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White Paper

Monitoring low dose API blend uniformity with Parteck® M mannitol using near-infrared (NIR) spectroscopy

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Direct compression is often used for tablet manufacturing because it is the shortest, most effective, and least complex method. The physical properties of active pharmaceutical ingredients (APIs) can, however, create a challenge for flowability and compressibility, and, as a result, affect tablet quality parameters.

Segregation is one of the critical issues for low dose actives in direct compression formulations. It occurs when one component of a particulate mixture separates from the other component(s) due to differences in their physical attributes (e.g., size, shape, surface properties, cohesion) and can be induced by gravity, vibration and/or shear, all of which occur during the tableting process.[1] Segregation can lead to variation in content uniformity, which in turn may result in a failure to meet product specifications[1] set by various pharmacopeias. The shape and distribution of particle size of excipients are therefore important to achieve the desired blend uniformity and homogeneity. The flowability and compressibility of excipients are also critical considerations when using direct compression to manufacture tablets.

Advantage of Parteck® M mannitol for direct compression

The large surface area and unique particle structure of Parteck® M excipient ensure that APIs adsorb strongly to it, preventing segregation during the manufacturing process. The unique surface structure of the Parteck® M particles also leads to an accelerated disintegration and dissolution of the tablets.

Therefore, the Parteck® M excipient structure and particle size are suitable for uniform blending of low dose APIs, facilitate formulation work and reduce production costs in direct compression (Figure 1).

Parteck® M excipient provides:

- High compactibility thanks to unique particle properties
- Uniform doses with homogenous distribution
- High dilution potential
- Rapid disintegration
- Excellent API stability thanks to low levels of hygroscopicity, reducing sugar content, and compression forces

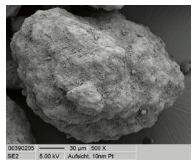

Figure 1.

Unique features of Parteck® M excipient and its structure shown in a scanning electron microscope (SEM) image.

Parteck® M excipient in direct compression for low dose formulations

This white paper describes the use of near-infrared (NIR) spectroscopy for the quantitative analysis of apixaban using Parteck® M excipient as a diluent. It is a rapid, non-destructive analytical method described in USP[2] and can be used for qualitative and quantitative analysis without sample preparation.[3,4] The NIR technique was also used to assess the blend uniformity of low dose API apixaban in a directly compressible composition. Apixaban is an anticoagulant which inhibits free and clot-bound FXa, and prothrombinase activity. The aim of the study was to demonstrate the suitability and reliability of Parteck® M excipient for blend uniformity and homogeneity for low dose and low particle size API using NIR spectroscopy.

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The study was conducted on apixaban (3.0% w/w, 2.5 mg) with Parteck® M excipient as a diluent for an 80 mg uncoated tablet. The particle size of the selected API is very small (d90 ~ 7 µm) in comparison to the other components of the formulation and, as such, powder blend homogeneity is a critical attribute in this formulation.

The formulation included 3% w/w apixaban, 85.63% w/w Parteck® M 200 mannitol, 6.25% w/w Parteck® CCS croscarmellose sodium, 3.75% w/w sodium lauryl sulphate and 1.25% w/w Parteck® LUB MST magnesium stearate. All excipients were mixed throughly using an octagonal blender. These blends were used for study.

NIR spectra were initially collected for identification of API peak regions. The performance and calibration of the instrument was completed prior to analysis of the data set. In order to build a calibration for this type of analysis, multiple API dosage strengths were created synthetically to extend the calibration curve above and below 100% (Table 1). This approach significantly reduces the prediction error, making the analysis more robust.[3] Placebo blends were prepared to study interference in selected regions of wavelengths.

Active content [%]	Calibration (n=5)	Validation (n=10)	Test (n=10)
70	1	0	0
80	1	0	0
90	1	1	0
100	1	1	3
110	1	1	0
120	1	0	0
130	1	0	0

(n = number of samples)

Table 1.

Composition of data set for blend uniformity.

Synthetic calibration samples were prepared in the range of 70% to 130% of label claim (1.75 to 3.25 mg) according to USP <905>.[5] Powder samples were added to vials and analyzed by NIR (Rapid content analyzer, XDS Masterlab, Metrohm) in reflectance mode with an iris black adaptor for wavelength range 400 to 2,500 nm. Figure 2 shows the runs analyzed using Vision software (Metrohm).

