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An optical method for continuous monitoring of the dissolution rate of pharmaceutical powders

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ABSTRACT

Monitoring systems providing fast and reliable, even on-line data, from a distinct process stage or final product are needed in drug development, from the early stages of drug discovery until the drug product manufacturing procedures. This includes also processes involving solid particles, such as drug dissolution. However, the existing in vitro drug dissolution test methods suffer limitations, such as long sampling times of 30–60 s and thus the inability to be adapted to continuous monitoring, time consuming sample preparation and consumption of large amounts of reagents. In this study, an optical method for monitoring the dissolution rate of pharmaceutical powders was evaluated with model drugs having different dissolution rates. The measuring system consisted of a laser source, light detector, oscilloscope, magnetic stirrer and sample vessel. The intensity of laser light transmitted through the dissolution medium was recorded and displayed by the oscilloscope. Dissolution curves were produced by fitting the raw data with mathematical functions. The optical method was found to be resource-saving, reliable and capable of detecting differences in even rapid dissolution rates of drug compounds. This technique might have targets of application in real-time monitoring of processes in many different sectors, including the pharmaceutical industry.

1. Introduction

Dissolution testing is one of the most important experiments conducted by the pharmaceutical industry for testing new drug candidates and drug delivery systems. Combinatorial chemistry, high-throughput (HT) screening and other drug discovery innovations produce large amounts of hit molecules and potential drug candidates for development [1]. In solubility screening for lead optimization, current HT assays determine solubility after a defined time but do not take a compound's dissolution rate into account which is an important factor for drug bioavailability [1,2]. Standard intrinsic dissolution tests [3,4] consume hundreds of milligrams of drug, which is far too much for routine testing of compounds, salts and polymorphs in early development stages. Thus, there is a need for simple and fast assays for powder dissolution that do not require large amounts of drugs. Additionally, these methods need to be media-sparing as well, especially when simulated intestinal fluid or human intestinal fluid is used.

Current dissolution tests [4] have limitations such as long sampling times of 30–60 s. Usually, the collected dissolution samples are analyzed off-line by UV or HPLC (high performance liquid chromatography) systems which result in discontinuous profiles. These methods also require relatively large amounts of dissolution medium, time-consuming procedures for sample preparation and the use of expensive organic mobile phase chemicals (HPLC) which is also an environmental issue. These are serious problems in pharmaceutical quality control where continuous monitoring of production processes has not been possible until the development and implementation of process analytical technologies (PATs) [5,6].

Automated systems, such as flow injection (FI), have been developed in order to solve the sampling problem [7,8]. Systems suitable for continuous monitoring of the dissolution profile include UV fiber-optic sensors [9–11] which are available also commercially [12], methods based on near-infrared (NIR) diffuse reflectance spectroscopy [13], potentiometric methods [14,15] and a method based on the measurement of the alternating ionic current (AIC) [16], which is able to operate in low liquid surroundings.

Light scattering phenomena can be used for studying many properties of materials in liquid and air. When a light beam passes through a medium (i.e. water) containing particles, the intensity of the transmitted beam becomes reduced. Some of the light lost is absorbed while the rest is scattered, depending on the wavelength of the light and the optical properties of the material [17]. Scattering occurs mainly when the dimension and wavelength of the light beam are similar or larger than the dimensions of the particulate material. In the case of spherical macroscopic particles, the Mie-

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theory for light scattering applies, since the size of the particles is similar or larger than the wavelength of the light. Another type of light scattering, Rayleigh-scattering occurs from microscopic particles, such as atoms or molecules, but its intensity is considerably weaker than that of Mie-scattering. Since many materials exhibit strong absorption in the infrared and ultraviolet regions, which greatly reduces scattering intensity, most light scattering measurements are conducted using visible light [17]. In the pharmaceutical field, laser scattering (i.e. nephelometry or turbidimetry) has been utilized for characterization of particle shape and the size distribution of powders, suspensions and sprays [17–19], also during dissolution [20–22]. In the PAT field, laser scattering is utilized in the chemical and petrochemical, and food and beverage industries for concentration measurements and detecting particles that should not be in the process stream [23].

In the present study, a method, where the loss in intensity (due to light scattering from particles) of laser light transmitted through the dissolution medium is measured, is examined as a way of achieving continuous monitoring of the dissolution rate of drug powders. The optical method is compared to the traditional dissolution test method and its reliability, advantages and drawbacks are discussed with some speculation about potential targets of application.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride (PRP, min. 99%), anhydrous caffeine (CAF, Ph Eur) and perphenazine (PPZ, USP) were used as model drugs in this study and were purchased from Sigma–Aldrich (Sigma–Aldrich; Steinheim, Germany). PPZ in all measurements and PRP when determining the repeatability of the optical method, were used as received. Otherwise, two different particle size fractions (<15 μm and 90–100 μm) of PRP and CAF, obtained by sieving, were used in the dissolution studies. PPZ was also used as a component in the powder mixture with a fast dissolving drug. Starch acetate (SA, Polymer Corex Kuopio Ltd., Kuopio, Finland), ethyl cellulose (EC, Ethocel Standard Premium 10), hydroxypropyl methylcellulose (HPMC, Methocel K15M Premium, DOW Europe, Germany), crospovidone (CP, Polylasdone XL-10, ISP Technologies, Inc., Calvert City, KY) and calcium silicate (CS, Rxcipients FM1000, J.M. Huber Corp., Huber Engineered Materials, Havre de Grace, MD) were also tested as components in the powder mixture with a fast dissolving drug. Two fast dissolving perphenazine (PPZ)/polymer solid dispersion systems were also used in this study. In the solid dispersions, the polymer was either polyvinyl pyrrolidone K30 (PVP) or polyethylene glycol 8000 (PEG), both from Sigma-Aldrich (Sigma–Aldrich; Steinheim, Germany), and the PPZ/polymer weight ratio was 1/5. The preparation procedure and the physical properties of the solid dispersions are discussed elsewhere [24]. The chemicals used in the preparation of buffer solutions (i.e. hydrochloric acid (min. 39%), NaOH and K_2PO_4) were all analytical grade.

