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Prediction of drug dissolution from Toremifene 80 mg tablets using NIR spectroscopy

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Tyylin kuvaus: Otsikko 2: Sisennys:Vasen: 0 cm, Monitasoinen + Taso: 2 + Numerointityyli: 1, 2, 3, … + Aloittava nro: 1 + Tasaus:Vasen + Tasaa: 8,75 cm + Sarkain jälkeen: 9,77 cm + Sisennä: 9,77 cm, Sarkainkohdat: 1,02 cm, Luettelosarkain + Ei ole kohdassa 5,77 cm + 9,77 cm

Tyylin kuvaus: Kuvaotsikko

Kommentoinut [OK1]: Were other factors such as precision and intermediate precision evaluated in this study? This is included in ICH / FDA / EMA guidance as a requirement for spectroscopic methods in pharmaceuticals. This is important and it shows how robust the method is and if it will remain valid over time. If not, please comment on this.

Abstract

The aim of this study was to justify substitution of conventional QC dissolution analysis for non-invasive NIR measurement of Toremifene 80 mg tablets. The idea was to study if it is achievable to justify implementation of a NIRS method by integrating the method development initially to discrimination power of the dissolution method. Discriminatory power of the current dissolution method was evaluated by analyzing 20 tablet batches manufactured according to a Design of Experiments approach. The critical formulation factors affecting dissolution were statistically studied for their significance by multivariate regression analysis. In order to study if these factors can be detected by NIRS, PLS calibration models were developed. Finally, PLS model was built to correlate NIR data with the actual dissolution results to predict the released amount of toremifene in 30 minutes. To obtain the data the tablet batches were measured by NIR using diffuse reflectance technique and multivariate analysis tool was used to calibrate the NIRS models. Correlations between the critical formulation factors and the NIR spectra of Toremifene 80 mg tablet were shown and it was thus justified to develop a NIRS prediction model for dissolution. The NIRS model indicated good prediction capability and adequate accuracy.

Acronymes

QC	Quality control
NIR	Near infrared spectroscopy
NIRCI	Near infrared chemical imaging
PLS	Partial Least Squares
DoE	Design of Experiments

Key words

Toremifene, dissolution, discrimination capability, Design of Experiments, near infrared spectroscopy, PLS calibration model

Kommentoinut [OK2]: The authors state the aim of the study is to 'justify substitution of a conventional QC dissolution analysis', however it is not clear from the abstract why this is needed. I.e. what is wrong with conventional dissolution? Why is NIR needed?

Kommentoinut [OK3]: Abstract, line 27: The authors state the model showed good prediction capability and accuracy - it would be useful to provide some numbers here (i.e. R2 and SEE / SEP values) to prove this.

Kommentoinut [OK4]: Abstract, line 17: The following sentence doesn't make sense: 'The idea was to study if it is achievable to justify implementation of a NIRS method by integrating the method development initially to discrimination power of the dissolution method'. Please rephrase to make it clear what the aim of the study is.

Kommentoinut [OK5]: Acronyms need defining. E.g. QC, NIR, NIRS, PLS. None of these have been defined and will mean nothing to the lay reader

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1. INTRODUCTION

Currently, dissolution is a key method to evaluate the pharmaceutical oral dosage forms for their drug release, consistency and similarity from batch to batch. As an analytical method, dissolution testing, however, is time consuming and provides tasks like instrument calibration, media preparation, sample collection and manipulation, data collection and carrying out a drug assay analysis by suitable quantification technique. Hence, due to multi-phased analysis procedure dissolution results may be affected by the variability associated with dissolution methodology itself.

An optional way to assess dissolution behavior of a pharmaceutical drug product is to utilize near infrared spectroscopy (NIRS) and to combine it with multivariate statistical methods. Linking NIRS to dissolution behavior enables on-line non-invasive measurement of the production batch and further, together with multivariate modeling, predicting of the release rate of an active ingredient from a dosage form. This approach is also in line with the current ICH Q8 and European guidelines which encourages carrying out real-time control of drug product rather than testing limited samples on final product (ICH, 2009), (EMEA, 2014).

