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Near infrared spectroscopy to monitor drug release *in-situ* during dissolution tests

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ABSTRACT

Dissolution tests can be used to demonstrate suitable in *vivo* drug release through *in vivo*/*in vitro* correlations. This work explores the possibility of using near infrared spectroscopy (NIRS) to monitor *in-situ* dissolution tests. It aims at expanding surrogate methods in quality control of drug products. Laboratory designed tablets of an immediate-release formulation containing folic acid and four excipients were used as case study. The dissolution tests were performed on a 1 L vessel filled with 500 ml of Milli-Q water with a rotating paddle apparatus (apparatus 2, Ph. Eur.) at 50 rpm and 37 ± 0.5 °C. Near infrared (NIR) spectra were acquired *in-situ* with a transflectance probe connected to a Fourier-transform near infrared spectrometer. NIR spectra were regressed against folic acid concentration by partial least squares (PLS) regression. Folic acid concentrations during dissolution tests were obtained by periodically sampling the dissolution vessel and resourcing to an UV method. The proposed real-time NIR method was tested on a validation run yielding a root mean squared error of 0.25 μg ml^{-1} (0.16 μg ml^{-1} for the calibration runs) and a R^2 of 0.93 (0.95 for the calibration runs). The results suggest that NIRS is a suitable analytical technique for monitoring *in-situ* dissolution tests.

1. Introduction

Dissolution testing is an *in vitro* laboratory test method that assesses how efficiently a drug is released by a solid oral dosage form. This test is mandatory by the United States of America (USP, 2015) and European (Ph.Eur., 2014b) pharmacopoeias for solid dosage forms. Dissolution and absorption are necessary for the drug to exert the desired therapeutic effect. Dissolution tests are widely used in different stages of a drug product development, like drug substance selection, formulation development, manufacturing process development and optimization and as quality control test to determine batch-to-batch reproducibility (Anand et al., 2011; Rost and Quist, 2003). Data obtained from dissolution tests can be used to detect physical changes of the drug substance and drug product (*e.g.*, particle size variations) and to establish *in vitro–in vivo* correlations (IVIVC) of drug products (Hernandez et al., 2016). Additionally, dissolution testing plays a pivotal role in regulatory submissions to justify formulation/manufacturing changes that may occur during products life cycle (post-approval changes) (FDA, 1995). In the quality control context (Stuart et al., 2015), dissolution tests are frequently used to assess products quality and performance. This is particularly important for generics (Ozturk et al., 2015; Reddy et al., 2014). Dissolution tests re also relevant in the context of the drug discovery or synthesis of different forms of existing drugs. Many drugs that are poorly soluble in water, therefore classified as class II or IV of the Biopharmaceutical Classification System (BCS). In order to improve drugs solubility, a series of methods have been attempted and profusely described in the literature. Amorphization, complexation, cocrystallization, chemical modification are just a few of the

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available methods (Blagden et al., 2007). In this context, it is important to have an expeditious method to monitor the dissolution tests (Mannava et al., 2016; Zhang et al., 2016). When performing dissolution tests (Ph.Eur., 2014a), the adopted conditions need to be reposted and justified, namely the apparatus type, procedure, agitation rate, test time, volume and compositions of the dissolution medium. Depending on the drug substance or drug product being tested, the dissolution medium should reflect the conditions in the human gastrointestinal tract (GIT), providing an optimal *in vitro–in vivo* correlation (McAllister, 2010). A sensitive, accurate and precise analytical method is needed to determine the rate and extend of drug's dissolution from the drug substance or drug product (Graffner, 2006).

A substantial number of analytical methods for dissolution testing resource to high performance liquid chromatography with UV–vis or fluorescence detection, based on manually or automatically sampled aliquots from the dissolution vessel (Kassis et al., 2010). Most currently adopted methods for monitoring dissolution vessels have a significant number of limitations: requiring large sample amounts, long sampling times (30–60 s) and also the disruptive nature to the dissolution profile due to aliquots removal (Kassis et al., 2010; Laitinen et al., 2010). Additionally, chromatography methods are usually time and labour intensive, use high quantities of organic compounds and require sample preparation which can be a source of potential errors (Laitinen et al., 2010). UV–vis spectroscopy also presents limitations: only a limited number of drug substances are suitable for this technique, presence of excipients (active in UV–vis range), air bubbles and undissolved particles (may interfere with the measurements due to scattering of the light). Additionally, these methods do not provide information of the process that takes place within the tablet, like water sorption, swelling, polymer matrix erosion and drug diffusion.