2.2. Optical measurement system

2.2.1. Principle and setup

The optical measurement system consisted of He–Ne-laser (Uniphase 1202-2, JDS Uniphase Corp., Manteca, CA), beaker (V = 100 ml, ⌀ 4.5 cm), magnetic stirrer (Heidolph MR 3001, Heidolph Instruments GmbH & Co., Schwabach Germany), laser power meter (LaserMate-Q, Coherent Inc., CA) and oscilloscope (Tektronix TDS 3052B, Tektronix Inc., Beaverton, OR). The wavelength of the laser light produced by the He–Ne-laser was 633 nm and the laser power was 6 mW. A schematic diagram of the equipment is shown in Fig. 1a.

The stirring method, speed of the stirrer, height of the laser beam and detection method for the measurement were selected and optimized in preliminary studies using α-,β-, γ-cyclodextrins (CDs), since their different dissolution rates were known. Stirring was needed to prevent the sample, dropped into the surface of the medium, from settling to the bottom of the beaker and allowing it to distribute homogenously into the liquid volume. When using the magnetic stirrer (length of 3 cm and diameter of 0.6 cm), the measurement of the intensity of the transmitted laser beam was found to be the most suitable detection method. However, since any motion of the particles can create changes or fluctuations in scattering intensity [17], the speed of the stirrer and location of the laser beam had to be optimized in order to minimize disturbances to the measurement curve created by the stirrer vortex. Based on these matters and experimental observations in preliminary studies, 300 rpm was chosen for the speed of the stirrer and a distance of 1.4 cm from the bottom of the beaker as the height of the laser beam (Fig. 1b).

When performing a dissolution test, the drug powder sample was accurately weighed with an analytical balance (A200S, Sartorius, Germany) and then dropped onto the surface of the dissolution medium in a beaker placed in the pathway of the laser beam. However, different dispenser systems might be suitable, but sample particles could adhere into the walls of these systems. A gunpowder dispenser was tested during method development, but it was found to become blocked easily, particularly in the case of small sample particles. For these reasons, a special dispenser system should be designed in order to minimize material loss in cases such as solubility screening in the early stages of drug development.

The intensity of the laser light passed through the beaker was measured with the laser power meter, adjusted to the wavelength of the laser (633 nm). The oscilloscope recorded the output voltage which was dependent on the laser intensity passing through the beaker (i.e. voltage vs. time). The output voltage (U) obtained from the laser power sensor varied between 0 and 1 V and it was recorded and saved by the oscilloscope. As a result, a raw data curve (voltage vs. time) was obtained, which had to be converted to percentage of drug dissolved as a function of time curve.

2.2.2. Conversion of voltage versus time curves to percentage of drug dissolved versus time curves

In order to obtain a traditional dissolution curve, i.e. the proportion of drug dissolved as a function of time curve, the raw data curves were fitted with a mathematical function with Matlab program (Matlab®, The MathWorks, Natick, MA). The raw data curves were found to be exponential in the case of the faster dissolving model drugs (CAF, PRP and PPZ/polymer solid dispersions) and linear in the case of slowly dissolving drugs (PPZ).

In the case of linear raw data curve, such as shown in Fig. 2a, the dissolution rate constant could be determined by calculating the slope of the linear fitting of the raw data curve. In order to perform the fitting, the initial (descending) part of the raw data curve, which did not describe the dissolution but rather the wetting and distribution of the sample into the dissolution volume and the descent of the sample particles to the level of the laser beam, had to be removed. When the particles have been distributed homogenously into the liquid volume, dissolving (i.e. diminishing and disappearing of the particles) can be seen as the light scattering decreases and the intensity of transmitted light increases. Finally, the intensity will revert back to the original level when all the particles have dissolved. Thus, the time required for dissolving a certain amount

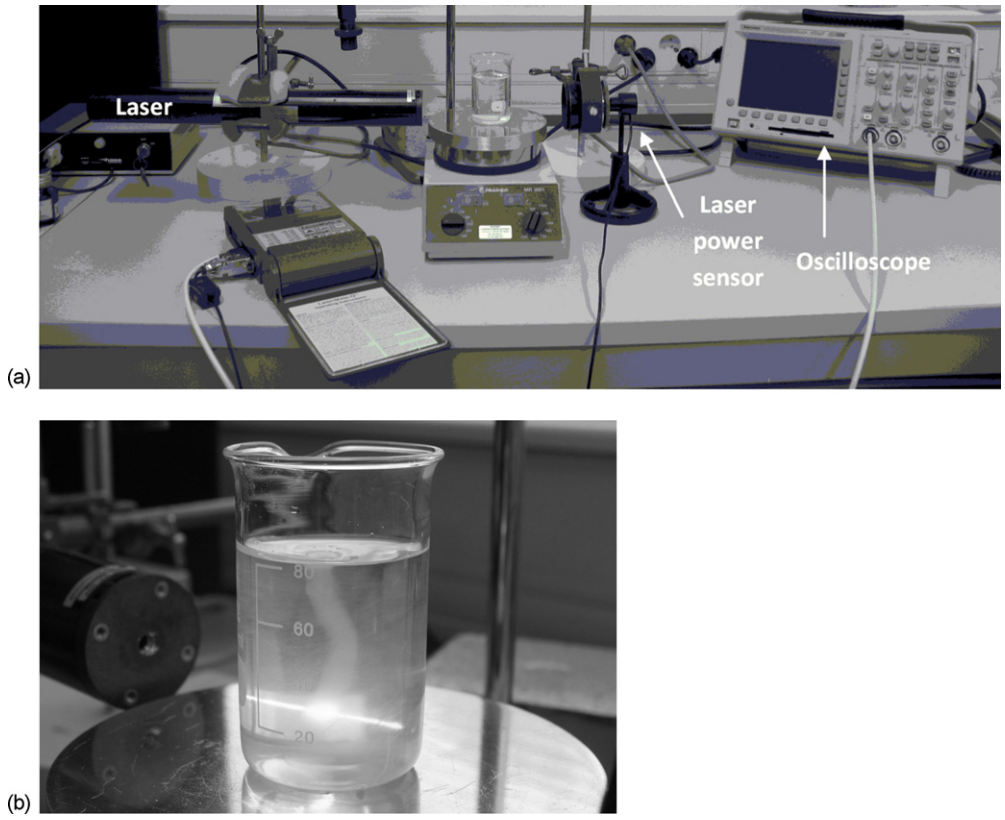

Fig. 1. (a) Assembly of the optical measuring system used for dissolution rate determination and (b) sample beaker showing the laser beam passing through the sample containing medium.

of drug can be always estimated from the raw data curve. However, determination of a quantitative dissolution profile requires further processing of the measurement data which might be complicated in the case of a noisy raw data curve.

