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Accelerated dissolution testing for improved quality assurance

Per-Ola Quist *, Göran Östling

Process Analytical Chemistry, Quality Control and Assurance, AstraZeneca Tablet Production Sweden, SE-151 85 Södertälje, Sweden

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Abstract

In pharmaceutical production of controlled release tablets and capsules, a rapid and automated at-line dissolution test for quality assurance of semi-products is advantageous. For effective control of the production, the analysis should not take more than about an hour, without loss of correlation to the ordinary (USP) dissolution test of the final product. For almost a decade, the ACDRA apparatus (ACcelerated Dissolution Rate Analysis) have been used for this purpose at AstraZeneca Tablet Production Sweden (TPS). In this paper, we give examples on different ways to accelerate the dissolution process. We use the USP dissolution calibrator tablets of salicylic acid (non-disintegrating type) to illustrate the strategy. We investigate the accelerated dissolution of the dissolution calibrator tablets, and show how it can be correlated with the dissolution in the ordinary USP-II equipment. The dissolution process was accelerated by variation of temperature, solvent and stirring. For example, we show that by increasing the temperature to 70 °C, changing the solvent to water, and increasing the stirring, it is possible to accelerate the dissolution by a factor of 5, without any loss of correlation to the dissolution process in the ordinary test.

Keywords: Dissolution; Quality assurance; Production; Salicylic acid; Dissolution calibrator

1. Introduction

At-line dissolution tests have become important tools for real-time quality control in large-scale pharmaceutical production of controlled release formulations. At AstraZeneca TPS, the ordinary operators in the production plant perform the at-line dissolution tests. This puts quite tough demands on robustness and simplicity of the at-line dissolution test and the equipment. Yet, the accelerated at-line test should be sufficiently accurate and correlate with the ordinary dissolution test. In this paper we describe the ACDRA system (ACcelerated Dissolution Rate Analysis), which is designed for this topic [1]. The gains of at-line dissolution tests are improved quality, reduced costs and cycle times. In addition, one gets a rapid quality feed-back to the operators in production, which must not be underestimated: the last decade we have noticed a continuously increasing quality

* Corresponding author.
E-mail address: per-ola.quist@astrazeneca.com (P.-O. Quist).

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of the megabrands, though the volumes and number of operators involved have increased dramatically.

Dissolution testing, a functionality test of the pharmaceutical formulation, is a quite complex process [2,3]. Yet, in-vitro tests have been judged as suitable for process control [4]. The dissolution process is sensitive to many parameters, such as temperature, stirring, solvent, shape of the vessel, as well as tablet compaction, particle size, shape and distribution, etc. [2,5–11]. To standardise different dissolution equipment, the USP have developed dissolution calibrator tablets and detailed instructions for the dissolution testing [12,13]. In this report we use the USP dissolution calibrator tablets of salicylic acid to illustrate a feasible strategy for the development of a new, accelerated at-line dissolution test.

2. Experimental

2.1. Materials

We use the USP dissolution calibrators non-disintegrating, salicylic acid, Lot N (USPC Inc., Rockville, MD). These dissolution calibrator tablets are originally intended for validation of dissolution test equipment, though their uniformity have been debated [4,6,7,14]. The tablets are 100% salicylic acid, and erode until all substance has dissolved. The nominal weight of each tablet is 300 mg. The tablets were stored in the original package in a desiccator until use. Care was taken to protect the tablets against moisture, which otherwise may cause problems [13].

Three different solvents were used: 0.05 M aqueous phosphate buffer (pH 6.8), 0.1 M HCl(aq) (pH 1.0) and purified water. The water was purified by reversed osmosis. The buffer and acid were prepared according to instructions in the USP. The solvents were stored in 10-l plastic cans, at ca. 22 °C, for at least 12 h before usage.

To calibrate the spectrophotometer (using the peak at 296 nm) we used salicylic acid (BDH, AnalaR, $\geq 99.7\%$). In general, the UV spectrum of weak acids depends on the degree of dissociation. For salicylic acid, it turned out that the absorption peak maximum was constant at 296 nm, but the absorbtivity varied slightly with the pH. It was therefore necessary to make separate calibrations for the three different solvents used.

