photograph of methyl orange and Povidone in mass proportion 1:1 (A), methyl orange and Mg stearate in mass proportion 1:1 (B).

In preparation for the study of non-coloured powder mixtures, the influence of some parameters thought to be important for the correct interpretation of ATR results were investigated. The relatively small area of the spectrometer crystal that is in contact with the powder sample (circle diameter of 2 mm diameter according to a producer of an IR spectrometer) was increased by increasing the sampling repetition to 20. Twenty repetitive ATR measurements of a powder mixture, each on a different sample, included the variation of particle distribution within the mixture. To improve contact between the crystal and the mixture a metal ring was placed on the plate with the diamond crystal, which prevented sliding of particles during turning of a screw of the ATR device. This improvement resulted in better contact between a sample and diamond crystal, increase of absorbance and decrease of its relative standard deviation (below 5%).

To test the possible mechanical change of particles during ATR analysis, peak heights of sieved fractions of powder mixtures were measured. The absorbance increased with smaller particle size in the case of Eudragit® and Povidone (Fig. 5). This can be explained by the smaller amount of void space between smaller particles than between large particles. Results also showed that the screw used in the ATR device does not deform particles of Eudragit® and Povidone in a way that could result into misleading conclusions about particle distribution

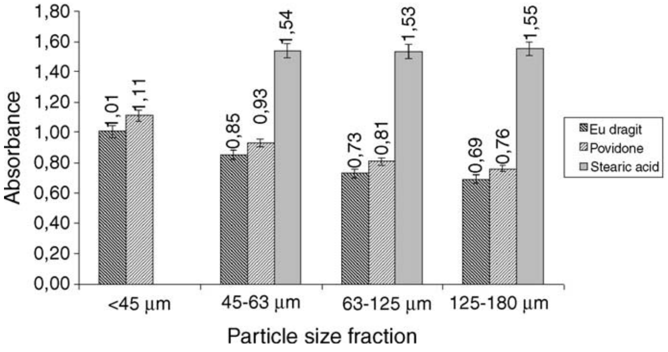

Fig. 5. Influence of particle size of the powder sample on the peak ATR absorbance at the chosen wavelength.

on the mixture surface. Different results were obtained with stearic acid, whose absorbance did not change with particle size increase, which correlates with the plastic properties of these powder particles.

A linear correlation of absorbance with the ratio of the components was next sought by the use of the same particle size fraction of Eudragit® and Povidone (63–125 µm). Apparent density after tapping was used to calculate the mass proportion of the components in the mixture, assuming that the same volume of the two components contains a similar number of particles with very similar specific surface area. The average particle sizes of Eudragit® and Povidone sieved fractions were measured to be 110 and 116 µm, respectively, with specific surface areas of 0.050 and 0.047 m^2/g, respectively. Peak heights in the ranges 1650–1660 and 1710–1724 cm^{-1} were used to quantify Povidone and Eudragit®, respectively at the surface of the mixtures. Fig. 6 shows the linear dependence of surface concentration of mixture components on actual volume concentration, confirming that the use of the Beer-Lambert law is appropriate for quantitative calculations. This result confirms the major influence of particle size and specific surface area on the surface concentration of both components. To confirm this assumption, two additional series of mixtures were prepared combining the 45–63 µm fraction (S.S.A. = 0.105 m^2/g) of Eudragit® with the 63–125 µm fraction of Povidone, and the 45–63 µm (S.S.A. = 0.079 m^2/g) of Povidone with the 63–125 µm fraction of Eudragit®. As expected, a positive deviation from linearity was detected for the smaller particle size fraction and a negative deviation for the larger particle size fraction for both series of mixtures (Fig. 7).