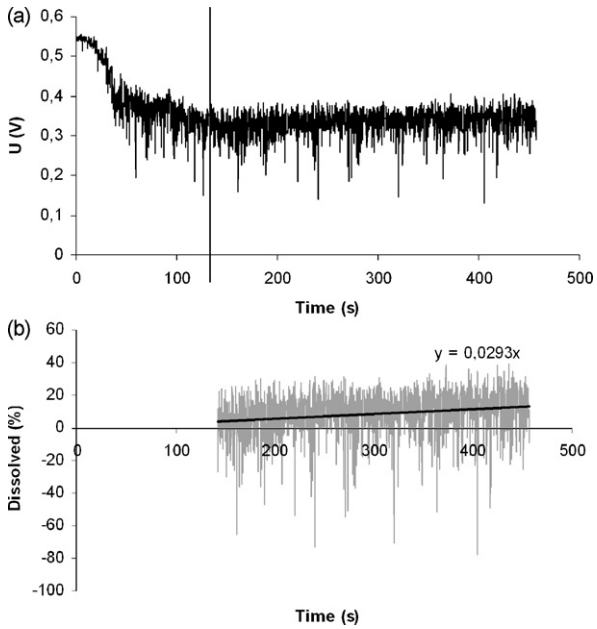

Fig. 2. Processing of the optical measurement data in the case of linear (i.e. slow) dissolution. (a) Raw data curve, i.e. voltage as a function of time, showing the two areas of the curve separated by a vertical line and (b) the raw data curve (after removal of the descending part of the raw data curve and *y*-axis conversion) with the fitted linear function, from which the amount of dissolved drug at time *t* can be obtained.

From the *y*-intersection of the fitted linear function, a point where no drug was yet dissolved was obtained (U_0). The voltage values were converted to relative values by:

$$y = \frac{U - U_0}{U_{\max} - U_0} \times 100 \quad (1)$$

where U is the voltage value at time t, $U_{\max}$ is the starting level value of the signal (voltage) in the raw data curve (i.e. the U value where the signal reverts back to when all of the drug is dissolved) and U_0 is the voltage value at $t = 0$. After the *y*-axis conversion the linear fitting gave the proportion of drug dissolved:

$$m_t = k_0 t \quad (2)$$

where m_t is the amount of drug dissolved at time t. By knowing the slope of the linear function, the amount of dissolved drug as a function of time could be obtained (Fig. 2b).

In the case of exponential dissolution, i.e. in the case of fast dissolving drugs, the dissolution raw data was fitted with the first order kinetics model (Noyes–Whitney equation) [25], where the logarithm of the amount of undissolved drug (m_t) is depicted as a function of time:

$$\ln m_t = \ln m_0 - kt \quad (3)$$

which can be presented in an exponential form as:

$$m_t = m_0 \ e^{-kt} \quad (4)$$

In Eqs. (3) and (4) m_t is the amount of undissolved drug at time t, m_0 is the amount of undissolved drug at time 0 and k is the dissolution rate constant.

The raw data curve (Fig. 3a) was reversed and the starting level of the measurement signal (voltage) was taken as the zero level by

Table 1
Dissolution experiments performed by the optical method, designed with a full 2-level experimental design for five factors (amount of drug, temperature and pH of the dissolution medium, drug and drug particle size).

Run	Factor A: amount of drug (mg)	Factor B: temperature (°C)	Factor C: pH	Factor D: drug	Factor E: particle size (μm)
1	40	37	6.8	CAF	<15
2	100	25	1.2	CAF	<15
3	100	25	1.2	CAF	90–100
4[a]	40	37	6.8	PRP	<15
5	40	25	6.8	CAF	90–100
6[a]	100	25	6.8	PRP	90–100
7	100	37	6.8	PRP	<15
8	40	25	1.2	PRP	90–100
9	40	37	6.8	CAF	90–100
10	40	37	1.2	CAF	<15
11	100	37	1.2	CAF	90–100
12[a]	40	25	1.2	CAF	90–100
13	100	37	6.8	CAF	<15
14	100	25	6.8	CAF	90–100
15	100	37	6.8	PRP	90–100
16	40	37	1.2	PRP	<15
17	100	25	6.8	CAF	<15
18	100	37	1.2	PRP	<15
19	40	25	6.8	PRP	90–100
20[a]	100	37	1.2	CAF	<15
21	40	25	6.8	PRP	<15
22	40	25	1.2	CAF	<15
23[a]	100	37	6.8	CAF	90–100
24[a]	100	25	1.2	PRP	<15
25	40	37	6.8	PRP	90–100
26[a]	40	37	1.2	PRP	90–100
27	40	37	1.2	CAF	90–100
28	100	25	1.2	PRP	90–100
29	100	37	1.2	PRP	90–100
30	100	25	6.8	PRP	<15
31	40	25	1.2	PRP	<15
32[a]	40	25	6.8	CAF	<15

[a] Experiments selected with the Plackett–Burman 2-level design for simultaneous chemical analysis.

the following equation:

$$y = (U - U_{max}) \times (-1) \quad (5)$$

where U_{max} is the starting level of the measurement signal. After removing again the first part (Fig. 3a) of the raw data curve, Eq. (4) was fitted with the raw data which allowed the determination of k (Fig. 3b), thus the time required for dissolving of a certain amount of drug could be calculated from Eq. (4) as follows:

$$t = \frac{\ln p}{k} \quad (6)$$

where $p = m_t/m_0$ (m_t is a certain proportion of m_0, i.e. of the amount of undissolved drug at time 0, and thus m_t/m_0 can have values between 0 and 1).