2.2. Methods

The dissolution experiments were performed on an ACDRA system [1]. The ACDRA system used in this study consisted of an ACDRA apparatus (model 2100, Götalab, Sweden), a computer (Compaq, running with Windows NT4), and an UV spectrophotometer (Hewlett Packard HP 8452A), with a 0.5 mm flow cell.

The ACDRA system and analyses are designed to be highly automated—the analyses are usually performed at-line by the operators in the factory. Once the operator has defined the sample, the test to run, etc., the ACDRA system prepares itself for the analysis (filling, heating, stirring, etc.). The system tells the operator when ready, and then performs the analysis after sample addition. After an analysis the system rinses itself. About 20 000 analyses have been performed on the ACDRA systems at AstraZeneca TPS.

The computer in the ACDRA system is used for interfacing and control, using the software WinACDRA 2.0 and a number of dissolution methods (developed at AstraZeneca TPS). This includes windows-based interface of instructions to the operators, automatic distribution of analytical records by e-mail, and automatic transfer of results to an ER/ES-compliant database. In addition, there are methods for instrument test and calibration of the system. The latter methods are available to a staff of laboratory engineers, who takes care of the service, tests and trouble shooting. All actions are logged and the ACDRA software is ER/ES-compliant.

The UV spectrophotometer can be either a Hewlett Packard HP 8452A or a Varian Cary 50. During an analysis, the solution is pumped from the dissolution vessel through a flow cell, in the spectrophotometer, and back to the vessel. Depending on the flow through the sampling pump, it takes about 5–30 s to replace 80% of the content in the flow cell with fresh solvent from the vessel.

The ACDRA apparatus, outlined in Fig. 1, is basically a type II USP apparatus modified for automated, flexible, and robust at-line dissolution tests. It is equipped with three pumps to fill, empty, or rinse the vessel (ca. 850 ml). These pumps can also be used for level control in the vessel. A fourth pump can be used for either level control or sampling to the flow cell. The conductometer cell is used for concentration measurement (of ionic species) or for level control. An optical sensor is used for top level control. The volumes in the vessel can be controlled to within ± 2 ml. With two heaters and a thermometer, the temperature is regulated in the range 30–90 °C to within ± 0.2 °C. The stirring is by a USP-type paddle, and can be set in the range 40–250 rpm (to within ± 2 rpm). With a simple macrolanguage, one has full control of the pumps, stirrer, levels, temperature, etc. to prepare the system for an analysis. It is also possible to include pop-up windows with instructions to the operators at any time.

In this study, three dissolution calibrator tablets were analysed in each experiment. The average weight of the three tablets was 902 mg, with a standard deviation of 7 mg. To compensate for this variation, the software calculated the fraction released (Q) with respect to the actual weight of the three tablets. In all experiments, the fraction dissolved was determined by the absorption maximum at 296 nm. The absorbance was measured once every minute.

2.3. Evaluation of the dissolution profile

The dissolution test method can be configured to measure the fraction released (Q) at any instant during the analysis. In this investigation, however, we make use of the linear least-squares fit module in the WinACDRA software. This module fits a line to the dissolution profile in a selected range (here being $Q = 10–40\%$), and calculates the Rate (in %/h) and the Lagtime (in h) for this part of the dissolution profile. As shown in Fig. 2, the Rate is the slope of the best-fit line, and the Lagtime is the point of time where the line cross the time-axis.