Since last decade, NIR spectroscopy has been increasingly used for real-time measurements of critical process and product attributes in pharmaceutical industry. ~~In addition to final product testing there are several steps in manufacturing processes where at-line, in-line or on-line measurements are beneficial. Räsänen and Sandler (2007) reviewed the applications of near infrared spectroscopy in development of solid dosage forms. Utilization of spectroscopy methods in development and characterization of solid pharmaceutical products has been reported by Aaltonen et al. (2008). Later De Beer et al. (2011) summarized studies of utilizing NIR and Raman spectroscopy in in-process monitoring and production processes. Various applications have been reported related to utilization~~ currently move towards continuous manufacturing. Goodwin et al. (2018)

Kommentoinut [OK6]: Introduction: Again, grammatical errors are present throughout the manuscript. Please amend. Introduction, line 58: The studies listed here are all over 10 years old. There have been many advancements in the use of PAT in prediction of drug product variables. I would recommend citing and focussing on more up-to-date articles.

Kommentoinut [OK7]: Introduction, lines 111 - 116: The way that the aims have been written are confusing and vague. Please list the exact aims of the study e.g. this study aims to evaluate the use of NIR spectroscopy as an alternative non-destructive method to predict drug release. The impact of X, Y and Z on drug release have been studied.... or something along those lines. Be clear and concise.

Kommentoinut [OK8]: Introduction, line 98: Define NIRCI

Kommentoinut [OK9]: Introduction: The introduction is overly long - I would recommend reducing the length and focussing only on those articles that are 1) up-to-date and 2) relevant to your study.

pioneered in the field of dissolution and NIR with a work in which they built a NIRS model to predict release of theophylline from film-coated tablets. Later several workers have presented examples of

to changes in NIR spectra. Based on these results NIRS can be used in combination with multivariate data analysis to predict dissolution behaviour with variation in process conditions. Pawar et al. (2016)

example of utilizing NIR was presented by Antonio and Maggio (2018) who linked polymorphic form I content of mefenamic acid with dissolution and thus showed that a NIR-PLS model may act

that NIRCI methodology could routinely complement and eventually replace dissolution testing by monitoring a critical material attribute, which was the disintegrant content in their study.

Earlier studies reported clearly show that relationship between pharmaceutical properties of a drug product including their dissolution time can be evaluated by NIR technique. In the studies the justification of methods, however, is focused on adjustment of the correlation between the actual dissolution results and NIR spectra. At present, no studies have been presented where the effect of several formulation factors on the primary result, dissolution, had been systematically investigated before building the mathematical prediction model with aid of NIRS. Therefore, our interest was to study if it is achievable to justify substitution of a conventional quality control dissolution analysis for non-invasive NIR measurement by covering all method development steps. That is, from proving the capability of the dissolution method to showing the validity of the predictive NIR model developed. In our study a holistic approach was pursued.

In this work, we studied if the dissolution method developed for Toremifene 80 mg tablet was capable to distinguish the tablet batches for the critical formulation and process parameters. Further, the aim was to investigate if NIR can capture these critical parameter changes. In other words, the objective of this case study was to find out if it is possible to justify implementation of NIR method by initially

integrating the method development to discrimination power of the dissolution method. The aim was to use Design of Experiments (DoE) approach to study the effects of variables systematically.

2. MATERIALS AND METHODS

2.1 Materials

Toremifene is a basic compound having pKa of 8.7 and thus showing pH dependent solubility within the physiological pH range. In Toremifene 80 mg tablets citrate salt form of the active ingredient is used. Twenty batches of Toremifene immediate release tablets were as study material in this work. The ingredients of the tablets were toremifene citrate, maize starch, lactose monohydrate, povidone (Kollidon K 30), cellulose, microcrystalline, sodium starch glycolate (SSG) type A, colloidal silicon dioxide, magnesium stearate. For each tablet batches, the same lot of each ingredient was used.

Dilute (0.02 M) HCl was used in the dissolution studies as the dissolution media. Toremifene citrate was accurately weighed and dissolved in the dissolution medium to prepare standard solution for spectrophotometric quantitation of the dissolution samples.

Kommentoinut [OK10]: The materials section should include all of the ingredients suppliers and locations.

