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Research paper

Solution calorimetry as an alternative approach for dissolution testing of nanosuspensions

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ABSTRACT

The formulation of poorly soluble drugs as nanocrystals/nanosuspensions has rapidly evolved during the past decade into a mature drug-delivery strategy. The major characteristic of these systems is the high drug dissolution rate, enabling bioavailability enhancement after oral administration. It is therefore of great importance to have access to analytical methodology that is able to accurately monitor the extreme fast dissolution process of such formulations. The aim of the present study was to evaluate solution calorimetry as a novel approach to measure the dissolution rate of nanosuspensions by recording the temperature change in the dissolution vessel during the dissolution process of the nanocrystals. The applicability was tested on different nanosuspensions made up of three model drugs: naproxen, cinnarizine and an investigational API, i.e. compound A. The dissolution process of all nanosuspensions investigated was completed within less than 1 min. During this period, sufficient data points were collected to transform temperature offset data to cumulative heat of solution pointing to the potential of this technique. However, of significant concern is the fact that this technique measures the total heat produced or consumed by all processes that occur during the dissolution, e.g. the heat of mixing when the nanosuspension comes in contact with the dissolution medium. Erroneous conclusions will result if phenomena other than dissolution are not accounted for.

1. Introduction

The number of compounds emerging from drug-discovery programs having low aqueous solubility and dissolution rate has significantly increased during the past two decades. The resulting problem of poor oral absorption of these compounds has been identified as one of the major obstacles of drug development. Different formulation strategies are available to tackle this problem, but novel possibilities emerging from the nanoscience field have attracted a lot of interest from pharmaceutical scientists. One of the nanoscience approaches that have rapidly gained a proven record within the pharmaceutical sciences is the formulation of poorly soluble compounds as nanoparticles. These particles have a size below 1 μm, typically a few hundreds of nanometers [1] and can be administered as a suspension (nanosuspension) or solid formulation.

Since an increase in dissolution rate of poorly soluble drugs is the main driving force for development of nanoparticle formulations, measurement of dissolution properties can be considered as one of the most important analytical techniques for this type of preparations. Several dissolution apparatus have been standardized as described in different pharmacopeia. Solid dosage forms and powders are mainly analyzed with the paddle (USP type 2) or basket (USP type 1) set up. An important step during sampling is filtration to remove undissolved particles; typically membrane filters having a pore diameter of 0.45 or 0.22 μm are used for this purpose. Although the risk of permeation of undissolved particles when using this traditional set up for dissolution testing of nanoparticle formulations is significant when the size of the nanoparticles is below 400 nm, today it is still most often used [2–5].

In order to perform dissolution testing more correctly, alternative methods were already investigated and tested for practical applications. One of the suitable alternatives lies in the use of turbidimetry. Chaubal and Popescu measured the transmittance through the dissolution medium in which nanoparticles were added [6]. As the nanoparticles dissolve the transmittance goes back to 100%, the point where dissolution is complete. Although scattering is a function of particle size, the advantage of such a set up is the possibility of automation. Recently, Peeters et al. [7] reported on the use of potentiometric sensors for in situ dissolution testing. The sensors allow determining the amount of API dissolved in the dissolution medium by measuring directly in the dissolution vessel. Although the sensors have adequate response

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times to allow quantification of fast releasing formulations and show no interference with undissolved particles (a clear advantage compared to fiber optic systems), the drawback is that for each API, a new set of sensors needs to be preconditioned.

It is important that novel approaches for nanoparticle dissolution are investigated. In this paper, we report on the potential of solution calorimetry for dissolution testing of nanoparticle formulations such as nanosuspensions. Dissolution testing was performed on nanosuspensions of three model drugs with low aqueous solubility, naproxen, cinnarizine, and a compound still under development, i.e. compound A. The heat absorbed or produced during the dissolution of nanoparticles was quantified and used to monitor the dissolution process. It will be demonstrated that the response time is fast enough to allow detailed dissolution testing of fast dissolving formulations. Also the drawbacks of this methodology will be discussed.

2. Materials and methods

2.1. Materials

Naproxen (mean particle size D(v, 0.5) 42.89 μm) and cinnarizine (mean particle size D(v, 0.5) 97.63 μm) were obtained from Fagron (Waregem, Belgium), compound A (mean particle size D(v, 0.5) 10.1 μm) was from Johnson and Johnson Pharmaceutical Research and Development (JJPRD, Beerse, Belgium), α-tocopherol-polyethylene glycol 1000 succinate (TPGS) from Eastman (Anglesey, UK), hydroxypropylmethylcellulose 2910 5 mPa s (HPMC) from Collorcon Inc. (West Point, PA, USA), polysorbate 20 from Janssen Pharmaceutica (Beerse, Belgium), sodium deoxycholate from Sigma Aldrich (Steinheim, Germany), glucose from B. Braun (Diegem, Belgium) and sodium carboxymethylcellulose (⩾99.5%) 40 mPa s from Ashland Aqualon (Wilmington, USA). Demineralized water (18 MΩ) was produced with an Elga maxima ultra pure water system (Elga Ltd., High Wycombe Bucks, England). All other reagents were of HPLC or analytical grade.