2.3. Drug dissolution studies

A total of 32 dissolution tests under variable conditions designed by experimental design program (Design-Expert 5, StatEase Corp., MN) for PRP and CAF were performed triplicate with the laser scattering method. The tests were designed by a full 2-level factorial design for five factors, where the factors were the amount of drug, temperature and pH of the dissolution medium, the model drug itself and the size fraction of the model drug (Table 1). The dissolution media were HCl (pH 1.2; 0.1 N) or USP phosphate buffer (pH 6.8; 0.2 M). From these measurements, eight experiments were selected with a Plackett–Burman 2-level factorial design in order to perform a chemical analysis simultaneously with the laser scattering method ($n = 3$) (Table 1). For the chemical analysis of dissolution profile, the samples (1 ml) were taken from the beaker at every 15 s without disturbing the laser beam (i.e. near the liquid surface). The sample volume was replaced with 1 ml of dissolution medium carefully without causing a strong vortex, which might disturbance the raw data curve. The samples were immediately filtered with a 0.45 μm filter and analyzed with a UV-spectrophotometer (Genesys 10uv, ThermoSpectronic, Rochester, NY) at wavelengths of 289 and 272 for PRP and CAF, respectively. PPZ was analyzed by Gilson HPLC system, consisting of 234 Autoinjector (Gilson, France), 321 Pump, UV/vis-151 detector at the wavelength of 254 nm, System interface module and Unipoint™LC System Version 3.01 Software, all from Gilson, USA. The sample injection volume was 20 μl and the mobile phase (flow rate 1 ml/min) was acetonitrile (ACN)–water (70/30, v/v) with 0.03% (v/v) triethylamine (TEA). A reverse-phase column (Inertsil ODS-3, 4.0 mm × 150 mm, GL Sciences Inc., Tokyo, Japan) was used. The retention time of PPZ was 3.75 ± 0.25 min. The PPZ standards were prepared in 70/30 ACN/pH 6.8 buffer solution. The standard curve was linear ($r^2 > 0.997$) over the range of the concentrations of interest (0.1–100 μg/ml). The method repeatability was tested before every analysis by injecting a 25 μg/ml standard solution five times in a row. The RSD of the obtained peak areas was always <3%.

2.4. Statistical analysis

Dissolution profiles obtained by the optical method were compared to the profiles obtained by the manual sampling followed by UV-analysis by calculating the similarity factors (f_2). Should the f_2-value be more than 50, the dissolution profiles were considered to be similar [26].

3. Results and discussion

3.1. Qualitative dissolution curves

Fig. 4a shows the raw data curves for measurements with PRP (runs 6 and 19, Table 1) where the dissolution conditions were oth-

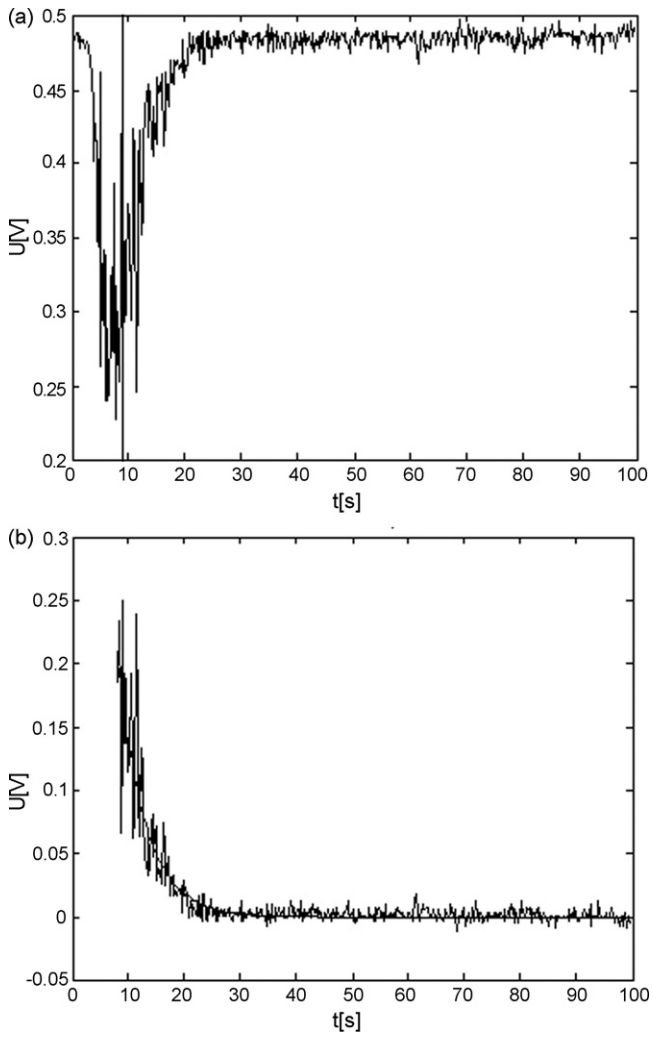

Fig. 3. Processing of the optical measurement data in the case of exponential (i.e. fast) dissolution. (a) Raw data curve showing voltage as a function of time and the two areas of the curve separated by a vertical line and (b) After reversing, rescaling and removal of the first part of the raw data curve, a curve according to the Eq. (4) was fitted with the raw data curve.

erwise similar, but the sample amounts were 100 mg and 40 mg for the runs 6 and 19, respectively. Fig. 4a reveals clearly that with a larger sample amount, the descent of the raw data curve was deeper and the noise of the curve was smaller. Instead, in the case of CAF no clear difference in the raw data curves attributable to the sample amount was observed (data not shown). Thus it can be concluded that the effect of the sample size on the curve shape and noisiness is dependent on the drug, since the amount of absorbed and scattered light is dependent on the optical properties of the material [17].