Muotoiltu: Riviväli: 1

2.2 Preparation of the tablet batches

Twenty (20) tablet batches were manufactured by following a Design of Experiments, DoE (~~Table 1~~). The twenty batches consisted of 17 batches and three centre point repetitions (batches 1, 15 and 20). As the target of the study was to investigate the discriminatory power of the aimed dissolution method and it was known that the dissolution rate of toremifene from the initial formulation is rapid, the investigation was addressed to the formulation variables, which were expected to decelerate dissolution rate. For that, a full factorial screening study design with two levels of three quantitative complemented with one qualitative factor was applied in preparation of the formulations. Quantitative factors of the study were the amount of magnesium stearate, the amount of SSG and tablet mass blending time. As a qualitative factor compression of the tablets was included. The amount of magnesium stearate varied from 1.9% to 3.9% and the amount of SSG, for one, was decreased from 4.7% down to 2.0% to represent normal low level of SSG employed in formulations. Formulation containing no SSG was also prepared. Final blending time of the tablet mass was increased from one minute to two and three minutes. Finally, the force in tablet compression varied from about 60 – 80 N to as hard as possible, 160 – 180 N.

The batches were manufactured by blending toremifene citrate granules with microcrystalline cellulose, SSG and colloidal silicon dioxide, then adding lubricant, magnesium stearate, mixing the mass for 4,5 minutes and finally compressing the tablets. All excipients were passed through 1 mm sieve before introduction for blending and lubrication phases. For tableting, Frogerais MR6 rotary tableting machine with engraved punches was used. In the manufacturing process, variables other than the actual study factors were kept constant.

Kommentoinut [OK11]: Please indicate the blending times

Kommentoinut [OK12]: Please the tableting machine manufacturer and location.

Kommentoinut [OK13R12]:

Muotoiltu: Vasen, Riviväli: 1

Kentän koodi muuttunut

~~Table 1 The composition of the tablet batches in relation to the levels of the study factors.~~

The 20 tablet batches were subjected to drug release analysis in chosen dissolution conditions to study the discrimination capability of the method. In the method USP II apparatus (Distek Inc., USA) was used at rotation speed of 50 rpm and 1000 ml of 0.02 M HCl at 37°C was studied as dissolution medium. Dissolution profiles at time points of 5, 10, 15, 20, 30, 40, 50 and 60 minutes were determined, and an infinity sampling time point was added to profiles. The sampling and quantification of the sample solutions were performed by semi-automated UV/VIS spectrophotometer (Distek Inc.). Six replicate tablets of each batch were analyzed and the dissolved amount of active ingredient was calculated in percentages of the theoretical drug load in one tablet, i.e. 80 mg. The mean dissolved amount and deviation (RSD) of the six replicates were calculated at each sample time points.

Before analyzing the actual study batches, intermediate precision and repeatability of the dissolution method was studied. The results obtained from the tests showed that the method is acceptably precise and repeatable for all the tablet compositions.

Statistical analyses were conducted to discover if the factors according to the design of experiments have influence on the mean dissolved amount at the time point 30 minutes (T=30 min). Regression analysis was utilized in evaluation and p-values were calculated to distinguish statistically significant effects (Minitab 14, Minitab Inc., USA).

~~2.1352.4~~ NIRS studies

In order to study if the critical formulation factors can be detected by NIRS, PLS calibration models for these factors were developed. The aim was to study if NIR spectrum is affected by the critical factors and relationships between the specified and estimated values are achieved. Finally, to predict

Muotoiltu: Otsikko 2

Kommentoinut [OK14]: It seems that batch 15 and batch 20 were the same. Can you check this is correct? If so, why are there 2 batches with the same process parameters?

Kommentoinut [OK15]: line 163: What was the UV wavelength that you used for detection? What was the cell size used?

Muotoiltu: Otsikko 2, Vasen

Kommentoinut [OK16]: : Please provide more information about the NIR spectrometer used. E.g. manufacturer, location

Kommentoinut [OK17]: Which software was used to create the PLS models? Were all wavelengths used for calibration model development? Was cross-validation used and if so, which method (e.g. leave one out CV, venetian blinds)

Muotoiltu: Vasen, Riviväli: 1

the released amount of toremifene in 30 minutes, PLS model was built to correlate NIR data with the actual dissolution results.

153 To obtain the data, the batches were measured by diffuse reflectance technique (Table 1~~Table 2~~). All NIR spectra were recorded at wave number range of 4 000 - 12 000 cm^{-1} with 2 cm^{-1} interval. Column centering (mean) of both spectra and property matrix data was used in the modeling. In centering, the 156 mean of the column is subtracted from the individual elements of this column; resulting a zero mean. To remove light scattering variations encountered during diffuse reflectance spectroscopy, Standard Normal Variate (SNV) without de-trending was used in the models for the amount of SSG and 159 dissolution. For crushing strength, model SNV was not used as the effect of property obviously correlates with scattering. To remove the systematic difference between spectra of standards in the calibration model, baseline correction (offset) was used for models for investigation of effects of 162 crushing strength and SSG. Derivation of the NIRS spectra was carried out for comparison with dissolution.