2.2. Methods

2.2.1. Preparation of nanosuspensions of naproxen and cinnarizine

A concentration of 60 g of API was suspended in demineralized water to which a stabilizer (TPGS or HPMC) was added in a concentration of 10%, 40% or 60%, relative to the amount of drug substance. Demineralized water was further added to a final weight of 600 g, and this crude suspension was homogenized using a magnetic stirrer before milling. Nanosuspensions were prepared from these crude suspensions by media milling using a Dyno-Mill Multilab (WAB, Bachofen, Switzerland). The milling chamber (300 ml; flow through set up) is composed of silicon carbide; the accelerator (64 mm diameter) is composed of zirconia. Milling was performed during 2 h using yttrium stabilized zirconia beads (0.3 mm; Tosoh Corp., Tokyo, Japan) at 2390 rpm. The temperature was always kept below 40 °C using circulating cooling water around the milling chamber.

2.2.2. Preparation of nanosuspensions of compound A

The nanosuspensions of compound A were prepared by media milling using a roller mill. Milling was performed by rolling the glass bottle on a roller mill (US Stoneware; Ohio, USA) at room temperature. The sample matrix contained: polysorbate 20, sodium deoxycholate and sodium carboxymethylcellulose dissolved in 5% glucose solution. The API was suspended in the sample matrix solution, including yttrium stabilized zirconia beads (Tosoh Corp., Tokyo, Japan) and milled at room temperature. The placebo solution contained the matrix solution with no API present.

2.2.3. Particle size measurements

The size distribution of the cinnarizine or naproxen nanoparticles was determined using a BIC90Plus (Brookhaven Instruments Co., Holtsville, NY, USA). Particle sizing was based on photon correlation spectroscopy. Measurements were performed within 48 h after preparation. Before measurement, the nanosuspension was properly diluted with demineralized water. The measurements consisted of one run of 2 min. The reported values are the intensity weighted mean particle sizes using the log-normal distribution. The particle size distribution of the starting API's was determined with laser diffraction using a Malvern Mastersizer Micro Plus (Malvern Instruments Ltd., Worcestershire, UK). The measurements were performed on sonicated suspensions of the API in a highly diluted polysorbate 20 solution. Pump speed was set to 1600 and 1 min of ultrasonication set to 10.00. The values are the 50% volume percentile (D(v, 50) calculated from volume distributions obtained using the Mie model. A dispersant refractive index of 1.33, a real particle refractive index of 1.15 and an imaginary particle refractive index of 0.1, were used.

The particle size distribution of compound A (API powder and nanosuspension) was measured by laser diffraction using a Malvern Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, UK), in the volume distribution mode. A diluted polysorbate 20 solution was used as the dispersant medium. The measurement was controlled in such a way that the light obscuration during measurement of the dispersed system was within a range of 6–8%. An average of 5 measurements in one run was reported for each sample.

2.2.4. Dissolution testing of naproxen nanosuspensions using filtration

Dissolution testing of nanosuspensions of naproxen using filtration was performed in the following manner. Test tubes of 12 ml were filled with 10 ml of a 2% sodium laurylsulfate (SLS) solution in demineralized water. A volume of 70 μl of nanosuspension was added to the test tubes to start the dissolution process. The tubes were placed in a rotary mixer to ensure proper mixing. The experiment was performed at room temperature. At every time point, 3 test tubes (triplicate analysis) were removed and a 1 ml aliquot was taken from each tube and filtered through a 0.1 μm filter (Whatman Inc., Clifton, NJ, USA). The first 0.3 ml was discarded and the rest was diluted with an equal amount of dimethylformamide prior to HPLC analysis. As a control, pure drug powder was also tested under the same conditions.

2.2.5. HPLC analysis

The quantification of the filtered samples was done using a Waters HPLC system (Milford, USA) consisting of a Waters 1525 binary HPLC pump. An isocratic method was used with a mobile phase consisting of 70% v/v methanol and 30% v/v of a 25 mM acetate buffer (pH 3.5) with 0.02 M SLS. The flow was set to 1 ml/min and UV detection at 331 nm was used. The column used is a Merck KGaA Lichrospher 60 RP-select B column (Darmstadt, Germany).