The particle size of the material also affects scattering and thus the optical measurement of the dissolution rate which was demonstrated. The obtained raw data curves for PRP (Fig. 4b) and CAF (not shown) with the particle size of 90–100 μm (run 6) were much clearer than those determined with the particle size of <15 μm (run 30) in similar dissolution conditions. Thus it can be concluded that with a larger sample particle size, a clearer measurement curve is obtained. This is due to that particle aggregation in the liquid phase might give rise to noise in the measurement signal, especially in the case of very small particles. Small particles tend to adhere to each other during the wetting phase and thus the particle size increases and dissolution rate decreases. Larger particles produce more scattering and thus the raw data curve becomes very

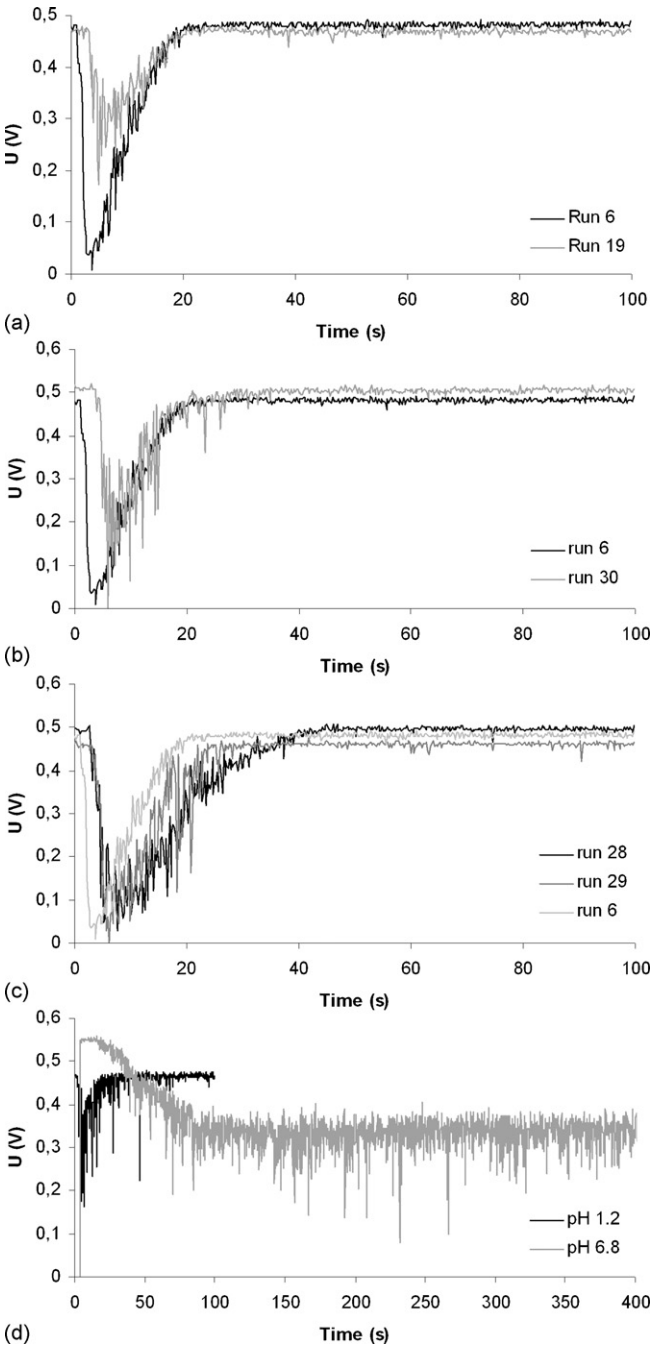

Fig. 4. Optical raw data curves of (a) PRP (particle size 90–100 μm) in pH 6.8 phosphate buffer at temperature 25 °C. In measurement run 6, the sample amount was 100 mg and in run 19 it was 40 mg; (b) 100 mg samples of PRP in pH 6.8 phosphate buffer at 25 °C. In measurement run 6, the particle size was 90–100 μm and in run 30, <15 μm; (c) 100 mg samples of PRP with particle size of 90–100 μm. In measurement run 28, the pH and temperature of the dissolution medium were 1.2 and 25 °C, respectively. In measurement run 29, the temperature was raised to 37 °C and in run 6, the pH was changed to 6.8; (d) PPZ in pH 1.2 and pH 6.8 at room temperature.

noisy which might hinder determination of the dissolution profile. Nonetheless, a qualitative estimation of dissolution time can always be made from the raw data curve. This phenomenon can be clearly seen in Fig. 4b, where the raw data curve of PRP with particle size <15 μm contained peaks caused by scattering of larger drug aggregates. Under the same conditions, drugs with a larger particle size produced a clearer raw data curve from which the dissolution profile could be easily determined.

Table 2
The dissolution rate constants and times required for dissolving 50, 80, 95 and 99% of PRP in pH 6.8 buffer at 25 °C with a sample size of 50 mg (n = 10).

Measurement	k (s^{-1})	T50 (s)	T80 (s)	T95 (s)	T99 (s)
1	−0.320	2.17	5.03	9.37	14.40
2	−0.284	2.44	5.66	10.54	16.20
3	−0.280	2.47	5.74	10.69	16.43
4	−0.278	2.49	5.78	10.76	16.55
5	−0.326	2.13	4.94	9.20	14.14
6	−0.280	2.48	5.76	10.71	16.47
7	−0.295	2.35	5.46	10.17	15.64
8	−0.298	2.33	5.40	10.06	15.46
9	−0.274	2.53	5.88	10.94	16.82
10	−0.263	2.64	6.13	11.40	17.53
Average	−0.29	2.4	5.6	10.3	15.9
SD	0.019	0.16	0.36	0.66	1.01
RSD%	6.6	6.4	6.3	6.3	6.3

The method was also capable of detecting the differences in dissolution rates of the PRP and CAF caused by different temperature and pH of the dissolution medium. Fig. 4c reveals the faster dissolution of PRP as a consequence of raising the temperature or changing pH of the medium. However, since the pK_a value of PRP is 9.5 [27] it should have dissolved slower at pH 6.8 than at pH 1.2. Instead, raising the temperature accelerated the dissolution of CAF, but since the pK_a value of CAF is 14.0 [27], its dissolution rate at pH 6.8 was slower than measured at pH 1.2 (data not shown). In addition, the most dramatic change in dissolution profile caused by pH change was seen with another model drug (PPZ, Fig. 4d). At pH 1.2, PPZ dissolved rapidly, i.e. all of the PPZ had dissolved within 30 s. Since the pK_a value of PPZ is 7.8 [27], the dissolution of PPZ was slow at pH 6.8, i.e. only a slight increase in measurement signal was detected. At pH 1.2 the dissolution was clearly exponential and at pH 6.8 it became linear.