Table 12 General measurement parameters for the calibration and validation of the NIRS models for Toremifene 80 mg tablets.

Parameter	Value/Setting
Instrument	Fourier-Transform NIR; Spectrum One, PerkinElmer (USA)
- interferometer	NTS
- light source	Michelson interferometer
- beamsplitter	Tungsten halogen source
- detector	Calcium fluoride (CaF_2) Indium Gallium Arsenide (InGaAs) for reflectance
Measurement mode	Diffuse reflectance (R) with NIRA accessory
Scale	
- abscissa	cm^{-1}
- ordinate	A; Log (1/R)
Data	
- range	4000 - 12 000 cm^{-1}
- resolution	16 cm^{-1}
- data interval	2 cm^{-1}
- scans per spectrum	30
Background	Interleaved mode by using internal reflectance sample: mixture of PTFE* and $BaSO_4$.
Mechanics	1.00 cm^{-1} scan speed J-stop 8.94 mm

*PTFE = Polytetrafluoroethylene.

Multivariate analysis tool, PLS (Partial Least Squares; Projection to Latent Structures) was used to calibrate the NIRS model. In the model, NIRS spectra response (x) was calibrated against verified property values (y); the crushing strength of the tablet, the amount of SSG in tablet and released amount of toremifene in 30 minutes.

PLS algorithm was based on Principal Component Analysis (PCA) in which data is presented in variables (scores) and loadings. In PCA, the idea is to extract only meaningful variations from the original spectral data by using two (2) steps. In the first step, new orthogonal variables are created that are linear combinations of the original x-variables. These are called as Principal Components (PC), which are used to visualize spectral variation (x) within the data set thus showing the data in more dimensional space. The first PC carries the most variance information of the data, whereas the

second PC contains most of the residual information, and so on. In the second step, the obtained scores are correlated to the known property values (y). This is performed by using a regression solution (MLR stage; Multiple Linear Regression). Like PCs in PCA, Latent Variable's (LV) in the PLS algorithm are used to explain the variation in the data set. In PLS, a regression solution is performed for the variation in both the spectral data (x) and in the property data (y). The variation in the property data (y) is correlated with the spectral data (x) by finding the best covariance to explain the both data sets.

Kommentoinut [OK18]: Why were only 14 batches used for calibration model development? Which samples were chosen out of the initial 20 batches created, and why?

To establish NIRS calibration model 14 tablet batches were utilized. The batches to build the models were selected to evenly represent the dissolution results range. 10 tablets from each batch were measured for their NIR spectra. Seven of the spectra were used to build the models and three to validate them according to independent validation approach. The models were built by correlating the mean value of each property data to replicate spectra of the sample batch.

3. RESULTS

3.1 Success of the study batch manufacturing

Muotoiltu: Vasen, Riviväli: 1

To assure the success of the manufacturing process and suitability of the study batches, appearance, crushing strength, weight of the tablets, friability, mean thickness and disintegration time were studied as in-process controls. Content uniformity of the batches was studied to assure assay and variability of each study batch and further, dissolution of center point repetition batches were carried out to establish repeatability of the manufacturing process.

Kommentoinut [OK19]: The authors report characterising tablet batches using friability / crushing strength / disintegration time / content uniformity etc. It would be useful to report this data here and please include info in the methods section about the techniques used.

3.2 Discriminatory power of the dissolution method

Table 2~~Table 3~~ shows the dissolution results of the study batches and the significant formulation factors affecting dissolution. Examples of dissolution profiles for the batches that are discriminated by the dissolution method and are further used in NIR model development as calibration samples are shown in Figure 1~~Figure 1~~.

Results of the statistical analysis show that the factors having significant effect on dissolution of
204 Toremifene 80 mg tablets at 30 minutes sampling time, *i.e.* at the specification time point, were the amount of SSG and the crushing strength of the tablets (p-values 0.009 and 0.007, respectively). Decrease in release rate was seen when no SSG was in the formulation, whereas the highest amount
207 of SSG, 4.7%, enabled rapid dissolution. Foreseeably, hard tablets provided slower dissolution than the tablets pressed to normal tablet strength.