2.2.6. Dissolution testing using solution calorimetry

Dissolution of the nanosuspensions, crude suspensions, placebo's and pure API's was performed by measuring the heat of solution using the Thermometric 2225 Precision Solution Calorimeter in combination with the 2227 Thermal Activity Monitor (Thermometric AB, Järfälla, Sweden). Approximately 800 mg (in the case of cinnarizine), 600 mg (in the case of compound A), or 400 mg (in the case of naproxen) of nanosuspension or crude suspension or 80 mg (in the case of cinnarizine), 60 mg (in the case of compound A), or 40 mg (in the case of naproxen) of pure API was weighed directly in glass crushing ampoules, which were then sealed with beeswax. The ampoules were subsequently placed into the calorimeter, a thin-walled 100 ml Pyrex glass reaction vessel fitted

with a thermistor and heater. After appropriate equilibration time, the ampoules were broken into the vessel which was filled with 100 ml of Simulated Gastric Fluid (SGF, USP 29) in the case of cinnarizine, 100 ml of Simulated Intestinal Fluid (SIF, USP 29) in the case of naproxen, or 100 ml of 0.05 M borate buffer pH 10 in the case of compound A. The stirrer speed in the vessel was set at 400 rpm; all experiments were done in duplicate.

When a compound dissolves, the solution calorimeter monitors the change in temperature via a thermistor which eventually is translated to the heat of solution.

The next paragraph will be dedicated to explain the conversion from a temperature measurement to the heat of solution for the reader who is unfamiliar with solution calorimetry. Details of this methodology can be found elsewhere [8].

All heat involved in the calorimeter must be considered. This can be done by describing a heat balance equation:

$$-\frac{dq}{dt}-\frac{dq_e}{dt}=c\frac{dT}{dt}+k(T-T_s) \tag{1}$$

dq/dt is the heat flow due to the dissolution process or the calibration by the heater; dq_e/dt is the heat flow caused by the stirrer and the thermistor; $c(dT/dt)$ is the heat flow accumulated in the system and $k(T-T_s)$ is caused by the exchange of heat between the glass vessel and the surroundings. For a true adiabatic calorimeter, this term would be zero, but in this case, since semi-adiabatic conditions hold, the term has a value. k is the heat exchange coefficient, T_s is the temperature of the surroundings, T is the temperature as a consequence of the dissolution process and c is the total heat capacity of the vessel. When no dissolution reaction is taking place and if it is assumed that the heat generated by the stirrer and thermistor equals the amount of heat exchanged with the surroundings (this is exactly true if time approaches infinity), then the following holds:

$$-\frac{dq_e}{dt}=k(T_\infty-T_s) \tag{2}$$

T_∞ represents the steady-state value of the temperature in the reaction vessel. This equation can be substituted into the general heat balance equation to yield after rearrangement:

$$-\frac{dq}{dt}=c\left[\frac{dT}{dt}+\frac{1}{\tau}(T-T_\infty)\right] \tag{3}$$

τ is the calorimeter time constant and equals c/k. Integration between the starting time of the dissolution reaction or the start of the electrical calibration (t_{start}) and the end of these processes (t_{end}) yields the heat of solution (or the heat of calibration):

$$-q=c(\Delta T_{obs}+\Delta T_{adj}) \tag{4}$$

With ΔT_{obs} being the observed temperature ($T_{t,end}-T_{t,start}$) and ΔT_{adj} being the temperature change from all factors other than the reaction or calibration that contribute to the observed temperature change. It is expressed by the following equation:

$$\Delta T_{adj}=\int_{t,start}^{t,end}\frac{1}{\tau}(T-T_\infty)dt \tag{5}$$

τ and T_∞ are determined from baseline sections immediately before and after a calibration or reaction. In one experiment, calibration runs are combined with those of a dissolution experiment. Regions that connect these sections are called baselines. Baseline sections show an exponential decay from the initial temperature offset in the direction of the water bath temperature. It can be described with the following equation:

$$T=T_\infty+\Delta T_{norm}e^{-t/\tau} \tag{6}$$

with $\Delta T_{norm} = T_0 - T_\infty$; T_0 being the starting temperature. This exponential function is used to calculate τ and T_∞ and hence ΔT_{adj}. The observed temperature change can thus be corrected and gives ΔT_{corr} ($=\Delta T_{adj}+\Delta T_{obs}$). Since the heat that is supplied by the electrical heater during calibration is known, the heat capacity of the system can be calculated:

$$c=\frac{q_{calibration}}{\Delta T_{corr;calibration}} \tag{7}$$

The heat involved in the dissolution process of the nanoparticles is then calculated based on the heat capacity of the system and the corrected temperature change during the dissolution process:

$$q_{dissolution}=\Delta T_{corr;dissolution}c \tag{8}$$

3. Results and discussion

Fig. 1 shows a representative response curve obtained with the Thermometric Precision Solution Calorimeter, SolCal during a dissolution experiment of a nanosuspension of naproxen stabilized with HPMC2910 (60% towards naproxen). The dissolution was performed in SIF and the amount of the formulation used in this particular experiment was ca. 400 mg. SIF was chosen instead of the 2% SLS solution that was used during dissolution testing with filtration-HPLC analysis. This was necessary in order to decrease the likelihood of having interfering heat effects from interactions with the micelles and/or surfactant in the medium. The fact that disturbing effects are possible will be demonstrated further in this paper. The amount of formulation required for dissolution testing simply depends on the heat produced or absorbed during a dissolution process. During the experiment, different events are taking place that cause a variation of temperature and these are indicated by the arrows in Fig. 1. The experiment was started when the temperature in the dissolution vessel (calorimetric vessel) was within a 200 mK range of the water bath temperature (25 °C). Three baseline sections (from point 1 to 2; from 3 to 4 and from 6 to 7), two electrical calibration sections (from point 2 to 3 and from point 7 to 8) and one dissolution section (from point 4 to 5) are noticeable in the figure. In this particular example, the time between the dissolution of the nanocrystals and the start of the subsequent baseline section (indicated as point 6) may be shortened although enough time for sufficient stabilization is required. This already points to the fact that this type of experiments takes considerable time. During the electrical calibration (a known amount of heat is supplied to the dissolution medium contained in the calorimetric vessel

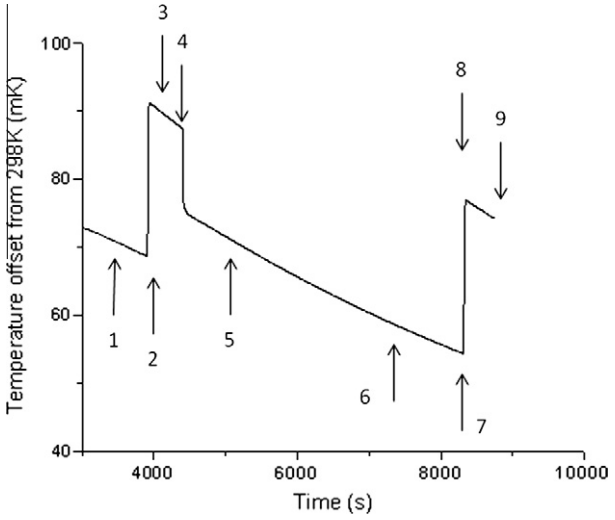

Fig. 1. Response curve for the dissolution of a naproxen nanosuspension stabilized with 60% HPMC (towards drug). For details see text.

using an electrical heater), the temperature increased, whereas during the dissolution reaction of this nanosuspension, the temperature decreased (endothermic dissolution process). The baseline sections are fitted to Eq. (6) using the multi-parameter least-square minimizing method provided with the Thermometric software to obtain values for T_∞ and τ. In the procedure applied in this study, baseline sections before and after breaking of the ampoule ("the break") were used to calculate T_∞ and τ. This procedure is called the "Regnault–Pfaundler" method or the "dynamics of break" method. The response curve shows the variation of temperature as a consequence of the occurrence of several events (a.o. dissolution of the nanocrystals) with the time of testing. Eventually, the heat of the dissolution reaction is calculated as described in previous section. However, one has to be aware that all events that produce or consume heat will eventually contribute to the calculated heat of solution, such as breaking of the ampoule and heat of mixing of the dissolved HPMC with the dissolution medium. The contribution of the breaking of the ampoule to the heat was in this case less than 1.6%, whereas the contribution of the heat of mixing of the dissolved HPMC was below the detection limit of the apparatus. Both events were therefore neglected in the further calculations. The heat of solution measured during the dissolution process of a nanosuspension is probably not the desired quantity for comparing different formulations of nanosuspensions or formulations in general. The heat of solution indicates the amount of material that was dissolved. It is however more interesting to obtain information about the rate of the dissolution process since nanosuspensions are formulated in the first place for their increased dissolution properties. In order to obtain dissolution curves that give information about the rate of the process, the raw data (temperature versus time) need to be converted. The Thermometric software allows to transform the temperature offset data into heat flow (power, J/s) using Eq. (3). However, an adequate transformation needs to take into account the inertia of the thermistor of the calorimeter. There exists a small lag time between the change of temperature as a consequence of the reaction (dissolution) and the time when this change is detected by the thermistor. This inertia can be accounted for by the thermistor time constant. It typically varies between 1 and 10 s and its value must be defined before the transformation to heat flow can be made. One has to take into account that the value of the time constant influences the shape of the heat flow curve. This is shown in Figs. 2A and 2B where different heat flow curves are generated from the data presented in Fig. 1 by applying values for the thermistor time