The NIR spectrum contains information on overtone resonances and combination of fundamental vibrational modes of the sample.[2] Three overtone peak distinguished regions were identified for apixaban. The first overtone region showed methyl groups at 1,120 nm to 1,150 nm; a second overtone region found for 1,950 nm to 1,990 nm may be attributed to a carboxamide group. The combination band region was observed at 2,180 nm to 2,210 nm and may be attributed to methoxyphenyl group as seen in Figure 3.

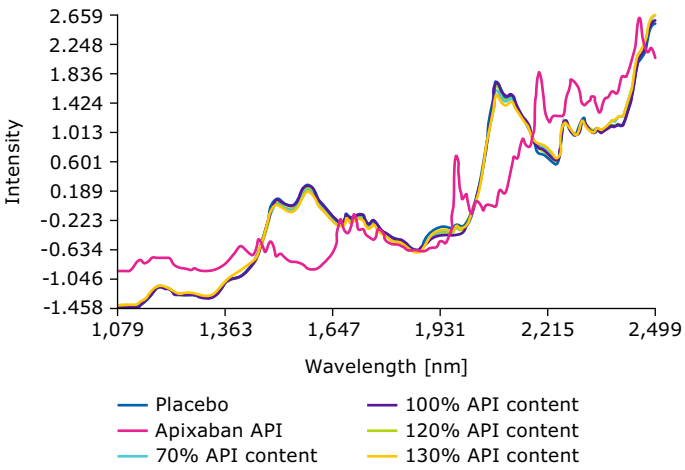


Figure 2.

Comparison of active, blends and placebo in standard normal variance mode.