On the other hand, it was shown, that the final blending time of the tablet mass or the amount of
210 magnesium stearate did not have an effect dissolution rate of toremifene. As the final blending time was increased to double and triple, *i.e.* substantially high, it can be concluded that blending is not a critical manufacturing step in relation to the rapid release of active ingredient. The same applies to
213 the amount of magnesium stearate which was blended into tablet mass in double quantity at maximum. The p-values for the final blending time of the tablet mass or the amount of magnesium stearate were 0.947 and 0.234, respectively, indicating insignificant effect on dissolution ($p>0.05$).

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Table 23 The composition of the tablet batches in relation to the levels of the study factors and the corresponding dissolution results.

Batch/ Sample	Amount of magnesium stearate % (w/w)	Amount of Sodium starch glycolate % (w/w)	Final blending time (min)	Crushing strength	Drug release in 30 min (Mean %±RSD)
1	2.9	2.0	2	Normal	96±3.8
2	1.9	4.7	1	Normal	97±2.3
3	1.9	4.7	1	Hard	82±9.9
4	2.9	2.0	2	Hard	77±9.3
5	3.9	0.0	3	Normal	92±8.4
6	3.9	0.0	3	Hard	56±15.6
7	1.9	0.0	3	Normal	82±4.7
8	1.9	0.0	3	Hard	80±9.0
9	3.9	0.0	1	Normal	89±11.8
10	3.9	0.0	1	Hard	56±16.2
11	3.9	4.7	1	Normal	96±1.8
12	3.9	4.7	1	Hard	88±6.9
13	1.9	4.7	3	Normal	96±2.2
14	1.9	4.7	3	Hard	89±4.4
15	2.9	2.0	2	Normal	98±2.1
16	3.9	4.7	3	Normal	97±2.3
17	3.9	4.7	3	Hard	87±5.4
18	1.9	0.0	1	Normal	86±4.1
19	1.9	0.0	1	Hard	87±6.7
20	2.9	2.0	2	Normal	98±1.0

Kommentoinut [OK20]: It seems that batch 15 and batch 20 were the same. Can you check this is correct? If so, why are there 2 batches with the same process parameters?