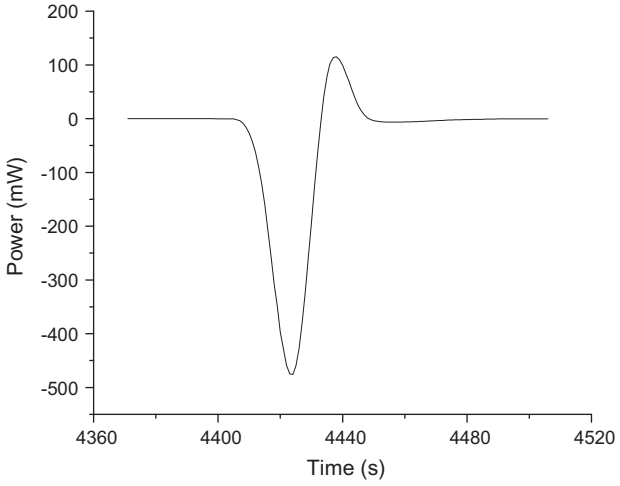

Fig. 2B. Power curve obtained with a thermistor time constant of 10 s for a naproxen nanosuspension stabilized with 60% HPMC (towards drug).

constant of 1 and 10 s. Large values lead to sharp peaks that cross the baseline. This has to do with the dynamic correction of the measured raw signal to get a corrected signal for which the time delay in the thermistor response is corrected. The total area was not significantly affected but the shape of the integrated curves differed significantly. Manual integrations of the curves in Figs. 2A and 2B are presented in Figs. 3A and 3B. Thermistor time constants of 1 and 2 s led to normally looking dissolution curves, while those with values of 5 and 10 s showed an extra peak. It was suggested by Yff and co-workers [9] to use thermistor time constants that give single peak areas for the calibration runs that match the number of joules supplied by the electrical heater. All data reported in this paper were obtained with thermistor time constants of 1 s.

The curves representing the cumulative heat were then transformed to "% dissolved". The time point indicating completion of the dissolution process ("100% dissolved") was defined as the point where the peak of the heat flow curve comes back to the baseline. Fig. 4 shows the dissolution profiles of three naproxen nanosuspensions differing in the amount of HPMC that was used as a stabilizer, one crude naproxen suspension containing the pure drug and HPMC (60% towards amount of drug; crude suspensions were suspensions that were prepared by simply suspending the drug

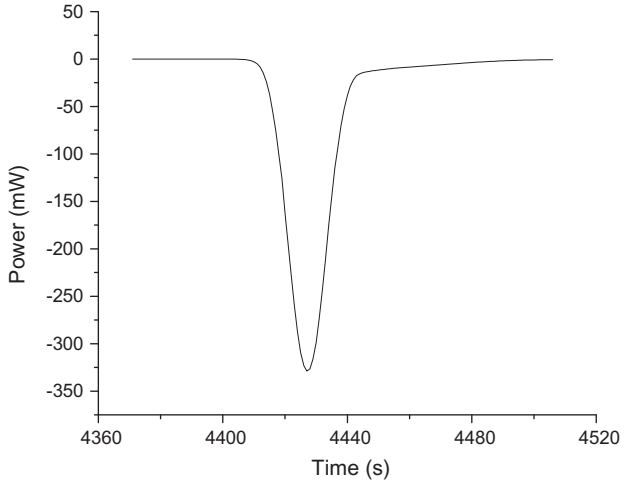

Fig. 2A. Power curve obtained with a thermistor time constant of 1 s for a naproxen nanosuspension stabilized with 60% HPMC (towards drug).

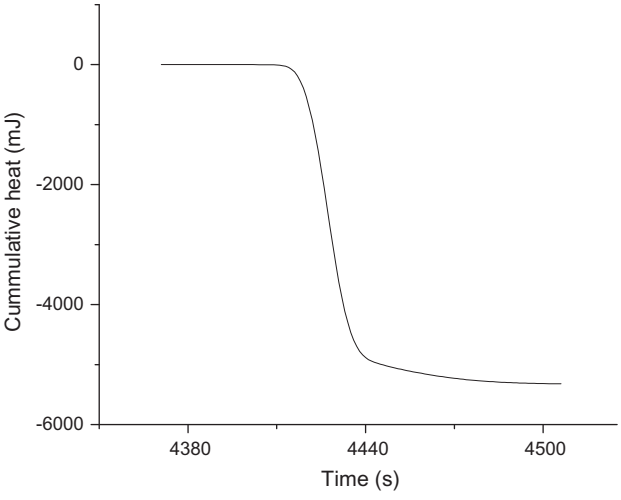

Fig. 3A. Cumulative heat curve for the dissolution of a naproxen nanosuspension stabilized with 60% HPMC (towards drug) using a thermistor time constant of 1 s.

