Non-destructive Dissolution Testing Correlation

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Abstract

To replace conventional laborious dissolution testing of immediate-release tablet formulations by non-destructive near-infrared (NIR) transmission spectroscopy, single and model-dependent dissolution parameters were examined to determine whether they yielded results similar to those of the primary method. The non homogeneous dissolution process made the dissolution models unsuitable for establishing calibrations. The best calibration was found using a single parameter: percent active substance dissolved after 20 min (%20min). Accuracy – 99.8% recovery – was in the same range as that of the primary method (100.4%) in which dissolution was monitored by fiber optics directly in the dissolution vessel; precision, on the other hand, was poorer [relative standard deviations: 1.13% (calibration set) and 3.70% (validation set) vs 0.75%]. This study strongly suggests that non-destructive dissolution analysis using NIR transmission spectroscopy can be used in dissolution testing.

Introduction

Non-destructive analysis using near infrared (NIR) spectroscopy is increasingly popular, especially for routine identification tests [1-4] and content determinations. The elimination of laborious sample preparation increases throughput. Application has therefore been investigated to other routine analyses [5, 6], e.g. content uniformity [7, 8], coating thickness and quality [9-11], and hardness testing of solid formulations [12-16]. The present study tested the feasability of NIR spectroscopy for determining particle size, crystallinity, hardness and coating characteristics, all of which are key parameters in the dissolution of solid formulations.

In the NIR range (0.8–2.5 μm, 12,500–4,000 cm-1 respectively), overtones and combinations of the vibration of CH, OH and NH bonds are mainly observed. Excitation is relatively low, enabling thick samples such as tablets to be penetrated. The NIR signal measured is a complex function of physical and chemical parameters that has to be resolved chemometrically [17].

A single sample parameter is normally correlated with the sample NIR spectrum in chemometry, meaning that the whole dissolution process has to be reduced to one value. This can be achieved using single points on the dissolution profile, e.g. the dissolution half-life ($t_{50\%}$) or percent active substance dissolved after 20 min (%$_{20min}$), or by using the dissolution pretreatments available in special dissolution models [18-20] (Table 1).

Experimental

Figure 1, page 23, illustrates the study design.

Samples

The feasibility study was conducted on immediate-release benzodiazepine tablets (N = 81) containing 6 mg active substance (Table 2).

40 tablets were assigned to the calibration set, 20 to

Table 1   Dissolution parameters and kinetic models [18-20].

Parameter	Explanation
$t_{50\%}$	Dissolution half-life (time to 50% dissolution).
%$_{20min}$	Percent active substance dissolved at 20 min.
MDT	Mean dissolution time: first statistical moment of the cumulative dissolution process, given by the area between the dissolution profile and its asymptote.

Kinetic model	Formula
RRSBW	$\log [- \ln (1 - M / M_0)] = b * \log t - \log a$
biexponential	$M = A_0 * [1 - \exp(- ka * t)] + B0 * [1 - \exp(- kb * t)]$
Hixson Crowell	$(M_0)^{1/3} - (M)^{1/3} = k_{HC} * t$
Higuchi	$M = k_H * t^{1/2}$

| Legend		
	a	scaling parameter
	b	shape parameter
	A_0	amount of active substance (process 1)
	B_0	amount of active substance (process 2)
	k_a	dissolving constant (process 1)
	k_b	dissolving constant (process 2)
	k_H	dissolving constant (Higuchi model)
	k_{HC}	dissolving constant (Hixson Crowell model)
	M	dissolved amount of active substance at time t
	M_0	total amount of active substance to be dissolved
	RRSBW	Rosin-Rammler-Sperling-Bennet-Weibull
	t	time
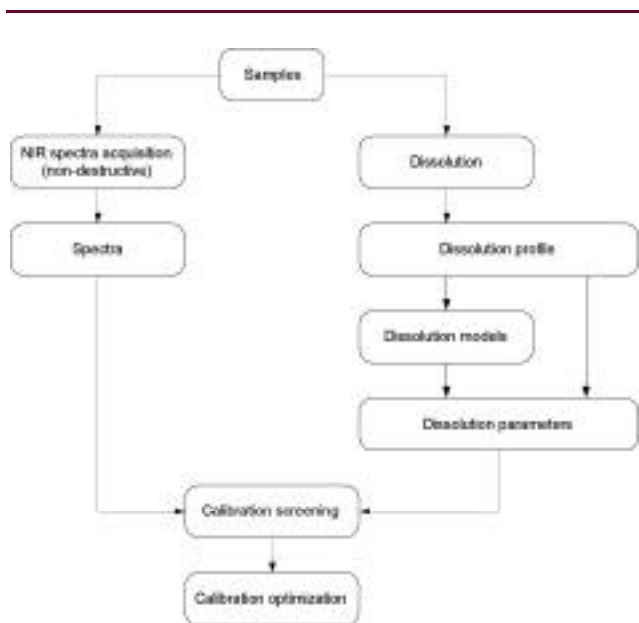
Figure 1 : Experimental Study Design