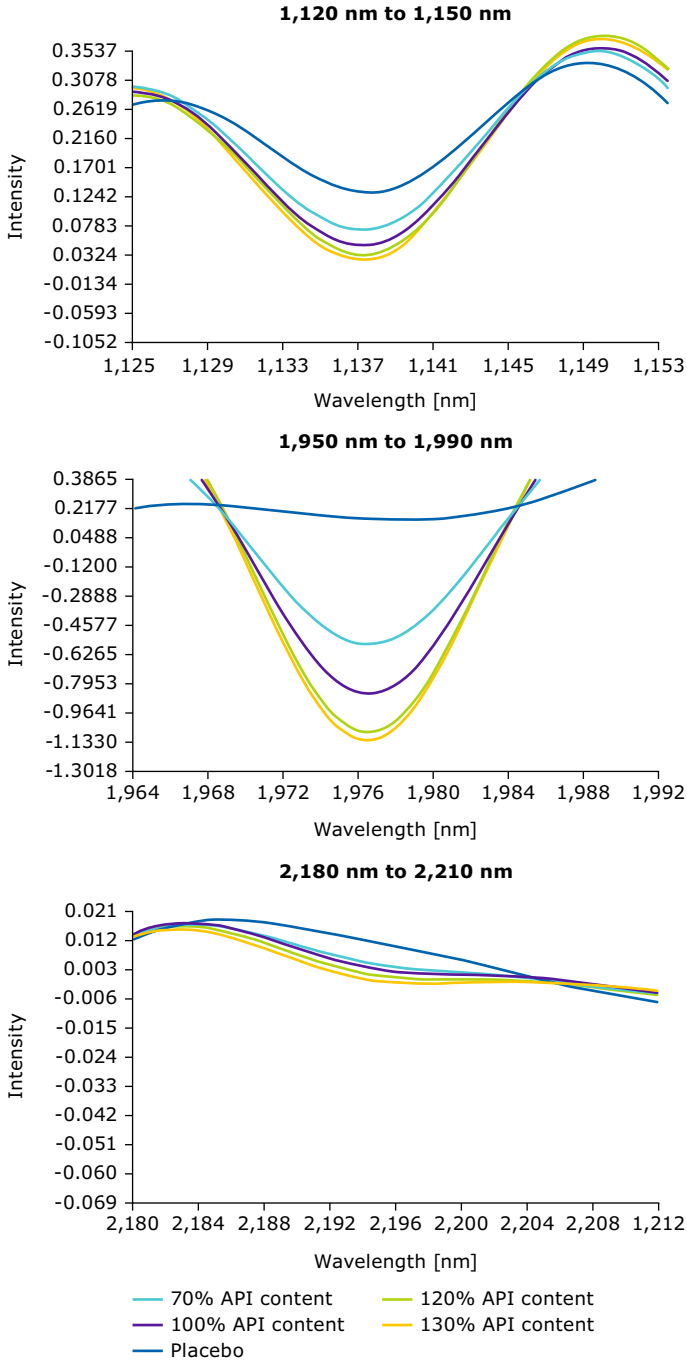


Figure 3.

Second derivative spectra of API and blends in identified regions.

Model	1	2	3	4	5	6	7
Pre-Treatment	TCSDSNV	TCSDSNV	TCSDSNV	TCSDSNV	TCSDSNV	**TCSDSNV**	TCSDSNV
Spectral range [nm]	400–2,500	400–2,500	1,100–2,300	400–2,500	400–2,500	**1,100–2,300**	1,100–2,300
Segment	10	10	10	10	7	**10**	7
Number of PLS factors	14	8	5	15	15	**13**	11
R^2	0.9965	0.9938	0.9859	0.9994	0.9996	**0.9989**	0.998

TCSDSNV: Thickness correction, Second derivative, Standard normal variate. PLS: Partial least square.

Table 2.

Summary of pre-treatment models used for apixaban assay determination.

A primary method based on UV spectroscopy served as the reference method for determination of apixaban content uniformity of blends. The quantitative analysis mode in the Vision software was used to develop and test calibration equations. The calibration equations can be used to validate, or during routine analysis, be used to predict unknown sample composition in real time. A prediction model was built using a partial least square (PLS) regression fit method. The results obtained by NIR spectroscopy were compared with a UV-Vis (90–110%) spectrophotometry method for validation batches.

In theory, NIR does not need an exact weight of sample. However, during NIR analysis, it is necessary to prevent the effect of outside light, especially diffuse reflectance mode. Therefore, the thickness and surface size of the sample are important factors. Sample thickness must be enough to ensure that light cannot travel through the sample and that the surface size (i.e. diameter) of the sample must be large enough to receive the whole NIR beam.[4]

Method accuracy was determined with a set of 95 samples (35 samples for calibration and 60 samples for validation) as shown in Table 1. This training set was validated with 60 validation standards spanning the same original range.

Table 2 provides a summary of pre-treatment of proposed models; for example for model 6, data were pretreated as a second derivative in standard normal variance mode with thickness correction to enhance spectral information and to reduce baseline drift, the segment length was set to 10 with no gap adjustments, and the spectral region was selected to be approximately 1,100 nm to 2,300 nm. The calibration curve is shown in Figure 4a, and the residual is shown in Figure 4b. The correlation coefficient (Pearson's coefficient) R^2 was 0.9989 as shown in Table 2, which indicated a strong correlation between the UV measurements (primary method of analysis) and the NIR predictions.

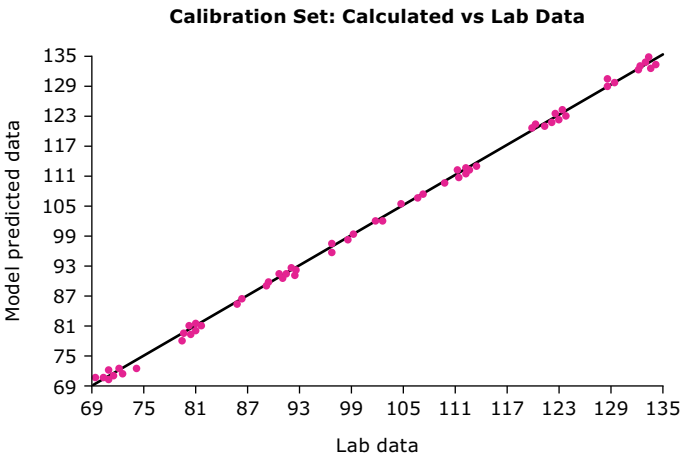


Figure 4a.

Regression of calibration samples (Primary method vs NIR data).