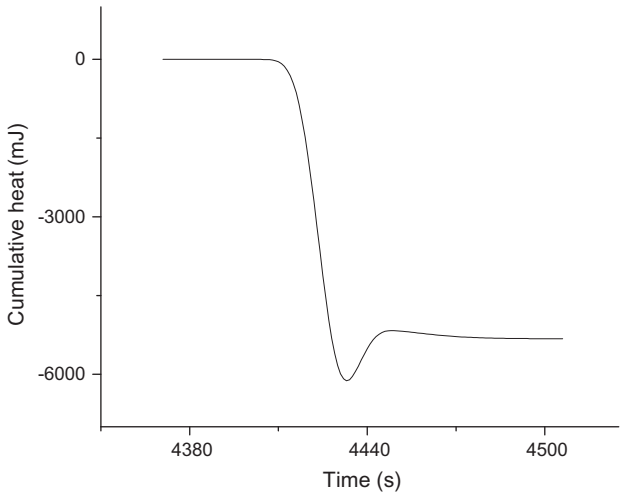

Fig. 3B. Cumulative heat curve for the dissolution of a naproxen nanosuspension stabilized with 60% HPMC (towards drug) using a thermistor time constant of 10 s.

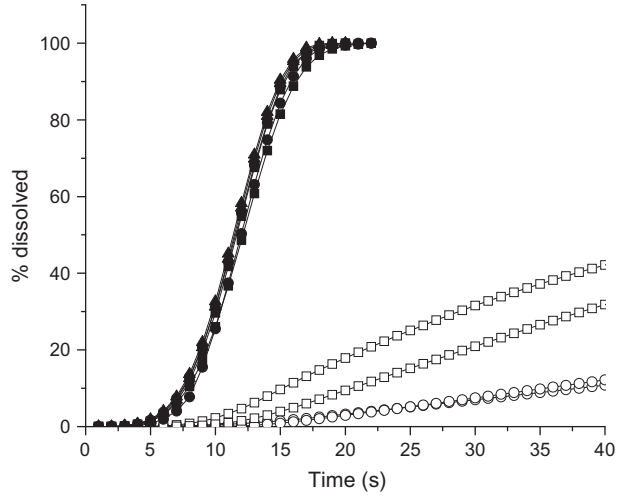

Fig. 4. Dissolution curves of naproxen nanosuspensions (■: naproxen with 60% HPMC; mean particle size 229.2 nm (PDI 0.236)); ●: naproxen with 40% HPMC; mean particle size 244.1 nm (PDI 0.214); ▲: naproxen with 10% HPMC; mean particle size 211.0 nm (PDI 0.144)), crude suspensions (○) and pure naproxen (□). The D50 value of the pure naproxen and that in the crude suspension was 42.89 μm.

substance as such in the stabilizer solution). The particle size of the nanosuspensions was comparable (221.0 nm, 244.1 nm and 229.2 nm for suspensions containing either 10%, 40% or 60% HPMC, respectively). It can be noticed that the dissolution rate of the different nanosuspensions was very fast: 100% was dissolved in less than 25 s (a short lag period preceding the dissolution can be noticed, indicating the breaking of the ampoule and mixing of the nanosuspension in the dissolution medium). The number of data points (one per second) in this time frame was sufficiently high to obtain adequate dissolution curves. Since these experiments were performed in SIF (pH 6.8, well above the p*Ka* of naproxen), the dissolution process of naproxen from the coarse suspension or from the pure naproxen was also fast (100% of the pure drug was dissolved in less than 15 min, while for the coarse suspension it was approximately 20 min). This is most likely also the reason why the amount of stabilizer (HPMC) did not seem to influence the dissolution rate in this non-discriminative dissolution medium. Due to lump formation, the dissolution of the coarse suspension was slower than that of the pure powder.

In order to compare dissolution testing using solution calorimetry with a more conventional method, we measured the dissolution process of naproxen nanosuspensions using a classical filtration set up combined with HPLC analysis. Fig. 5 shows the dissolution curves obtained with the "conventional" method of a nanosuspension containing 40% of HPMC 2910 (towards naproxen). One obvious observation from this figure is that the dissolution of the nanosuspensions is clearly faster than that of the coarse powder. The dissolution process itself of the nanosuspension cannot be measured and it is only possible to see that the sample dissolved within the first 5 min. The problem with increasing the number of points below 5 min is caused by the need to perform a lot of actions i.c. addition of the nanosuspension with a pipette to the test tubes, sampling, filtration of this sample through the small pores of a 0.1 μm filter with a high backpressure and the risk of breaking the filter membrane when pushing too fast or too hard. If replacement of the sample aliquot with fresh medium is needed and if a duplicate/triplicate measurement is preferred, increasing the sampling rate becomes very difficult.