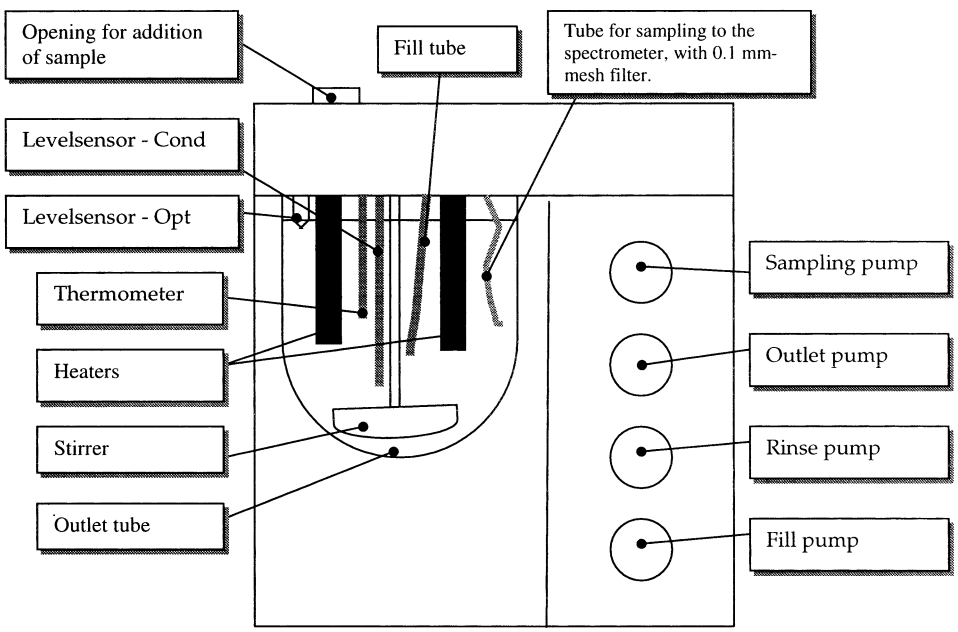

Fig. 1. Outline drawing of the ACDRA apparatus. A complete ACDRA system is built from an ACDRA apparatus, a computer, and if necessary an UV spectrophotometer.

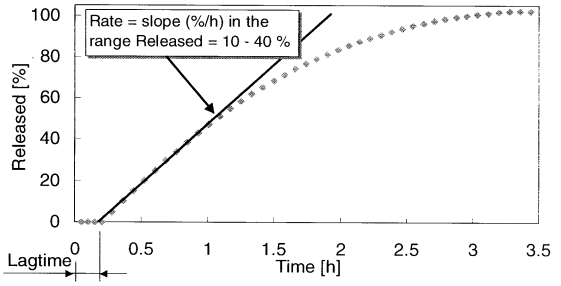

Fig. 2. Typical dissolution profile of salicylic acid dissolution calibrator tablets in the ACDRA system. The Rate and Lagtime are automatically calculated from a least-squares fit of a linear polynomial to the dissolution profile in the range $Q = 10–40\%$.

The dissolution calibrator tablets contain nothing but salicylic acid (not even a coating), so we expect a zero Lagtime. Experimentally the Lagtime was about 0.5 min in all cases, which is the time it takes to pump the solution from the vessel to the flow cell. Hence, only the Rate is reported below. Since the dissolution medium remained clear during the analysis, the background correction of the spectrum was simple: prior addition of the sample, a reference spectrum was measured. During the analysis, the reference was first subtracted from the measured spectrum, and then the absorbance at 296 nm was evaluated.

In production, it is not unusual that the dissolution media becomes slightly turbid during the at-line analysis (due to various particles from constituents in the formulations). The software then allows more advanced background correction. After the reference spectrum has been subtracted, the absorbance in a region of the spectrum without any sample peaks is also measured. A linear polynomial is fitted to these data. The polynomial is then extrapolated to the wavelength(s) of the peak(s) of interest in the spectrum. The extrapolation thus estimates the contribution to the absorbance from turbidity at the sample peak(s). Subtraction of this estimate yields the absorbance from the dissolved substance. The linear extrapolation works fine as long as the turbidity is not too high. For the salicylic acid calibrator tablets, however, the linear correction was not necessary.

3. Results and discussion

3.1. Screening

To characterise the effect on the Rate of the temperature, stirring, and solvent we performed a full factorial (two levels) design with three centre points and eight other experiments. The screening experiment was designed using MODDE 4.0 (Umetri AB, Sweden). The variables and results of the analyses are listed in Table 1.