3.2. Quantitative dissolution curves

3.2.1. Method evaluation.

Since in the optical method, it is variation of the laser intensity instead of absolute values which is measured, calibration of the equipment has no great bearing to the dissolution rate determination and the precision of the equipment is not a significant source of measurement error.

The repeatability of the measurement and the effect of the drug sample size on this parameter were estimated by using PRP (not sieved) as a model drug. In the evaluation, 10 parallel dissolution tests were performed in pH 6.8 phosphate buffer with a sample size of 50 mg at a temperature of 25 °C. The measurement data was processed as described in Section 2.2.2 and the dissolution rate constant (k) and times required for dissolving 50% (T50), 80% (T80), 95% (T90) and 99% (T99) were calculated; these are shown in Table 2. From the table it can be seen that the RSD values for k and T values were all less than 7%. Generally, there are no RSD% requirements set for dissolution testing. However, considering that for dissolution profile comparisons with similarity factor, it is stated that RSD should not be more than 10% [26], the RSD% of the dissolution measurement obtained with the optical method seemed to be acceptable. With a sample amount of 100 mg in similar conditions (Table 3) the calculated k value was found to be similar to the k calculated for smaller sample size (i.e. −0.29 s^{-1}). Thus, the dissolution was exponential and changing the sample size did not affect the dissolution rate, since sink conditions prevailed in both test series. However, the RSD values for k and T were higher with 100 mg sample size, i.e. 10–11% (Table 3). This might be due to the increased amount of scattering, since more particles with a wide particle size distribution are present in the solution, creating disturbances to the raw data curve.

Table 3
The dissolution rate constants and times required for dissolving 50, 80, 95 and 99% of PRP in pH 6.8 buffer at 25 °C with a sample size of 100 mg (n = 5).

Measurement	k (s^{-1})	T50 (s)	T80 (s)	T95 (s)	T99 (s)
1	−0.255	2.72	6.32	11.76	18.07
2	−0.349	1.98	4.61	8.58	13.19
3	−0.289	2.40	5.57	10.37	15.94
4	−0.272	2.55	5.91	11.01	16.92
5	−0.273	2.54	5.89	10.97	16.86
Average	−0.29	2.4	5.6	10.4	16.0
SD	0.033	0.25	0.58	1.08	1.65
RSD%	11	10	10	10	10

The limit of detection (LOD) and limit of quantification (LOQ) of the optical method was estimated by establishing LOD at three times the standard deviation of the baseline noise σ and LOQ at 10 times σ. Thus, LOD was estimated to be 17 mV and LOQ 56 mV. However, converting the mV into the proportion of drug is difficult since the attenuation of transmitted light depends on the optical properties of the drug, and thus it is drug-specific. Furthermore, establishing LOD and LOQ for a certain drug would be difficult since the attenuation of transmitted light, caused by increased amount of drug in the medium, is exponential.

3.2.2. Method applicability

3.2.2.1. Comparing the optical method with chemical analysis. From the 32 dissolution tests performed with the optical method, eight tests were selected according to Plackett–Burman design of experiment to be performed simultaneously along with a manual sampling and detection by UV-analysis (see Table 1). Fig. 5a shows the dissolution curves of the eight runs obtained by the chemical analysis and Fig. 5b depicts dissolution curves obtained by the optical method. The manual sampling interval was considerably longer, i.e. samples could be taken every 15 s, in contrast to the optical method where data was recorded every 0.2 s. Thus, with the optical method a continuous dissolution profile could be obtained.

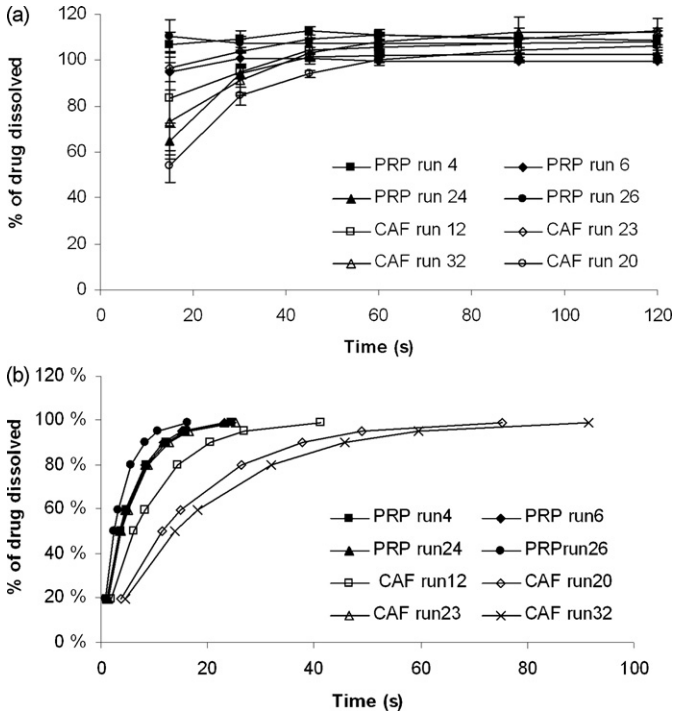

Fig. 5. Dissolution curves for measurement runs 4, 6, 12, 20, 23, 24, 26 and 32 obtained by (a) manual sampling and chemical analysis and (b) the optical method.

Table 4
Similarity factors for the dissolution curves obtained by chemical sampling and laser method, measurement codes from Table 1.