Table 2. Feasibility study samples.

Samples	Tablets/lots (n/n)	Storage
Regular	51/17	room temperature, humidity uncontrolled
Stability	15/5	25°C, 60% relative humidity, stored 2-5 years
Stability	15/5	30°C, 75% relative humidity, stored 2-5 years

the validation set, and the remaining 21 to the challenge set as a further test of calibration. All assignments were randomized.

NIR spectra acquisition

After optimization of instrument parameters (NIRTAB 5021, Büchi Labortechnik AG, Flawil, Switzerland), transmission spectra were acquired with 10 scans against 1 mm Spectralon references (Büchi) in the spectral range 6000–11,520 cm-1 using tablets placed in the 5 mm diameter flexible sample plate (Büchi).

Dissolution

The tablets were dissolved in apparatus 2 [21] in 900 ml pepsin-free simulated gastric fluid [21] at 37.0 ± 0.5°C [22]. The extent of dissolution was measured with a fiber optic immersion probe (Ultra Mini TS 10 mm + 2 LL UV Li/SMA

974725/18, Hellma GmbH & Co., Müllheim/Baden, Germany) and a scanning spectrometer (Varian Cary 50, Varian International AG, Zug, Switzerland) directly in the vessel [23]. The wavelength of 239 nm at the peak maximum (A_{239}) was used to quantify the amount of dissolved substance, with subtraction of excipient interference at the correction wavelength of 450 nm (A_{450}) [24]. The proportion of dissolved active substance (%$_{dissolved}$) was quantified using two standard solutions representing 100% dissolution. Using the averaged value of the two standard concentrations ($<c_{standard}>$) and their weight-corrected absorption readings at 239 nm ($<A_{standard}>$), single-point calibration was performed with 15,000 as the conversion factor (Formula 1).

Formula 1

$$\%_{dissolved} = (A_{239} - A_{450}) * <c_{standard}> * 15,000 / <A_{standard}>$$

For quality assurance reasons the difference between the weight-corrected standard absorption readings could not exceed 2.00%.

Tablet dissolution was monitored for 30 min at a stirring rate of 50 rpm [22], followed by an infinity test at 150 rpm for 5 min to measure the total amount of active substance.

Quantification measurements were acquired every 30 seconds with an averaging time of 1 second throughout the process.

The parameters t_{50}% and %$_{20min}$ were recorded and the mean dissolution time (MDT) calculated without including the infinity test period. The resulting profiles (0–30 min) were also transformed using the Rosin-Rammler-Sperling-Bennet-Weibull (RRSBW), Hixson Crowell, Higuchi, and biexponential kinetic models.

Calibration screening and optimization

Calibration screening was performed using the chemometric software (Nircal 3.01, Büchi) and the dissolution parameters $t_{50\%}$ and %$_{20min}$, MDT, and model-dependent parameters *(Table 3)* REF.

Calibration was optimized using partial least square (PLS) regression and fitted with a maximum of 8 factors. Spectra were pretreated by closure-based normalization methods.

Results
NIR data

The NIR transmission spectra showed clear differences in absorption properties between the stability and regular samples *(Figure 2, page 24)*.

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Table 3 Model-dependent parameters used in calibration screening.