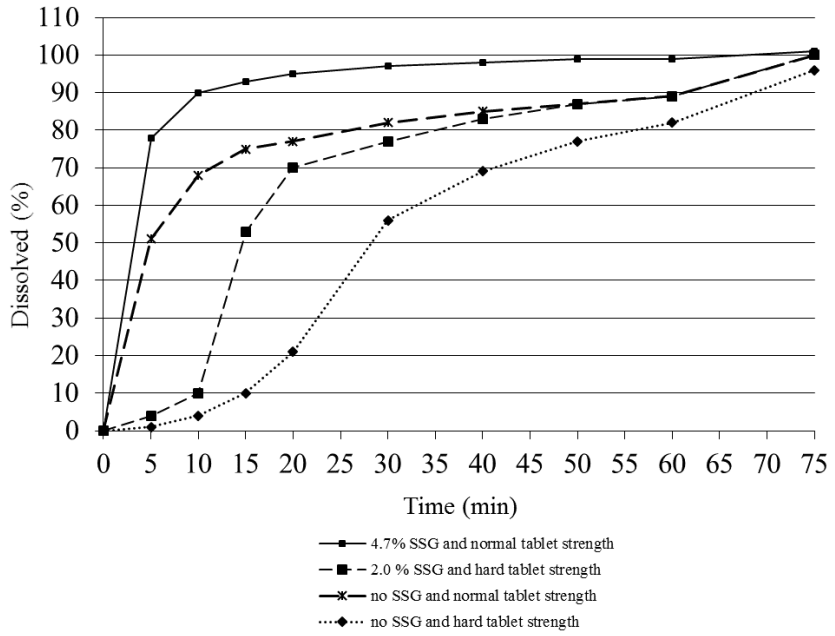


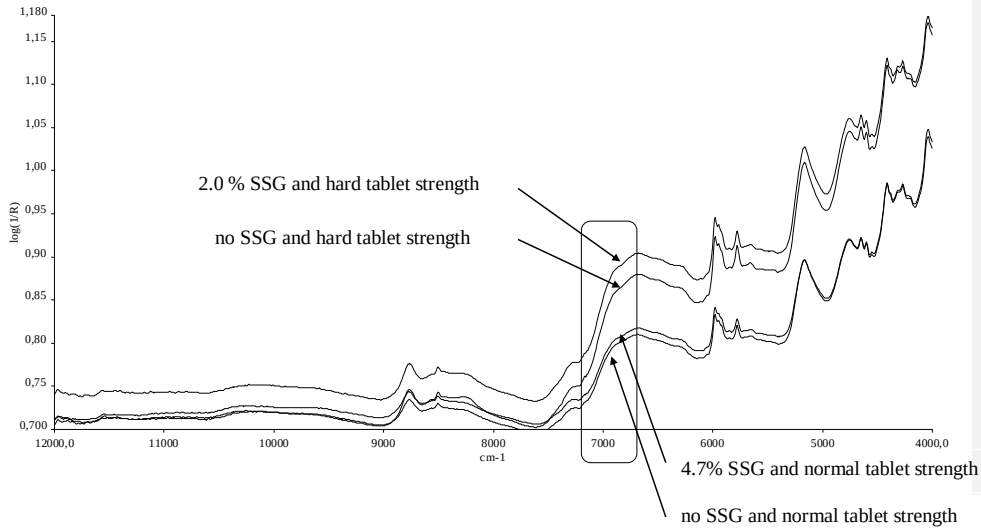
Figure 1 Examples of the effects of crushing strength and the amount of sodium starch glycolate (SSG) on the dissolution profile.

Kommentoinut [OK21]: Instead of writing 'batch 1, batch 7' etc, can you include the parameters that have been changed on the figure itself? E.g. no SSG and hard strength etc. It would be easier for the reader to understand. DONE

3.3 NIRS results

3.3.1 Spectral data

All NIR spectra were recorded at wave number range of 4 000 - 12 000 cm^{-1} with 2 cm^{-1} interval. It was shown that the formulation factors found critical in the discriminatory study affect the NIR spectra of Toremifene 80 mg tablet. Figure 3 shows the spectra of the example batches found to discriminate in dissolution (ref. Figure 2~~Figure 2~~).



231

Figure 2 Examples of the raw NIR spectra of the batches that are discriminated by the dissolution method and are further used in NIR model development as calibration samples.

234

Kommentoinut [OK22]: Why is there a baseline shift in the NIR spectra upon different process parameters? E.g. why does the addition of SSG (batch 4) cause an increased absorbance at the highlighted region, compared to 0% SSG (batch 10). More critical analysis of the spectra should be included

3.3.2 Prediction models for the critical formulation factors

Kommentoinut [OK23]: The models developed in this section use a high number of latent variables (5 and 7), and hence may pose a risk that you overfitted the model. Can you provide rationale as to why this number of latent variables are required? Did you check the loading spectra to ensure noise was not occurring upon increased latent variables? It would be interesting to report what percentage of data variation accounted for LV1 & LV2 to determine this.

237 The idea in NIRS model development for the critical formulation factors was to find out if the NIR spectra are affected by the factors and if relationships between the specified and estimated values can be achieved. The motivation for model development was to show correlation between the critical 240 factors and NIRS and thus justify the development of the actual NIRS prediction model for the released amount of toremifene in 30 minutes. Thus, to estimate crushing strength and the amount of SSG in Toremifene 80 mg tablets, NIRS prediction models were developed. A model showing 243 variance (R^2), standard error of estimate (SEE) and standard error of prediction (SEP) of 95.1%, 8.6 N and 9.3 N, respectively, was resulted for estimating the crushing strength of the tablets. Five (5) latent variables were in the PLS model and the mean property value in the model was 109.1. The 246 specified values used in building the model varied from 55 N to 165 N. R^2, SEE and SEP for the NIRS model predicting the amount of SSG in the formulation were 96.7%, 0.4% and 0.5%,

respectively. Regarding the model for SSG, the SEP can be considered acceptable, as the mean property value, i.e. the amount of SSG in formulation, is very low mean property value being 2.2%. Seven (7) latent variables were used in the PLS model for prediction. (No detailed data of the models is shown.)

