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Prediction of dissolution profiles by non-destructive near infrared spectroscopy in tablets subjected to different levels of strain

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ABSTRACT

This study describes how the strain on formulation components affects dissolution and how near infrared spectroscopy can be used to predict dissolution. Strain (exposure to shear stress) applied during powder mixing affects the interaction between formulation components. Particles experience shear strain when they move relative to each other in a process affecting the properties of the final product. This stress affects the dissolution of oral solid dosages forms. However, dissolution testing destroys the entire tablet, making it impossible to further evaluate tablet properties when an out of specification result is obtained. Thus, a nondestructive technique such as near infrared spectroscopy is desirable to predict dissolution. The aim of this study was to predict dissolution on tablets with different levels of strain (shear) using near infrared spectroscopy in combination with multivariate data analysis.

Shear was induced using a modified Couette cell on the powder mixture and tablets from these mixtures were produced using a tablet press emulator. Tablets produced with different strain levels were measured using near infrared spectroscopy. Spectra were obtained in diffuse reflectance mode and pretreated with baseline correction to maintain the physical and chemical information of the tablets. Dissolution profiles were obtained using USP Apparatus 2 as a reference method. Principal component analysis was used to study the sources of variation in the spectra obtained. Partial least squares 2 was used to predict dissolution on tablets with different levels of strain.

1. Introduction

Performance evaluations of a pharmaceutical product are essential and mandatory to assess and confirm the quality of a drug product that will ultimately be delivered to patients. In the pharmaceutical industry, dissolution testing is a key analytical tool in both drug development and quality control. The data obtained from dissolution tests can be used to detect physical changes in an active pharmaceutical ingredient (API) and formulated product, to establish *in vitro–in vivo* correlations of drug products, and justify post-approval changes [1,2]. Furthermore, it is useful in identifying critical manufacturing variables, such as mixing time, compaction speed and pressure, and coating parameters.

The standard-setting body, the United States Pharmacopoeia (USP) outlines the use of four industry standard dissolution testing protocols that describe the USP Apparatus 1 (basket), the USP Apparatus 2 (paddle), the USP Apparatus 3 (reciprocating cylinder), and the USP Apparatus 4 (flow-through cell). The choice of the equipment to be used depends on the physico-chemical characteristics of the dosage form. Immediate-release, modified-release, and extended release tablets are usually tested in the USP Apparatus equipped with paddles. In contrast, floating capsules and tablets are generally tested using USP Apparatus 1 equipped with baskets [3].

Despite its simplicity of design and the ease of use the dissolution apparatus lacks reproducibility, and this has become a concern

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Table 1
Calibration and validation set description for the model.

Set	Shear level (revolutions)	Number of tablets	Number of spectra	Cross validation group
Calibration	0	5	10	1
	160	5	10	2
	640	5	10	3
	2560	5	10	4
Validation	0	3	6	N/A
	160	3	6	
	640	3	6	
	2560	3	6	

to the Food and Drugs Administration (FDA) as well as to the pharmaceutical industry. The variability observed in dissolution results often stems from uneven mixing within the dissolution vessels. Studies have shown that tablet position in the vessel, USP Apparatus, and operators have also contributed to variability in drug release profiles [4,5]. Additionally, the most significant challenge has been lack of biorelevance as dissolution methods are often not correlated to *in vivo* performance [6]. Difficulties in having suitable USP calibration tablets, physical-chemical (temperature, particle size, solubility, and polymorphism) and mechanical (position of the aliquot, vibrations, paddle or vessel position) factors can contribute to dissolution variability [7]. Drug release concentration in the dissolution medium is determined with High Performance Liquid Chromatography (HPLC) or Ultraviolet/Visible Spectroscopy (UV/VIS) using solvents with high cost and leading to significant solvent wastes generated in the analysis. However, use of quality by design (QbD) has been introduced in the pharmaceutical industry, and efforts have been underway to control the variance observed in the USP Apparatus [8,9].