Model	Parameters
RRSBW	$a \, / \, b \, / \, T_D$
biexponential	$A_0 \, / \, B_0 \, / \, k_a \, / \, k_b$
Hixson Crowell	$k_{HC} \, / \, Tc$
Higuchi	k_H

Legend		
	a	scaling parameter
	b	shape parameter
	A_0	amount of active substance (process 1)
	B_0	amount of active substance (process 2)
	k_a	dissolving constant (process 1)
	k_b	dissolving constant (process 2)
	k_H	dissolving constant (Higuchi model)
	k_{HC}	dissolving constant (Hixson Crowell model)
	RRSBW	Rosin-Rammler-Sperling-Bennet-Weibull
	T_c	critical time at which first particles of active substance disappear
	T_D	time to 63.2% dissolution

Dissolution data

The mean all-tablet dissolution profile *(Figure 3)* showed great variation over 30 min. The small error bars at the end of the infinity test (30 to 35 min) indicate a constant amount of active substance in each tablet (uniformity of content).
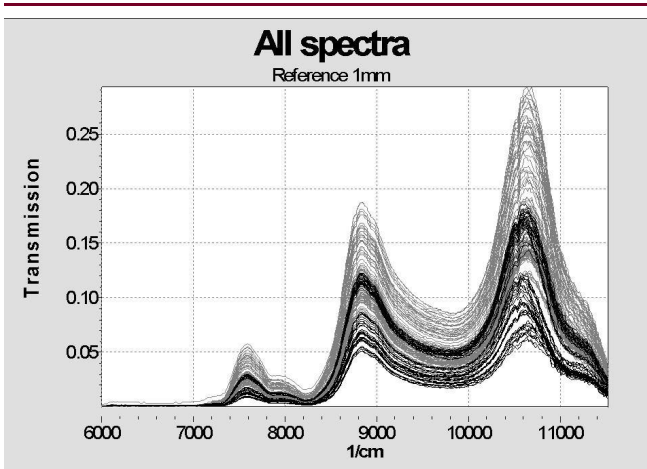

Figure 2 NIR tablet spectra [N = 81: regular (grey), n = 51; stability (black), n = 30].
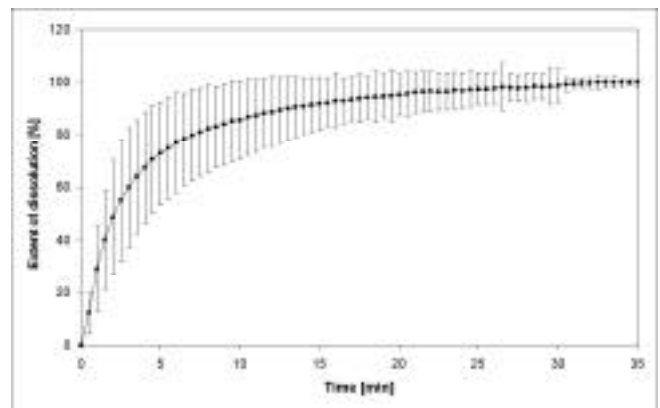
Calibration screening

Best results were achieved using $\%_{20min}$. Dissolution half-life ($t_{50\%}$) values were too similar in all tablets for calibrations to be possible [mean: 2.3 min; relative standard deviation (RSD): 0.8%]. MDT values were better distributed but did not produce good calibrations, while those obtained with all the model-dependent parameters were poorer still.

Calibration optimization

The $\%_{20min}$ parameter *(Figure 4)* gave the best calibration,

with the stability and regular samples almost forming three different clusters reflecting the impact of the storage conditions on the formulation characteristics. These changes could also be seen in the NIR spectra *(Figure 2)* and dissolution behavior.

The coefficients of correlation were 0.8279 and 0.8379 for the calibration and validation sets, respectively. The so-called Q value [17] (between 0 and 1, with values between 0.9 and 1 indicating very good calibration) was 0.8046. Accuracy was 99.8% and consistency, at 98.6, close to the ideal of 100. Precision (RSD) was 1.13% and 3.70% for the calibration and validation sets, respectively. Quality was demonstrated by the fact that inclusion of the

Figure 3   Mean dissolution profile in all tablets (N = 81). Error bars:± 2 standard deviations.
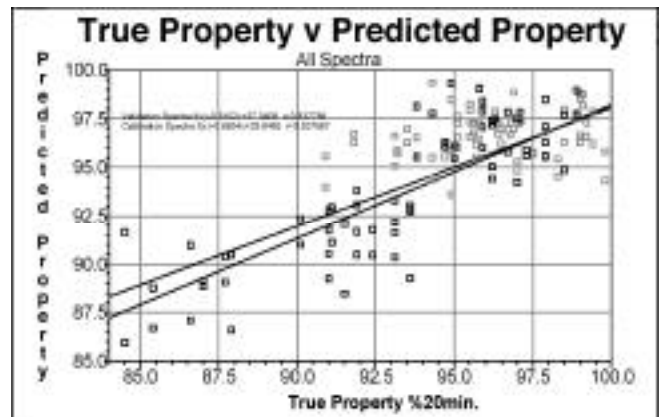

Figure 4   Optimized calibration using the $\%_{20min}$ parameter (black = stability samples; grey = regular samples).