As we can see in Table 1, the Rate increases as the temperature, stirring frequency, or pH is increased. This is because we increase the molecular diffusion, the flux-transport away from the tablet surface, and the solubility, respectively [2]. In Fig. 3, we show a contour plot of the effect of temperature (°C) and stirring frequency (rpm) on the Rate. It is quite clear that, in the investigated range, the easiest way to accelerate the dissolution process is to increase the temperature. In Fig. 3 the solvent is 0.1 M HCl(aq), where salicylic acid has a quite low solubility. If we change the solvent to 0.05 M phosphate buffer with pH 6.8, the solubility increases by about a factor of 3. As expected from the Noyes–Whitney equation [2], cf. below, the Rate also increases by a factor 3.

The temperature, stirring, and solvent are actually the three most important parameters when an accelerated at-line method is to be developed.

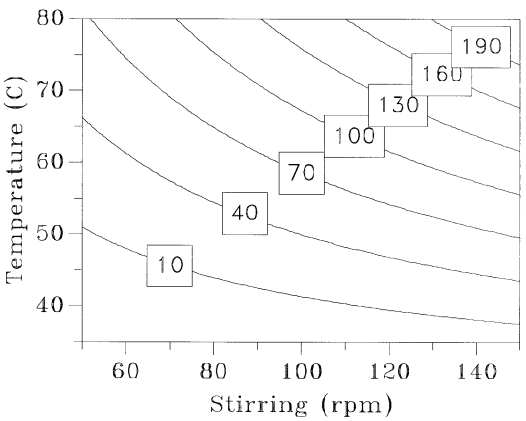

Fig. 3. Contour plot showing the effect of temperature (°C) and stirring frequency (rpm) on the Rate (%/h). The solvent is 0.1 M HCl(aq).

Table 1
Variables and results from the screening experiment

No.	Stirring (rpm)	Temperature (°C)	Solvent	Rate (%/h)	Q (0.5 h) (%)	Q (1.0 h) (%)	Q (1.5 h) (%)	Q (2.0 h) (%)	Q (2.5 h) (%)
1	50	37.0	0.1 M HCl	7	5	10	14	18	22
2	150	37.0	0.1 M HCl	21	12	23	33	43	51
3	50	70.0	0.1 M HCl	60	32	56	74	87	87
4	150	70.0	0.1 M HCl	155	69	98	102	102	102
5	50	37.0	pH 6.8 buffer	22	13	25	35	44	53
6	150	37.0	pH 6.8 buffer	58	30	56	75	88	97
7	50	70.0	pH 6.8 buffer	95	45	73	88	96	96
8	150	70.0	pH 6.8 buffer	249	91	100	100	100	100
9	100	50.0	0.1 M HCl	30	18	32	45	56	65
10	100	50.0	0.1 M HCl	29	17	32	44	55	65
11	100	50.0	0.1 M HCl	29	17	32	44	55	64

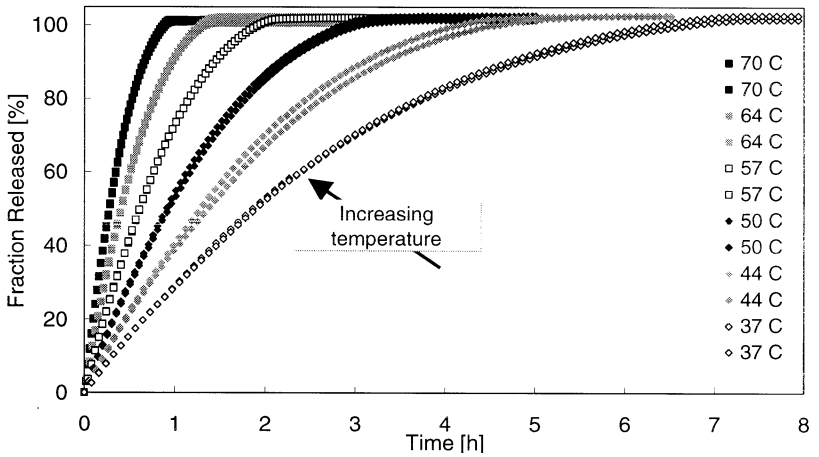

Fig. 4. Release profiles of salicylic acid calibrator tablets as the temperature is increased. Stirring frequency = 150 rpm, solvent = water, temperature = 37, 44, 50, 57, 64 and 70 °C. The dissolution process accelerates with increasing temperature.