3.3.3 Prediction model for released amount of toremifene in 30 minutes

Since correlation between the critical formulation factors and the NIR spectra of Toremifene 80 mg tablet was shown, it was justified to develop a NIRS prediction model for dissolution. Six (6) latent variables were used in the PLS model for prediction of the released amount of toremifene within 30 minutes, i.e. at the specification time point. Variance (R^2), standard error of estimate (SEE) and standard error of prediction (SEP) of the model were 90.0%, 4.3% and 5.9%, respectively. The mean property value of the dissolution model was 83.8%. In the model, 91.3% of the x-variance explains 90.0% of the y-variance indicating good prediction capability. However, it was during the NIRS method development and data analysis discovered that even more capable prediction model would be attainable: the robustness of the model could be improved by measuring the spectra of each individual tablet used in the calibration model and further subjected to dissolution analysis.

Kommentoinut [OK24]: Same as above - 6 latent variables is fairly high. Can you provide details about LV1 and LV2 data variation? And also comment on whether noise was seen at higher LVs.

3.3.4 Linearity of the calibration curve for released amount of toremifene in 30 minutes

Linearity of the NIRS predicted values versus the specified *i.e.* the actual measured values for released amount of toremifene within 30 minutes was studied. The calibration curve was shown to be linear with a non-significant y-axel intercept. Results of fourteen (14) different tablet batches were used to study the linearity (Figure 3~~Figure 3~~).

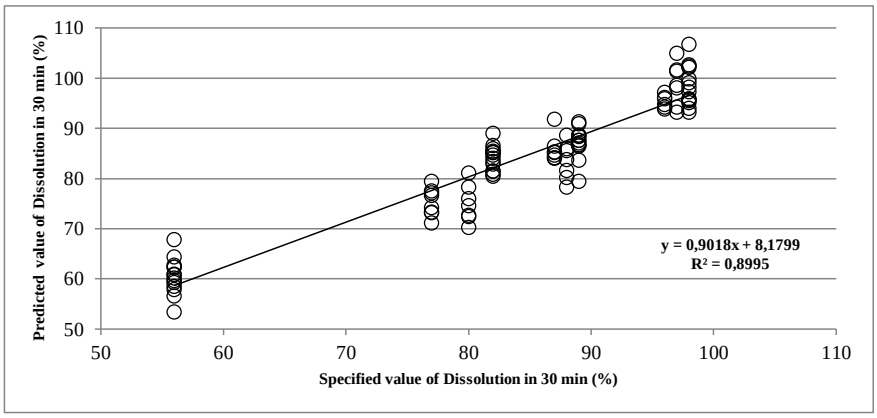


Figure 3 Predicted NIRS values as a function of the actual released amount of toremifene from Toremifene 80 mg tablets.

3.3.5 Accuracy of the model for released amount of toremifene in 30 minutes

Toremifene 80 mg tablet batches analyzed by the dissolution method were scanned by NIR and further analyzed by the NIRS dissolution model (Table 4). It shows the result comparison performed using the mean dissolution values of both methods. In general, it is shown that the dissolution results obtained by the NIRS model are similar to the results obtained by the primary method. The overall bias, sum of the difference of NIRS and dissolution results, was -11.0 percentage units indicating that the obtained values by the NIRS are slightly lower than the corresponding values by the dissolution UV method. By dividing the total bias with the number of batches, 14, one will get a bias value of -

0.8 percentage units per batch indicating good correlation with the NIRS model and the primary dissolution method. Compared to general accuracy criteria for dissolution method, 5%, no significantly increased inaccuracy is originated from the NIRS model.

Table 34 Results of the accuracy test Toremifene 80 mg tablet batches. Comparison of dissolution results obtained with primary dissolution method and NIRS model.

Specified value: Released amount of toremifene in 30 minutes (mean, %)	Predicted value by NIRS (mean, %)	Residual Average NIRS-Specified (%-units)*
96	93	-2.9
97	101	4.4
82	85	3.0
77	77	-0.4
56	63	7.3
82	87	5.4
80	72	-8.2
89	82	-7.4
56	63	6.9
88	83	-5.3
89	90	0.6
98	93	-4.5
87	81	-5.9
98	94	-3.8
96	93	-2.9
	Bias (%-units)	-11.0
	Bias per sample (%-units)	-0.8

*) *Calculated from accurate values.*

4. DISCUSSION

In our study, correlation between *in vitro* dissolution and NIRS was initially built on critical formulation factors found via systematic Design of Experiment study. Our results showed that it is justifiable to use the multivariate NIRS model to predict the dissolved amount of toremifene within 30 minutes *i.e.* at the specification time.