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control set in the optimized calibration changed the calibration parameters only slightly. Accuracy was 99.6%, consistency 106.2 and precision (RSD) 1.10% and 3.58% for the control and validation sets, respectively.

Since the NIR results are based on the primary dissolution test method, they had to be compared with the 100.4% accuracy and 0.75% precision (RSD) of the latter. The residuals (true property - predicted property) were plotted against their true properties *(Figure 5)*. The maximal residual was -7.15% and the graphic suggests a slight trend towards an exponential line.

Discussion and conclusions

This feasibility study has proved that the dissolution of immediate-release tablets can be correlated with the NIR spectra.

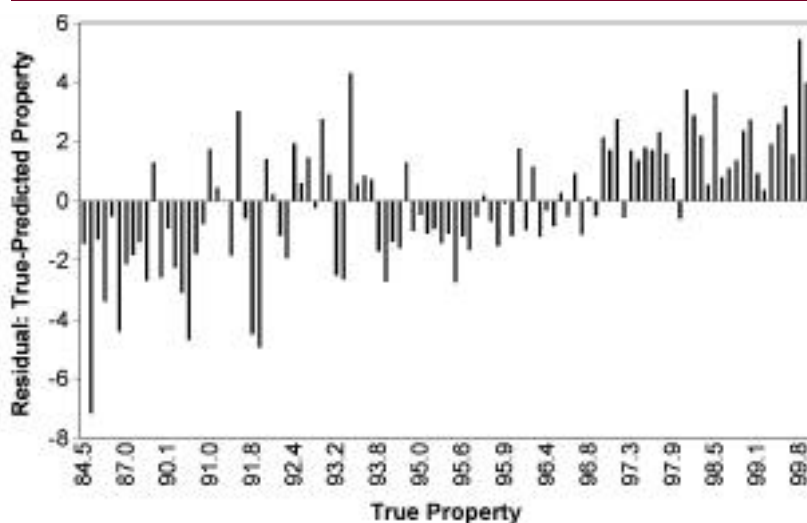The number of scans chosen for the spectra – 10 – was

Figure 5   Residual plot (%) of the optimized %$_{20min}$ calibration.

relatively small, accounting in particular for the noise level in the 10,600 cm-1 region of the 1 mm reference spectra (Figure 2), confirmed by the prefered NIR spectra pretreatment normalization. On the other hand, higher scan numbers could warm up the tablets and create spectroscopic artefacts.

Multiple profile shapes were detected in the dissolution process. Factors responsible for the non-homogeneity were tablet hardness, the particle size and crystallinity of the active substance, the crystallinity and distribution of the breaking excipient, and production by direct compression. Together they made it difficult to apply dissolution models and their parameters to calibrations with the immediate-release formulation. For extended-release formulations, on the other hand, with

their more homogeneous dissolution process, such models could be a great help in establishing calibrations.

Regular and stability samples both covered only the 85–100% dissolution range (Figure 4). The trend of the residual plot (Figure 5) was due to the effect of the different storage conditions on the regular and stability tablet parameters. Clearly, therefore, better calibration models could be achieved if the two sample categories were not mixed. Given the cluster behavior, regular samples with a lower extent of dissolution should be used to extend the calibration range. Such samples must be specially produced by varying tablet hardness, the particle size and crystallinity of the active substance, and the crystallinity and amount of breaking excipient. However such a strategy is cost-intensive and time-consuming during method development, hindering the application of NIR transmission spectroscopy to dissolution. The benefits of routine NIR are fast and non-destructive dissolution analysis. Compared to conventional dissolution testing, a potential decrease in precision could readily be compensated by increasing the required sample number.

In conclusion, this study strongly supports the correlation of NIR transmission spectroscopy to dissolution testing of immediate-release formulations.

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