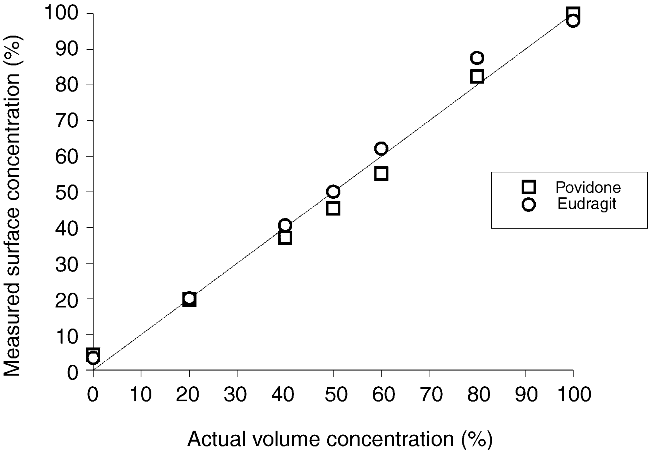

Fig. 6. Plot of measured concentration of Povidone (63–125 µm) and methyl orange (63–125 µm) at the surface, using ATR FTIR, against volume concentration of the component in the mixture.

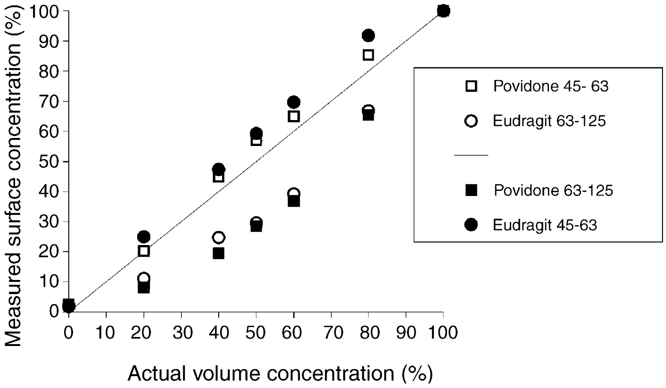

Fig. 7. Plot of measured concentrations on the surface of Povidone and Eudragit®, using ATR FTIR, against volume concentration of the components in the mixture (open signs: mixture 1 with smaller particles of Povidone, and closed signs: mixture 2 with smaller particles of Eudragit®.

Two additional series of mixtures containing NaCl (NaCl-Eudragit® and NaCl-Povidone) were prepared with the same size fraction (63–125 µm) of the components. NaCl does not absorb IR radiation and thus cannot be quantified by ATR. The particles of NaCl used in these experiments contained a small particle fraction from 0.40 to 3.0 µm which was shown to be about 3% of the sample volume (Fig. 8). This small particle size fraction may result from the milling of particles during sieving or from an inefficient sieving procedure. The ATR results show negative deviations from linearity for both Eudragit® and Povidone in the mixtures with NaCl. The small particle size fraction in the NaCl component contributes significantly to the specific surface area (0.129 m^2/g), which is larger than the surface area of Eudragit® and Povidone (0.050 and 0.047 m^2/g, respectively). It was calculated that 3% of the particles with an average diameter of 1 µm have a larger surface area than 97% of the 100 µm particles. In practice this can make an important contribution of the small particle size fraction of any component to the properties of a mixture.

Non-coloured mixtures containing stearic acid and Eudragit® were also examined. The particle size fraction of each component was 100–125 µm, with similar average particle size and specific surface area. The height of the peak between 2860 and 2840 cm^{-1} was used to quantify stearic acid and that between 1630 and 1660 cm^{-1} for Eudragit®. Results for surface quantification of both components in the mixtures are shown in Fig. 8. Positive deviation from linearity for stearic acid and negative deviation for Eudragit® can be explained with plastic properties of stearic acid, which can deform and surround Eudragit® particles during turning of a ATR device screw. Additional measurement of a mixture containing a Eudragit® particle size fraction smaller than 45 µm and a large particle size fraction of stearic acid in volume proportion 1:1 (Fig. 9) showed also deviation