Carrying out a discrimination study according to a design of experiment protocol presented in this work is a labour intensive and time-consuming stage in a development project. However, the data produced is thoroughly considered, qualified and possible to exploit from various perspectives later on. In the present study, discriminatory power of the proposed dissolution method was shown based on the systematic study (Figure 1~~Figure 1~~, Table 2~~Table 3~~) and thus the substitution of the method for NIRS model developed (Figure 3~~Figure 3~~, Table 3~~Table 4~~) was proven sustainable. As presented, we achieved an accurate prediction model, although it was during the NIRS method development and data analysis discovered that even more capable prediction model would be attainable if the spectra of each individual tablet were used in the calibration model and only after that further subjected to dissolution analysis. By doing so, it would be possible to increase the robustness of the model.

Kirsch and Drennen pioneered in the field of dissolution and NIR with a work where they built a NIRS model to predict release of theophylline from film-coated tablets (1995). In the study correlation between NIRS and time to 50%, dissolution was shown for uncoated, 2% and 3% coated tablets. Later several workers have correlated spectral properties to dissolution behaviour of a drug product. The diversity in dissolution results utilized in the studies originates from variables like compression pressure of the tablets (Donoso et al. (2005), and Otsuka et al. (2007) and lubricant mixing time in manufacturing process (Abe H. and Otsuka M., 2012). Latterly Antonio and Maggio (2018) built a NIR-PLS model between polymorphic form I content of mefenamic acid and dissolution. NIR chemical imaging (NIRCI), was used by Yekpe et al. (2015) when they built a model

to API dissolution based on chemical information of disintegrant obtained with NIRCI. Although accurate prediction models were resulted in all these studies, justification of the discrimination capability of the primary method was not incorporated into the studies.

Currently, no studies are published where the effect of several formulation factors on the primary result, dissolution, had been systematically investigated before building the mathematical prediction model with aid of NIRS. In our work, the NIR method development was based firstly on the knowledge of the sensitivity of the primary dissolution method followed by the correlation between the two independent analytical methods. Hence, we demonstrated that NIR could recapture the dissolution rate changes due possible deviations in composition of the final drug product of Toremifene 80 mg tablet. Consequently, in the present case rapid dissolution accordant with the specification can be ensured for the whole production batch and thus the intended *in vivo* behaviour of the product is possible to achieve. Applied as in-line, at-line or on-line method utilization of the NIRS model to qualify the production batches for their dissolution criteria provides a powerful tool to assure consistent quality of the batches, reduces analysis costs and time and accelerates the batch release procedure.

5. CONCLUSION

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The present work illustrated the powerful ability of NIRS to be utilized as a substitutive non-invasive real-time analysis method for conventional dissolution method when the capability of the prime method is proven. In this study discriminatory power of the dissolution method for Toremifene 80 mg immediate release tablet was investigated and NIR spectra of the product were correlated to formulation factors affecting dissolution. Linking of the NIR spectra to dissolution behavior was for the first time justified by a comprehensive dissolution method analysis in which the effect of formulation factors on drug release were examined via full factorial study design. Results of the statistical analysis showed that the factors having significant effect on dissolution of Toremifene 80

mg tablets at 30 minutes sampling time were the amount of SSG and the crushing strength (p-values 0.009 and 0.007, respectively). After this pre-justification NIRS was finally linked with released amount of toremifene within 30 minutes. Based on the Partial Least Squares calibration model developed it is thus justifiable to determine if the dissolution specification of the drug product is met.

Our results show that it is possible to substitute a conventional six sample dissolution analysis of Toremifene 80 mg tablet by non-invasive NIR scanning of the production batches. Among other at release tests this would promote consistent quality of the batches, reduce analysis costs and time and accelerate the batch release procedure. Rapid dissolution accordant with the specification can be ensured for the whole production batch, thus enabling the intended *in vivo* behaviour of the drug product.

We see that our study provides an insight to a holistic and systematic way of building and justifying a methodological correlation model to assure the quality of a pharmaceutical product. There are no studies presented in the literature where building the correlation between *in vitro* dissolution and NIRS is initially based on critical formulation factors found via systematic Design of Experiment study. Therefore, our case study provides valuable information for pharmaceutical scientists developing methods for real-time prediction of drug release. The present work justifies implementation of NIR method by integrating the method development initially to discrimination power of the *in vitro* dissolution method.

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