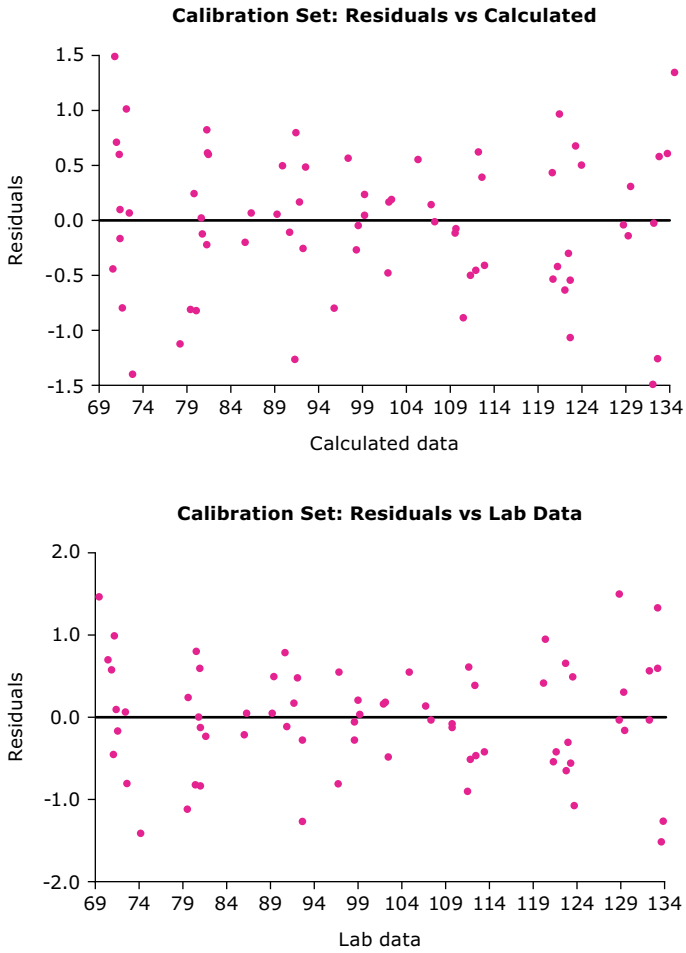


Figure 4b.

Residual plots of calibration samples (Calculated by NIR and Lab data).

The program automatically selects the number of factors for the method based on keeping the PRESS (predicted residual error sum of squares) value to a minimum. The PRESS plot is shown in Figure 5. The shape of the PRESS, was indicative of a reasonable correlation with the UV data.[3]

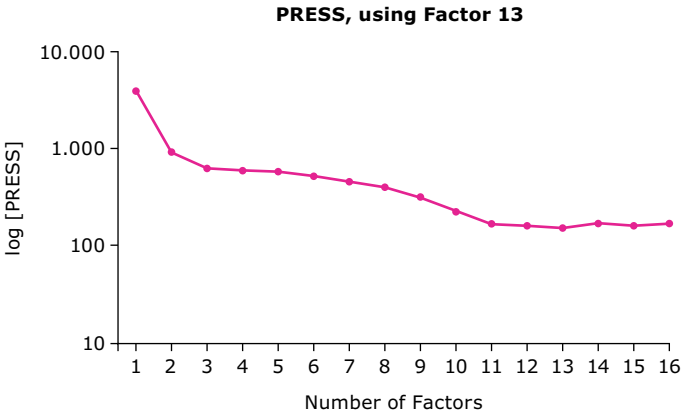
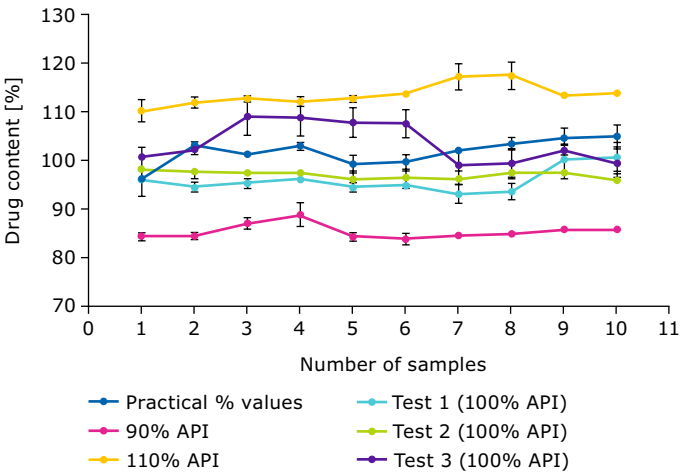


Figure 5.