Run	f_2
4	48
6	97
12	59
20	31
23	58
24	52
26	43
32	64

Also, the standard deviations with the optical method were clearly smaller than could be achieved with chemical analysis. Dissolution curves obtained by the two methods were compared with f_2 values which are shown in Table 4. From the table it can be seen that with measurement runs 6, 12, 23, 24 and 32, the dissolution curves obtained with the optical method and chemical analysis can be considered similar (similarity factors higher than 52). In the case of measurement runs 4, 20 and 26, the dissimilarity of the curves (similarity factors smaller than 48) might be due to the inaccuracy of the chemical method. For example, the dissolution data obtained by chemical analysis in this case might be distorted, i.e. the obtained drug concentration in the sample was greater than the actual concentration in the dissolution vessel, leading to results such as 110% dissolved instead of 100%. This might have occurred since at the beginning of the dissolution test, many sample particles were still present in the dissolution medium and these undissolved drug particles might have been transferred into the pipette while taking a sample. These particles would have dissolved into the small sample volume in the pipette before the sample was filtered. Also, delivery of the sample into the dissolution vessel in the case of chemical method is important, i.e. all of the weighed sample should be accurately dispensed into the vessel in order to avoid inaccurate results (i.e. 90% dissolved instead of 100%). Instead, in the case of the optical method, an accurate sample amount is not so important since the relative amount of drug dissolved is determined from the amount that has been actually delivered into the dissolution vessel.

3.2.2.2. Suitability of the optical method for fast dissolving systems. The suitability of the method for determining the dissolution rate of a fast dissolving drug/polymer systems was evaluated by using 1/5 PPZ/PVP and 1/5 PPZ/PEG solid dispersions. In the case of these kinds of systems the optical method can detect the disappearance of particles consisting of the drug and/or the excipient, but it cannot measure the individual dissolution rates of the soluble components. Fig. 6a and b illustrates the raw data curves (optical method) and dissolution curves (chemical method) of PPZ from the systems. In the case of 1/5 PPZ/PEG solid dispersion (Fig. 6a), no fitting of the raw data curve could be made due to the noisiness of the curve (due to small and variable particle size of 1/5 PPZ/PEG solid dispersion), thus no dissolution curve could be obtained with the optical method. However, the dissolution rate and the time of complete dissolution could be estimated qualitatively from the raw data curve. Dissolution could be considered to be complete when sharp signals (i.e. undissolved particles passing through the laser beam) in the curve were no longer seen, which could be also confirmed from the dissolution curve determined with the chemical method. Instead, as can be seen from the dissolution curve in Fig. 6b, obtained with chemical method, PPZ dissolved much slower from 1/5 PPZ/PVP solid dispersion than from 1/5 PPZ/PEG solid dispersion. This was due to the poorer wettability of 1/5 PPZ/PVP solid dispersion powder due to which the particles did not properly reach the laser beam, and no dissolution curve could be obtained with the optical method.

This observation demonstrated that wetting properties of the drug powders have a significant impact on the success of the optical measurement. It is important that the whole sample is wetted rapidly so that it can be distributed into the dissolution medium. Poor wetting properties are generally a problem with hydrophobic and electrically charged particles which wet so slowly that they do not distribute quickly enough into the medium in order to be detected. The raw data curve becomes very noisy if the sample becomes wetted slowly and consequently, is distributed gradually into the liquid. Thus, no fitting of the measurement data can be performed in order to obtain a dissolution curve.

3.2.2.3. Suitability of the optical method for poorly soluble drugs. At pH 6.8, PPZ dissolves poorly and thus it was used as a model drug in these measurements. Linear fitting of the optical raw data of PPZ was performed (Fig. 7). From the figure it can be seen that the results obtained with the two methods (chemical and optical) were similar, with f_2 of 96. However, the standard deviation of the results obtained with the optical method was considerably smaller (less than 1.2×10^{-07}) compared to the chemical method (less than 1.5) with all data points. Also, the dissolution rate constants obtained with the chemical method ($0.0288 \pm 0.0054\,s^{-1}$) and with the optical method ($0.0287 \pm 0.0021\,s^{-1}$) were found to be similar. Thus, the optical method is also suitable for determination of the dissolution rate of poorly soluble drugs, at least when their wetting properties are sufficiently good.

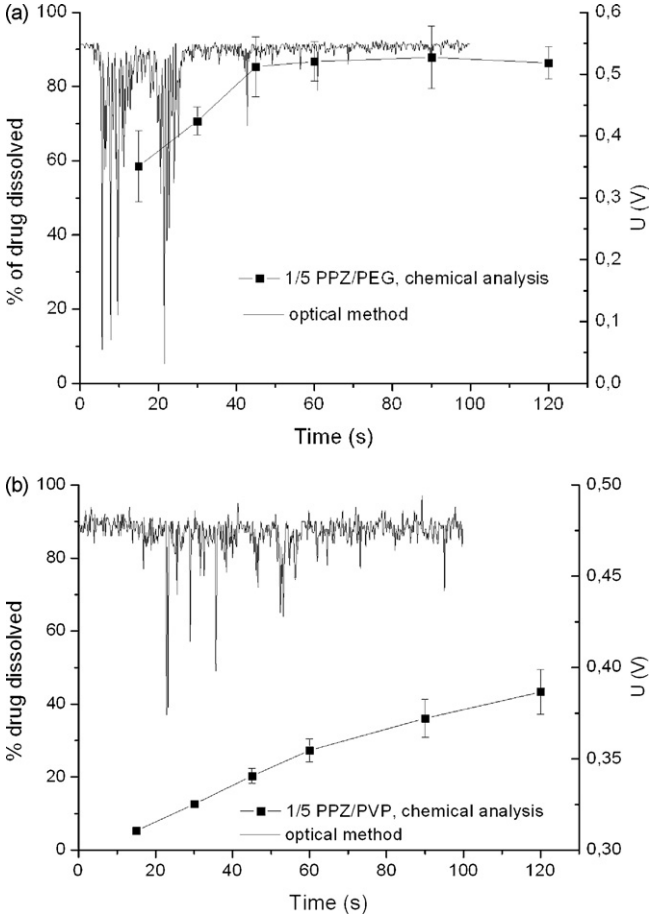

Fig. 6. Optical raw data curves (right *y*-axis) and dissolution curves determined with the chemical method (left *y*-axis) for (a) 1/5 PPZ/PEG solid dispersion and (b) 1/5 PPZ/PVP solid dispersion.