Data on dissolution testing of nanosuspensions of the weakly basic drug cinnarizine are given in Fig. 6. In this case, the dissolution process was exothermic in nature. The nanosuspensions were completely dissolved within a time frame of 20 s, whereas in case of a coarse suspension or the pure compound, it took approximately 8 and 15 min, respectively. As discussed earlier, the contributions of breaking of the ampoule and heat of mixing of the dissolved stabilizers (HPMC and TPGS) with the dissolution medium were neglected. Also, in this case, the choice of the dissolution medium did not permit to discriminate between the different nanosuspensions. However, finding discriminative dissolution conditions was not the purpose of this study.

The dissolution tests described in this paper point to the value of solution calorimetry in dissolution testing of systems which proceed with a very high rate, certainly compared to the classical dissolution set up using a filtration step followed by a concentration determination using HPLC or UV spectroscopy. Such a set up would hardly permit to generate data from the beginning of the dissolution process. The cinnarizine and naproxen nanosuspensions described in this paper were all dissolved within 20 s.

One of the practical drawbacks of solution calorimetry is the long experimental time compared to the classical dissolution testing procedures. One experiment to determine the dissolution rate

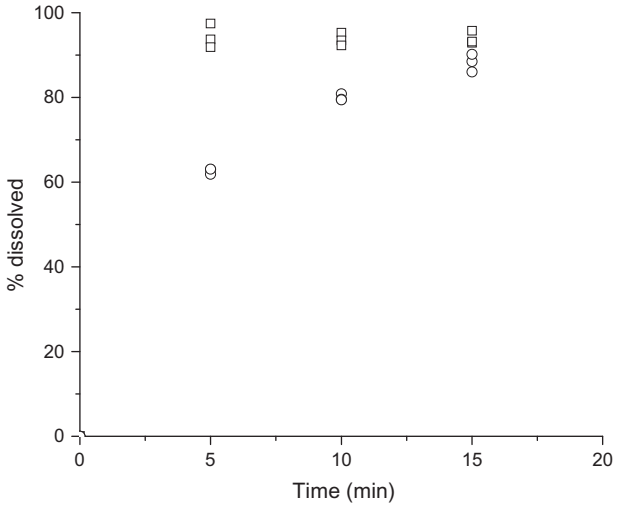

Fig. 5. Dissolution of naproxen obtained by filtration-HPLC analysis of a naproxen nanosuspension containing 40% HPMC (↑) (mean particle size 244.1 nm (PDI 0.214)) and pure naproxen (○).

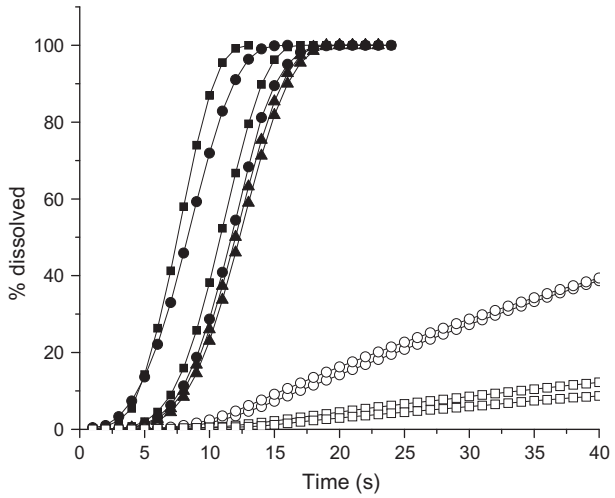

Fig. 6. Dissolution curves of cinnarizine nanosuspensions (■: cinnarizine with 40% HPMC; mean particle size 419.2 nm (PDI 0.243); ●: cinnarizine with 10% HPMC; mean particle size 785.1 nm (PDI 0.305); ▲: cinnarizine with 10% TPGS; 310.7 nm PDI 0.193)), crude suspensions (○) and pure cinnarizine (□). The D50 value of the pure cinnarizine and that in the crude suspensions was 97.63 μm.

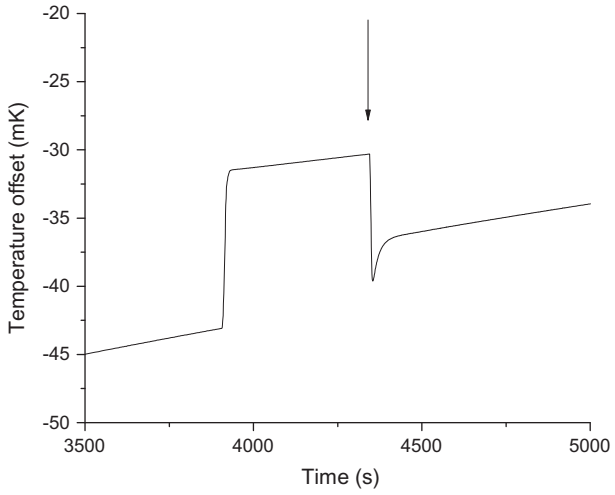

Fig. 7A. Response curve for the dissolution of a nanosuspension of compound A (the arrow indicates the break).