Predicted error sum of squares (PRESS) plot.

The apixaban-NIR (%) predictions obtained for three validation and three test batches showed satisfactory results (Figures 6, 7 and 8). The standard deviations for some batches were up to 4.0% which indicates that blending time optimization may be necessary to further improve content uniformity. Since even a small deviation where can create a large variance in low dose applications, content uniformity is critical.

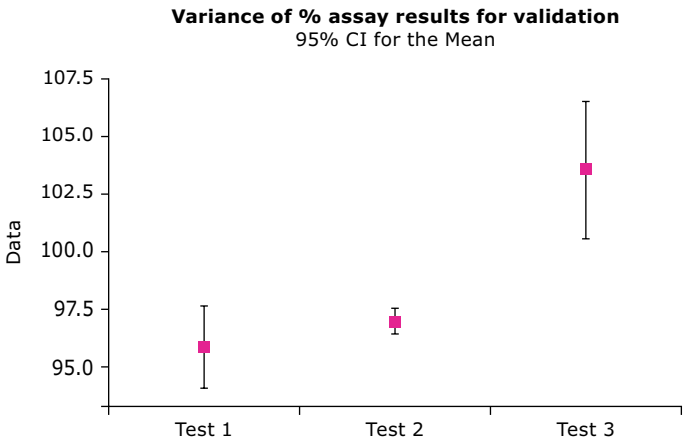
Although there is potential to further improve the outcome through process optimization, the results clearly show that all six batches achieved blend uniformity with Parteck® M excipient which confirms that Parteck® mannitol is very well suitable as a diluent for the low dose apixaban tablet formulation.



100% API and Test 2 (100% API) are with same sample set.

Figure 6.

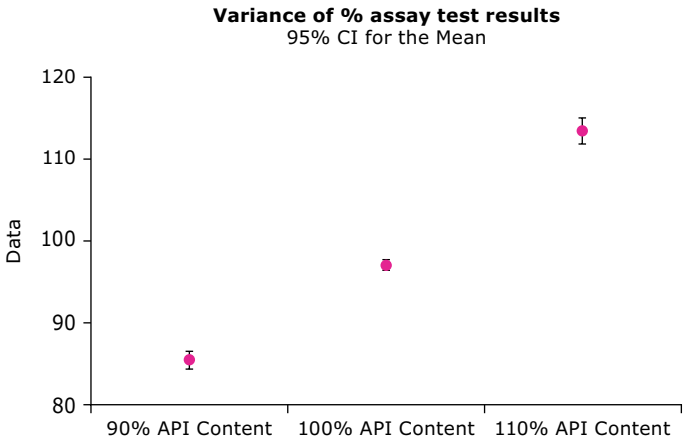
Comparison between % drug content obtained by primary method vs model predicted values.



Individual standard deviations are used to calculate the intervals.

Figure 7.

Variance of apixaban % assay (100%) in blend uniformity samples as determined with model 6.



Individual standard deviations are used to calculate the intervals.

Figure 8.

Variance of apixaban % assay (90–110%) in blend uniformity samples as determined with model 6.

Conclusion

Low dose solid dosage forms are especially prone to experience issues with drug content uniformity and, as a direct result of the segregration of blends, a sub- or super-potency of the dosage form which is a risk to the patient and therapeutic efficacy. This de-mixing may occur due to formulation or processing factors and it is very important to take measures to ensure sufficient content uniformity. In direct compression, blend uniformity can easily be achieved using Parteck® M excipient as a diluent. The large and highly structured surface area of Parteck® M mannitol leads to good adsorption of small API particles to the excipient surface and plays a key role for an efficient blending process to achieve critical attributes such as content uniformity for low dose formulations.

NIR analysis is an accurate and rapid method for analyzing blend uniformity in low dose formulation. The validated NIR method was suitable for prediction of API content using a direct compression technique with Parteck® M excipient as a diluent.

References

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