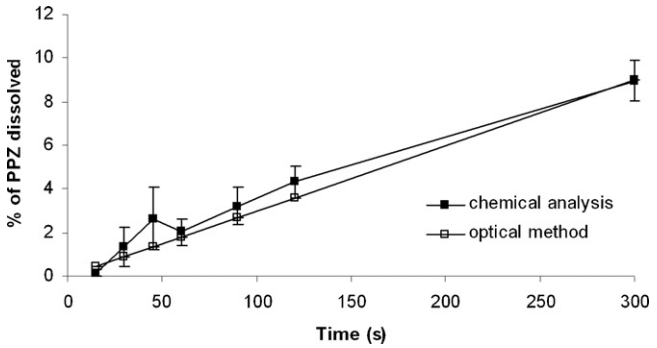

Fig. 7. Dissolution curves for PPZ at pH 6.8 determined by the optical and the chemical method.

3.2.2.4. Suitability of the optical method for mixtures of a drug and excipients. Dust in the air and particles (other than the drug itself) in the medium evoke disturbances in the measurement curve. This can be prevented by using purified water and performing the measurements in a clean environment, which eliminates the Mie-scattering from small dust particles. However, if the powder sample contains components other than the soluble drug, it might not be possible to distinguish the scattering produced by the drug particles from the scattering produced from the other components, i.e. poorly soluble or insoluble particles, in the sample. Thus, the effect of insoluble components on the dissolution rate determination of a drug was studied with different PRP/excipient mixtures (20/80, 50/50 and 80/20, w/w), the excipients being SA, EC, CP, HPMC and CS. However, since they were hydrophobic materials, SA and EC remained floating on the surface and the experiment failed. Instead, in the measurements with CP, HPMC and CS, the intensity of transmitted light was decreased to zero with all mixture ratios since the laser light became scattered totally from the insoluble particles. The laser power in the measurements with an insoluble component needs to be considerably higher, since with lower laser power the intensity of transmitted light decreases to zero due to the insoluble components and the dissolving component cannot be detected. Instead, when PPZ was used as a model of an insoluble component (since it dissolves poorly at pH 6.8, Fig. 7) with mixture ratios of 20/80, 50/50 and 80/20 (PRP/PPZ, w/w), it was possible to determine the dissolution profiles of PRP at two mixture ratios i.e. 80/20 and 50/50. Fig. 8a illustrates the raw data curves of the three mixtures and a pure PRP sample. The figure shows that the laser intensity of transmitted light decreases with increasing PPZ content. Fig. 8b shows the dissolution profiles of 50/50 and 80/20 mixtures determined from the optical measurements and with the chemical method. With the 20/80 mixture, no dissolution profile could be determined since the laser intensity declined to zero. The similarity factors of dissolution curves determined with the two methods were found to be 66 (80/20) and 60 (50/50), i.e. the two methods gave similar results. As observed also in the previous tests, the standard deviations of the optical measurements (i.e. less than 3.7) were much lower than the corresponding values obtained with the chemical method (i.e. less than 10.8). Thus, it can be concluded that, the amount of any insoluble component should be kept rather small or the intensity of laser light should be high if one wishes to distinguish the dissolution of a soluble component. Otherwise, the intensity decreases readily to zero since the extinction of light is exponential.

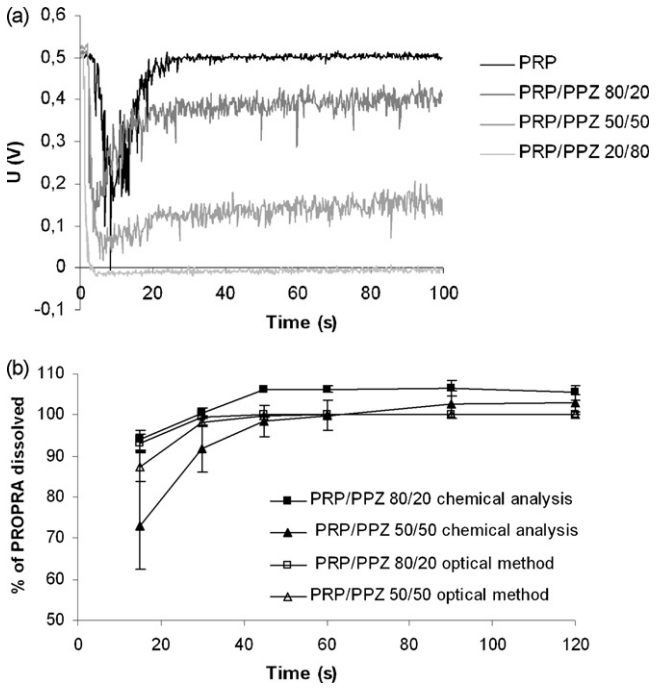

Fig. 8. (a) Optical raw data curves of PRP (40 mg) and 20/80, 50/50, 80/20 (w/w) PRP/PPZ mixtures (40 mg PRP in the sample) and (b) dissolution curves of PRP determined from 20/80 and 50/50 PRP/PPZ mixtures by chemical sampling and optical method. In the chemical sampling method, the proportion of dissolved PRP was obtained by subtracting the amount of dissolved PPZ from the total amount of dissolved drugs (i.e. PRP + PPZ).

4. Conclusions

In the present work, a novel optical method for monitoring the dissolution of drug powders was devised. The method, based on scattering of laser light from the particles in a liquid medium, is suitable for all drugs, since all particles scatter light. It is fast and resource-saving, providing a reproducible and accurate on-line monitoring of even rapid dissolution processes with a sampling interval of 0.2 s. The measurement system is economical and needs no calibration. The method needs further development in order to extend its applicability, since the raw data curve and thereby the goodness of fitting done in order to obtain the dissolution profile might be affected by drug particle size, aggregation of small particles, powder sample size and amount of noise created depending on the drug. Furthermore, poor wettability of drug particles might complicate the measurement. Monitoring the dissolution of drugs formulated with insoluble excipients might be possible if one had access to higher laser intensities in which case the dissolution process of the drug could be distinguished from the baseline attributable to the excipient.

The present system might be applicable in drug discovery where a fast measurement system, capable of distinguishing differences in even fast dissolution rates of compounds, is needed to help in selecting the final polymorphic or salt form of the lead molecule. From the PAT point of view, this system might be suitable for detecting particles that should not be present in the process stream or final products, such as in the case of infusion or injectable products. It might also be utilized in the detection of process changes, such as the onset of crystallization.

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