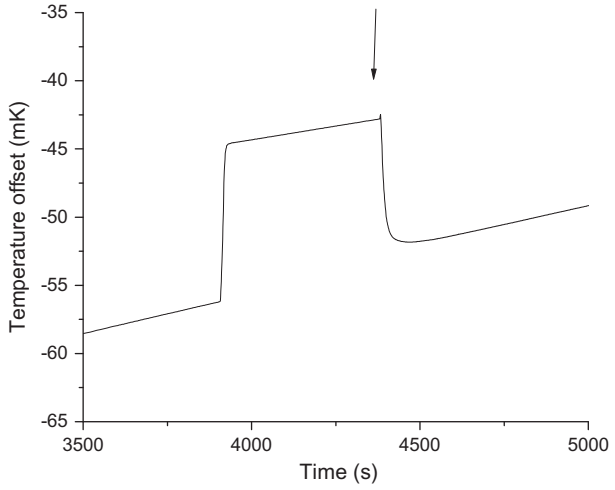

Fig. 7B. Response curve for the dissolution of compound A (the arrow indicates the break).

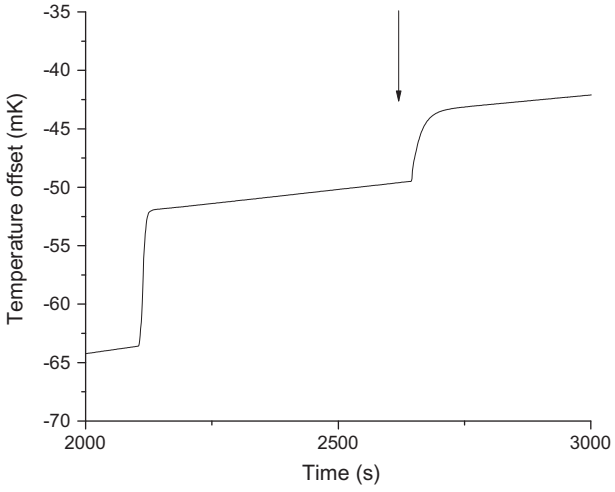

Fig. 7C. Response curve for dissolution of the placebo nanosuspension of compound A (the arrow indicates the break).

of a system that dissolves in ca. 20 s takes significantly more than 1 h due to the long equilibration times. Application of solution calorimetry for routine dissolution testing is therefore not first choice. However, even more important is the fact that during solution calorimetry the total heat involved in a given process is measured and the contribution of other phenomena to the total production or consumption of heat must be compared to that of the dissolution process of the nanoparticles. This is illustrated in the following example where the dissolution process of a nanosuspension of compound A is monitored. Besides the drug substance, this nanosuspension also contained polysorbate 20, sodium deoxycholate and sodium carboxymethylcellulose. Fig. 7A shows the temperature offset data of the dissolution process of this nanosuspension in 0.05 M borate buffer pH 10. After the ampoule break, the temperature decreases but this is immediately followed by an increase. Such a pattern points to the fact that at least two phenomena are occurring at approximately the same time, one of which is endothermic while the other is exothermic. In this specific case, it was clear that the dissolution process of the pure drug substance was endothermic and that of the placebo (in this case the heat of mixing) was exothermic (Figs. 7B and 7C). Hence, transformation of the temperature offset data to cumulative heat will not yield acceptable and practically useful dissolution curves. Ideally, before dissolution measurement of nanosuspensions can be considered, preliminary tests to rule out or to take into account of interfering phenomena should be conducted. However, such a procedure will again lead to increase in analysis time.

4. Conclusion

The present paper reports on the use of solution calorimetry as an alternative for dissolution testing for nanosuspensions, or for fast dissolving dosage forms in general. This is undoubtly an advantage over the classical dissolution testing set up. Moreover, errors due to filtration or sample preparation in general can be avoided. One of the drawbacks is that dissolution testing using solution calorimetry takes much more time than the classical set up. However, of more concern is the fact that this technique measures the total heat produced or consumed by all processes that occur during the dissolution, e.g. the heat of mixing when the nanosuspension comes in contact with the dissolution medium.

Erroneous conclusions will result if phenomena other than dissolution are not accounted for.

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