Whereas it is easy to accelerate the dissolution process, the trick is to do it without loss of the correlation to the ordinary dissolution test. One must understand that from a quality assurance perspective, there is no use of a fast at-line dissolution analysis if the correlation to the ordinary dissolution test is lost. On top of this demand, the at-line analysis should be robust, simple to use, and finish within an hour or so. The latter is a special requirement from the production management at our site.

Lack of correlation between an accelerated and its corresponding ordinary dissolution test is not unusual. It could be due to (for example) a phase transition in one or several of the components (excipients or active) in the formulation. The phase transition could be due to an increased temperature, or a different interaction with a new solvent.

Drastic changes in the stirring could also cause a lack of correlation [5,14]. The stirring in the USP dissolution tests is quite moderate, and the in-vitro dissolution of some formulations may be critically dependent on the flow patterns in the vessel. This may be the case when the ACDRA should be correlated to a flow-through cell dissolution test (where the flux of solvent around the sample could be quite different from that in a paddle bath).

Though the formulation of the salicylic acid dissolution calibrator tablets is fairly simple, we shall use the tablets as an example on how one can accelerate the dissolution process and still understand what is going on. We illustrate the strategy by increasing the temperature of the solvent.

3.2. Increasing the temperature

To further investigate the effect of temperature on the Rate, we performed experiments at $T = 37$, 44, 50, 57, 64 and 70 °C. The stirring frequency was set to 150 rpm and the solvent was purified water. The dissolution profiles are shown in Fig. 4. As expected the dissolution process accelerates with increasing temperature.

The effect of the temperature on the Rate can be understood from the Noyes–Whitney equation [2] under sink conditions ($C \ll C_s$).

$$\frac{dW}{dt} \propto \frac{DA}{h} C_s. \quad (1)$$

Here, dW/dt is the dissolution Rate; D, diffusion coefficient of salicylic acid in the stagnant layer; A, area of the tablet(s) in contact with the solvent; h, thickness of the stagnant layer; and C_s, solubility of salicylic acid in water [15]. For simplicity, we shall assume that the area is constant during the fraction of the dissolution that is of interest

for us ($Q = 10$–40%). This is, of course, not absolutely true, though it is likely that the area reduction will be independent of temperature. We therefore, introduce the same systematic error at all temperatures.

The temperature dependence of the diffusion coefficient may not always be known. However, it can then be estimated from the Stokes–Einstein equation [2,16], which states that:

$$D \propto \frac{T}{\eta}, \tag{2}$$

where η is the viscosity of the solvent (water) [17]; and T, temperature in Kelvin. Combination of Eqs. (1) and (2) yields:

$$\text{Rate} \propto \frac{T}{\eta}\frac{A}{h}C_s. \tag{3}$$

According to Eq. (3) we expect a linear dependence on the Rate with the product C_sT/η. (We tacitly ignore a likely, though small, temperature variation in the thickness of the stagnant layer, h.) From the temperature variation of C_s and η, we can calculate C_sT/η at the temperatures of interest, and plot the Rate vs. C_sT/η. This plot is shown in Fig. 5, and as we expected there is a linear variation. The Noyes–Whitney equation is usually regarded as too simple for detailed studies. However, if we repeat the analysis using, for instance, the convective diffusion model [14], there is still a linear variation of the type shown in Fig. 5. This indicates that the dissolution process accelerates as expected with increasing temperature.

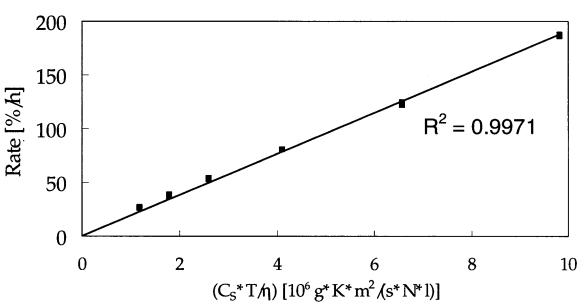

Fig. 5. Variation of the Rate with the product C_sT/η. The values of C_s and η at the various temperatures are taken from the literature [15,17].