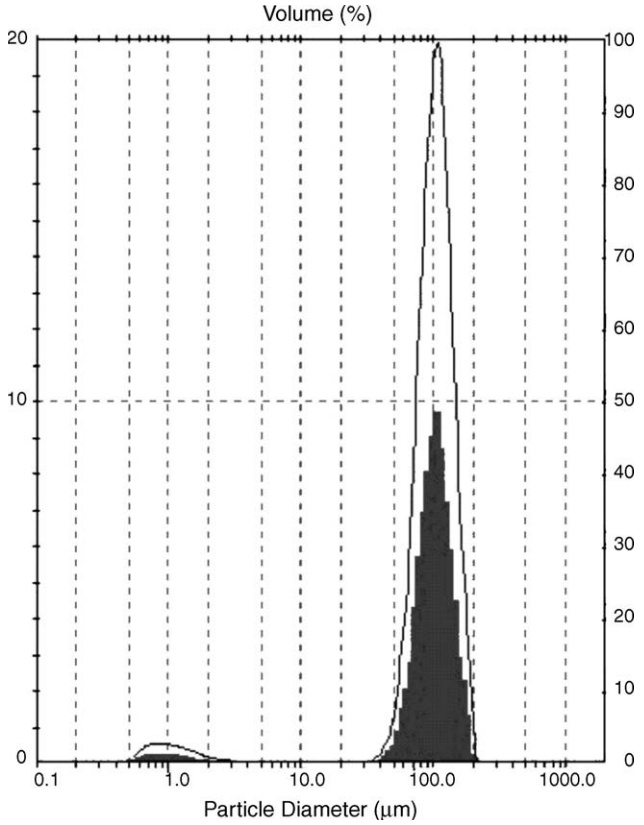

Fig. 8. Particle size distribution of NaCl sieved fraction 63–125 µm (determined in ethanol).

from linearity for both components, confirming that the surface of this mixture cannot be correctly analysed by ATR FTIR.

In some previous articles authors tried to correlate distribution of the particles in the mixture with spreading coefficient (Barra et al., 1998; Ahfat et al., 1997). When these values correlate with mixture properties, it can be concluded that cohesive and adhesive properties influence mixture performance. Most mixtures analysed in this research consisted of particle sizes larger than 45 µm, where rotational and translational forces play a major role in the process of mixing. It was comfirmed that the appearence of one component on the surface in higher amount than expected from mass proportion depends on particle size. This result correlates with published findings, where gravitational forces of particles above size of few 10 µm start to dominate adhesion and cohesion (Podczeck, 1998). It is believed that in investigation using components of particles smaller than 10 µm distribution of the components within the mixture could crucially depend also on surface energy of the powders and relative humidity. Future investigation should include most common excipients used in mixtures for direct tabletting. Raman spectroscopy should be tested in combination with ATR IR for mixtures analysis as it is also appropriate method for surface analysis. Also influence of humidity on the particles distribution in the mixture should be studied, since it is well-known that agglomeration of particles is influenced by water content. It is believed that certain powder material particles can adhere to a vessel walls, which can alter the composition of the mixture surface and the future work will focus also on this challenges.

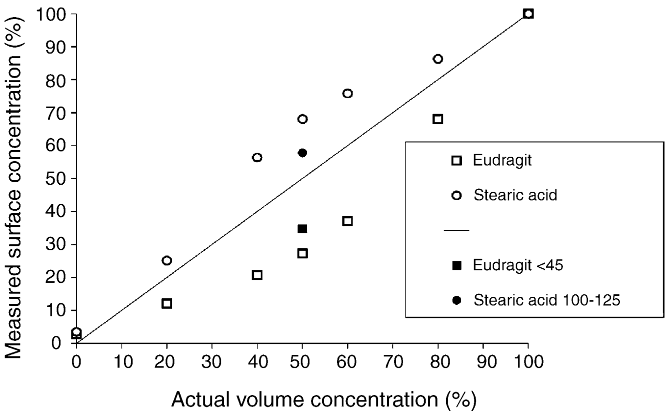

Fig. 9. Measured concentration of surface stearic acid versus volume concentration in a mixture with Eudragit® using ATR FTIR.

4. Conclusion

It has been confirmed that ATR FTIR spectroscopy can be a useful method for semiquantitative determination of components on mixture surfaces. Each component must have an appropriate IR spectrum with specific peaks that can be used for surface concentration determination. In addition to using peak height as a measure for quantitative measurements, different mathematical treatment of spectra should be used in further investigations. The results of this investigation showed that particle size and specific surface area play major roles in the distribution of components in the mixture. It is believed that in combination with appropriate statistical analysis ATR FTIR can be used for the quality assurance of the product during the development and manufacturing. It can help in process understanding, such as powder blending, which is the important aspect to be considered within the process analytical technology (PAT).

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