Besides formulation parameters, dissolution rate is also affected by process parameters such as tablet press speed and compaction force. One such process parameter that is often neglected is the total amount of strain that the powder experiences, before it goes into the tablet press. Pingali et al. found that the amount of powder strain becomes all the more important when the formulation contains hydrophobic, low melting lubricant such as magnesium stearate, which often is the case [10]. For batch mixing in a V-Blender, Murthy et al. confirmed that the amount of lubricant and strain experienced by the blend leads to a decrease in the rate of *in-vitro* dissolution [11]. Dissolution performance can be affected by the nature of the process stress within the manufacturing steps (batch or continuous). Studies have been carried out to predict the sources and nature of shear and strain that are related to the process stress in such a continuous process. Vanarase et al. explained the effect of number of blade passes (which depend on the residence time and the blade (rpm) and the lubricant feeding point on powder

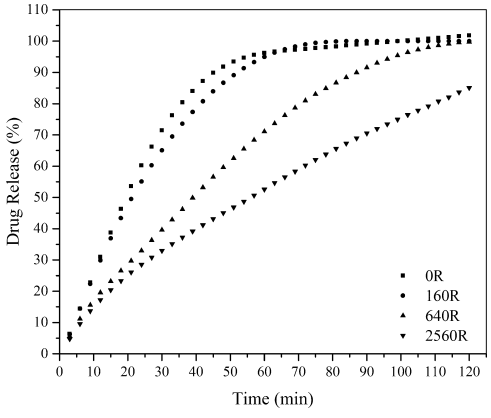

Fig. 1. Dissolution profiles obtained from USP Apparatus 2.

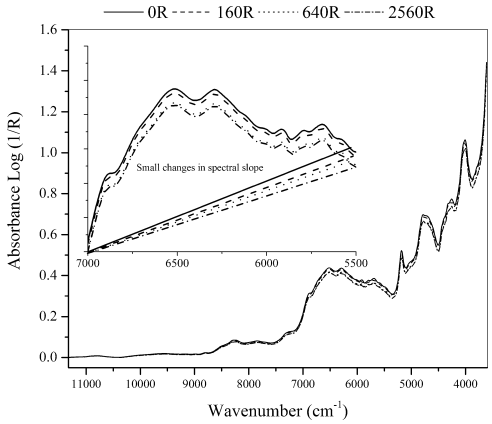

Fig. 2. NIR spectra for tablets subjected to different levels of strain. Zoom of the spectral region of 7000–5500 cm^{-1} where slope changes that is observed.

properties for a continuous mixer [12]. Mendez et al. investigated the increase in hydrophobicity of tablets and hence dissolution time, owing to the strain exposure in feed frame of tablet press [13]. NIR can be used to investigate effects of such shear strain and thus help predict dissolution of oral solid dosage forms. Near infrared spectroscopy (NIRS) gives the opportunity to obtain information on the physical and chemical properties, obtaining a high signal to noise ratio spectrum in one minute and without destroying the unit dose.

NIRS is widely used in the pharmaceutical industry as a fast and non-destructive technique for evaluation of quality attribute of solid oral dosage forms. Near infrared (NIR) spectroscopy provides information on the physical properties (compaction force, shear, etc.) and chemical composition (content uniformity, water content, etc.) of the sample [14]. This information can be filtered out or maintained, depending on the quality attribute of interest. This is achieved using multivariate data analysis. Multivariate data analysis provides several analysis techniques such as principal component analysis (PCA) and partial least square (PLS), and principal component regression (PCR) for extracting this information.

Several researchers have worked with NIR and multivariate data analysis to evaluate the drug release from the final product. Zannikos et al. related the dissolution profiles of carbamazepine tablets exposed to different levels of humidity with NIR spectra [15]. Donoso et al. related the NIR diffuse reflectance spectra using linear regression, nonlinear regression and PLS models to predict drug release of theophylline tablets with different compaction forces at different time points of the dissolution. [16]. Freitas et al. correlated the dissolution profiles with NIR reflectance spectra using a PLS calibration model to predict drug release behavior at different time intervals and for media with different pH [17]. Blanco et al. used a single PLS-2 model to predict the dissolution profiles of tablets made at different compaction forces and consisting of different API concentration[18]. PLS-2 gives the opportunity to predict multiple variables in a single calibration model [19]. Otsuka et al.