What would then be the effect of a phase-transition with increasing temperature? For simplicity, let us assume that salicylic acid goes from one crystalline form to another at 55 °C (which is purely hypothetical). In this case, the solubility of salicylic acid in the two crystalline forms would be different [2,16]. In Fig. 5, we would then observe this (hypothetical) phase transition as a step-like change in the plot. Similar argumentation could be applied to phase transitions in the excipients. To conclude, if a phase transition occurs in the formulation, we expect a non-linear variation in plots like the one in Fig. 5.

3.3. Correlation with the USP-II apparatus

As we mentioned earlier, the production management at AstraZeneca TPS demand an at-line dissolution test that correlates with the ordinary analysis, and is finished within about an hour. We have found that a powerful way to investigate the correlation is by a, so-called, time-scale correlation of the accelerated with the ordinary dissolution test. The time-scale correlation concept is not novel, though seldom explicitly expressed: in 1951 Edwards noticed that "… a given fraction of the tablet dissolves in a given fraction of the total time almost independently of the solvent and temperature" [18]. This means that it was only the *pace* of the dissolution process that changes when the solvent or temperature varied—not the *shape* of the dissolution profile.

The time-scale correlation is thus based on the following idea: if the only difference between the ordinary and accelerated dissolution profile is the time-scale on which the dissolution processes occur, we will find a linear relationship between the two dissolution profiles. This means that the shape of the dissolution profile is identical, which indicates that the accelerated dissolution process is identical to the ordinary dissolution process—with the exception of an increased pace. In order to illustrate the time-scale correlation, we recall the results from Nicklasson et al. [19]. In 1986, these authors investigated the USP dissolution calibrator tablets of salicylic acid in a number of USP XXI dissolution apparatus (type II, paddle). The experiments were performed with six tablets

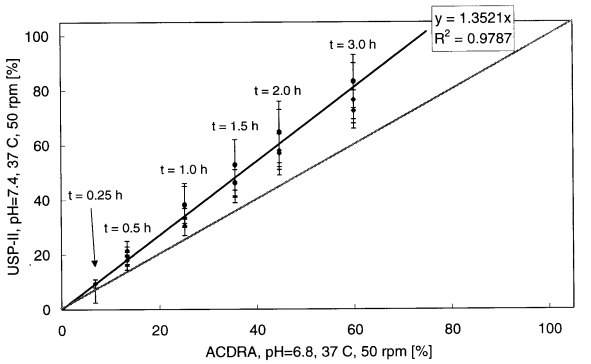

Fig. 6. Correlation between the dissolution profile of salicylic acid calibrator tablets in the ACDRA (pH 6.8, 37 °C, 50 rpm), and in the USP-II apparatus (pH 7.4, 37 °C, 50 rpm). The greyish diagonal is added as a guide for the eye. The error bars are estimates derived by Nicklasson et al [19].

at 37 °C, 50 rpm, and pH 7.4 in four different laboratories. The fraction released was determined after 0, 0.25, 0.5, 1, 1.5, 2, 3 and 4 h.

We may now ask ourselves, does these results correlate with the ones we obtain using the ACDRA at 37 °C, 50 rpm, and pH 6.8 buffer? In Fig. 6, we show a simple way to check if there is any correlation—we plot the fraction released in the two systems, at the same point of times, versus each other. According to Fig. 6, there is a linear relation between the two dissolution profiles. Though the release process is slightly slower in the ACDRA system under the selected conditions, the correlation looks good. It seems that by adjusting the stirring, temperature, or solvent in the ACDRA it should be no problem to obtain the same dissolution process as in the USP-II apparatus.

Although a plot like the one in Fig. 6 is instructive, it breaks down and becomes non-linear as any of the two dissolution profiles approaches 100% released. A better way to prove the correlation between the ordinary and accelerated dissolution process, is by the time-scale correlation plot. In such a plot we compare the time-scales of the dissolution process in the two systems directly. To illustrate this we take the data obtained by Nicklasson et al. on an USP-II apparatus (at 37 °C, 100 rpm, and pH 7.4) [19]. Nicklasson et al. measured the fraction released after 0, 0.25, 0.5, 1, 1.5, 2, 3, 4 h and obtained $Q_{\text{USP-II}} = 0$, 11, 22, 40, 55, 68, 86 and 96%, respectively.