In-process control requires fast and non-destructive techniques. Imaging techniques allow detailed insight of the tablet dissolution process. Approaches such as magnetic resonance imaging (MRI) (Nott, 2010) and Fourier transform infrared-attenuated total reflection (FTIR-ATR) spectroscopic imaging have been applied in this field. FTIR-ATR was applied to investigate the release of poorly soluble drugs, using a flow-through dissolution test (van der Weerd and Kazarian, 2004; Van der Weerd and Kazarian, 2005) and a USP Apparatus type II (Kassis et al., 2010). Additionally, UV imaging provides spatially and temporally resolved absorbance maps of tablets dissolution behaviour (Østergaard et al., 2014a). It has been extensively used in combination with Raman spectroscopy for capturing the initial stages of the dissolution process of amlodipine besylate (amorphous, dehydrated and free base forms) (Boetker et al., 2011) and to investigate release profiles of theophylline, indomethacin, ibuprofen (Hulse et al., 2012) and sodium naproxen (Østergaard et al., 2014b) in a flow-through dissolution apparatus. Potentiometric sensors (Peeters et al., 2008) and UV fiber optics technology (Guillot et al., 2013; Mirza et al., 2009; Nie et al., 2009) were evaluated as feasible analytical tools for *in-situ* real time monitoring of dissolution tests.

Near infrared spectroscopy (NIRS) combined with chemometric techniques satisfy these requirements and has been intensively used in different fields of pharmaceutical research and manufacturing (Blanco et al., 2006; Ishikawa et al., 2013). The prediction of the released amount of the drug over time using NIRS is restricted to applications were the spectrum obtained from the tablet is correlated with the dissolution profile by means of a chemometric method (Blanco et al., 2006; Freitas et al., 2005; Hattori and Otsuka, 2011; Neves et al., 2012; Tabasi et al., 2009). The estimation of the dissolution profile is therefore merely a mathematical estimation from the NIRS of the intact tablet. NIRS was also used to predict a drug dissolution profile during a running pellet coating process (Pomerantsev et al., 2011) and in tablets subjected to different levels of shear stress applied during powder mixing process (Hernandez et al., 2016). Near infrared imaging was also used as a tool to study the dissolution of ascorbic acid tablets (Ishikawa et al., 2013).

This study proposes NIRS to monitor a drug dissolution test using an *in-situ* transflectance probe. Immediate-release tablets containing folic acid were selected for this study. An immediate release drug product was selected to demonstrate that the NIRS method is sufficiently fast to follow the disintegration and dissolution phenomena.The selected dissolution apparatus was a rotating paddle apparatus (apparatus 2) as recommended by the European Pharmacopoeia (Ph.Eur., 2014b).

NIRS in this context has a limitation coming from the high absorbance of the O-H group of water in the NIR region. However, it was already shown in previous studies that it is possible to monitor to some extent, aqueous and highly complex systems such as bioreactors with NIRS (Cruz et al., 2015). That said, it is not possible to state that all drug substances potentially active in the NIRS region will be properly analyzed using the proposed method. Raman spectroscopy could be seen as an alternative to NIRS since it is also real-time and is not affected by liquid water. However, it has disadvantages such as high background noise due to florescence (especially if a high frequency laser is used) and may present limitations in terms of limit of quantification. Raman also requires the vessel to be protected from external radiation.

As far as the authors are aware, the *in-situ* monitoring of dissolution tests is being reported for the first time.

Table 1
Composition, compression force and hardness of the produced tablets.

Batch	Folic Acid (%)	Lactose (%)	Povidone (%)	Crospovidone (%)	Magnesium stearate (%)	Compression force (t)	Hardness (N)[b]
A	2.55	89.79	3.38	3.38	0.91	2	41
B	2.55	88.34	4.83	3.38	0.91	2	37
C	2.55	86.41	6.76	3.38	0.91	2	41
D	2.55	89.79	3.38	3.38	0.91	5	91
E	2.55	88.34	4.83	3.38	0.91	5	87
F	2.55	88.41	6.76	3.38	0.91	5	81
G[a]	2.55	89.78	3.38	3.38	0.91	2	86
H[a]	2.55	93.00	3.38	3.38	0.91	5	122

[a] Lactose, povidone and crospovidone were added as Ludipress®.
[b] Average of ten determinations.