To obtain the time-scale correlation between the dissolution process in the ACDRA and the one in the USP-II apparatus, we determine the instants when the fractions $Q_{\text{USP-II}}$ are released in the ACDRA. After that we plot the points of time obtained in the ACDRA vs. the corresponding time in the USP-II apparatus. In Fig. 7 we show three plots of this kind. They correspond to three different experiments performed on the ACDRA system: the stirring was 150 rpm, the solvent was

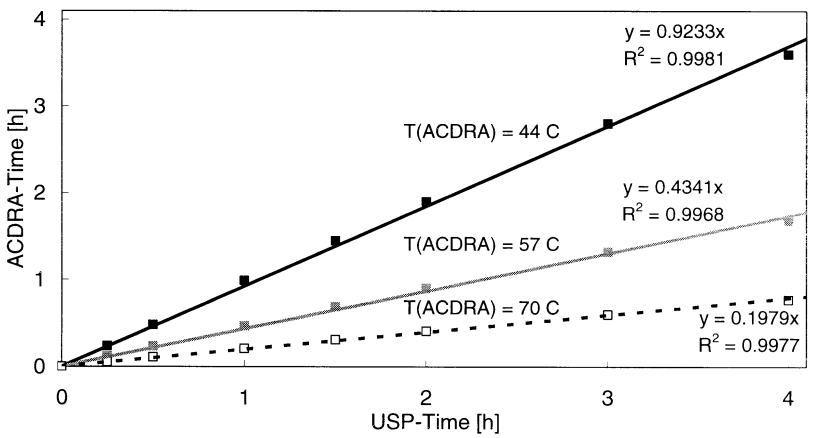

Fig. 7. Time-scale correlation plots of the release process in the USP-II apparatus (37 °C, 100 rpm, pH 7.4 buffer) with respect to the accelerated process in the ACDRA (T, 150 rpm, water). The temperatures in the ACDRA were $T = 44$, 57 and 70 °C, respectively.

water, and the temperature was 44, 57 or 70 °C, respectively.

From the plots in Fig. 7 we notice that:

1. There is a linear correlation at all temperatures.
2. 44°C, 150 rpm, and water in the ACDRA is similar to 37 °C, 100 rpm, and pH 7.4 buffer in the USP-II. This is because the slope (≈ 0.92) is close to unity. Here, the reduced solubility of salicylic acid in water is compensated by an increased temperature and stirring. (The pH rapidly decreases to about three as salicylic acid dissolves in pure water.)
3. The release process can be accelerated by about five times in the ACDRA (70 °C, 150 rpm, and water), as compared to the ordinary USP-II method at 37 °C, 100 rpm, and pH 7.4 buffer (the slope $\approx 0.20 = 1/5$).

Finally, we emphasise that when developing a new at-line dissolution test method for a controlled release product, it is important to prove that one obtains the *same* time-scale correlation plot for all grades of the (semi)product. (This includes 'good' batches as well as the 'bad' ones with too fast or slow dissolution.) If the same time-scale correlation is obtained for good as well as bad batches, the accelerated test is sensitive to the quality variations. This means that the accelerated test can be used at-line for real-time quality control, which should improve the overall quality and/or shorten cycle times. For future development, it is therefore important to save samples from 'bad' batches, in particular from those that are out of spec.

4. Conclusions

At-line dissolution tests are important diagnostic tools for real-time quality control in large-scale pharmaceutical production of controlled release formulations. In this paper we have described the ACDRA system, which is designed for this topic.

We also discuss some of the problems one may run into at the development of new, accelerated at-line dissolution test for pharmaceutical production. The most common reasons for lack of correlation are phase transitions in the formulation, or drastically changed stirring conditions. We have also discussed some possible solutions to these problems. We use the USP dissolution calibrators, non-disintegrating type, salicylic acid tablets to illustrate our ideas.

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