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In Situ Fiber Optic Dissolution Monitoring of Combination Drug Product Containing Three Actives

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PURPOSE

Dissolution testing is an assay commonly used during the **drug product development** stage as well as a part of the **quality control** (QC) testing of the final dosage forms of drug products.

Concentration monitoring using ***in situ* fiber optic** UV **automates the dissolution measurements** eliminating uncertainties related to filter selection, timing of volume withdrawal, manual sample handling, etc.

More and more **drug products** are reaching the market as combination of a **several APIs** making ***in situ* approach difficult** while **HPLC** is **time and resource intensive**.

This study introduces a **developed computational method** for **real time concentration measurements** of **multiple APIs** using *in situ* **fiber optic** UV-Vis monitoring.

METHOD(S)

The **Rainbow Dynamic Dissolution Monitor®** instrument (RDDM, Figure 1) controlled by **AuPRO™** software version 6.0 (Pion Inc.) was used to collect and analyze UV-VIS spectra and calculate concentrations of the active pharmaceutical ingredients (APIs).

Figure 1. Rainbow® instrument (Pion Inc.) shown with standardization station collects 8 full UV-Vis spectra (200 – 720 nm) in less than 2 seconds.

OTC medicine Excedrin® Migraine (Figure 2) containing three APIs listed in the Table 1 was used in the study to validate the method.

Figure 2. Excedrin® Migraine capsule shaped tablets.

Table 1. APIs and their doses

API	Dose, mg
Acetaminophen (AAP)	250
Aspirin (ASP)	250
Caffeine (CFN)	65

Dissolution was performed in 900 mL of DI water HEPES buffer (pH 7.0) in USP-2 apparatus (100 RPM) at 25 ºC.

RESULT(S)

Multi-component Regression Analysis (MCRA)

Theoretical Background

The method implemented in the **AuPRO™ version 6.0 software** is based on the modified **classical least squares** (CLS) technique to determine a contribution of known spectra (a.k.a. standard spectra) in their superposition by finding coefficients x_i that minimize the difference:

$$\chi^2 = \sum_{\lambda_1}^{\lambda_2}\left(A_{Measared}(\lambda) - \sum_{i=1}^{N} x_i A_{st,i}(\lambda)\right)^2 \quad \text{(Eq. 1)}$$

where $A_{Measured}(\lambda)$ is absorbance at wavelength λ of a sample containing N absorbing component, $A_{st,i}(\lambda)$ is absorbance of a standard for component i and coefficients x_i obtained by the procedure determine the contribution of each standard component into the sample spectra.

Data Collection Strategy

1. **Collect** at least **1 standard** (spectrum at a known concentration) for **each API**. **No standards of mixtures are necessary!**
2. **Identify** the **analytical wavelength region** where all spectra have unique signature either in the direct absorbance or in the 2nd derivative spectra.
3. **Validate** the analytical wavelength region **by measuring concentrations** of APIs in the mixtures **of known compositions**. Adjust the analytical parameters if necessary.
4. **Perform dissolution** experiment monitoring release of **multiple APIs** in **real time**.
5. **Adjust the analytical parameters** if necessary after experiment is finished to optimize the quality of data.

Standards of APIs contained in the Excedrin®

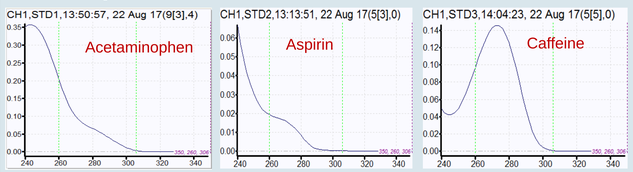

Figure 3. Direct standard spectra of APIs

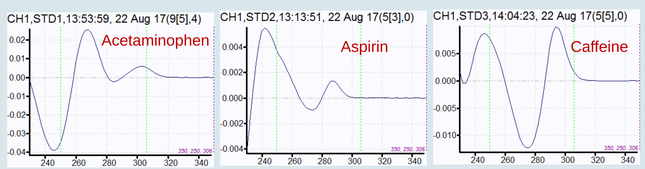

Figure 4. 2nd derivatives of API spectra.

Validation/Feasibility Study

To prove that MCRA can reliably de-convolute spectra of API`s in the multicomponent mixtures the experiments outlined in the Table 2 were conducted.

Table 2. Brief description of the assays that were setup to identify the analytical wavelength region for MCRA and demonstrate the feasibility of the method.

Assay#	API 1 Concentration (µg/mL)	API 2 Concentration (µg/mL)	API 3 Concentration (µg/mL)
1	AAP - 280 (constant)	ASP ~35 – 277 (varied)	CFN ~ 8 - 63 (varied)
2	CFN – 80 (constant)	AAP ~35 -270 (varied)	ASP ~35 -270 (varied)
3	ASP – 284 (constant)	AAP ~ 4 – 260 (varied)	CFN ~ 3 – 70 (varied)

Figure 5 shows changes in the 2nd derivative spectra upon adding aliquots of a concentrated solution of an API into a constant concentration of another API corresponding to the assays design described in the Table 2.

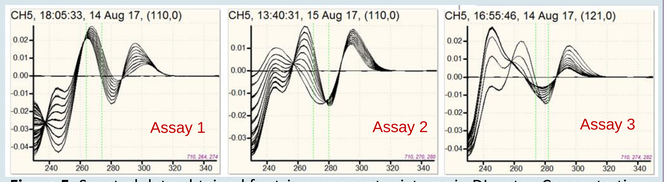

Figure 5. Spectral data obtained for tri-component mixtures in DI water. Concentration of one of components was fixed at the "dose" concentration, while concentrations of other APIs varied within selected concentration range.

MCRA tool available in AuPRO™ software (Figure 6) allows assessing the quality of the regression by comparing the model spectrum with measured one guiding an analyst in selection of the regression wavelength region.

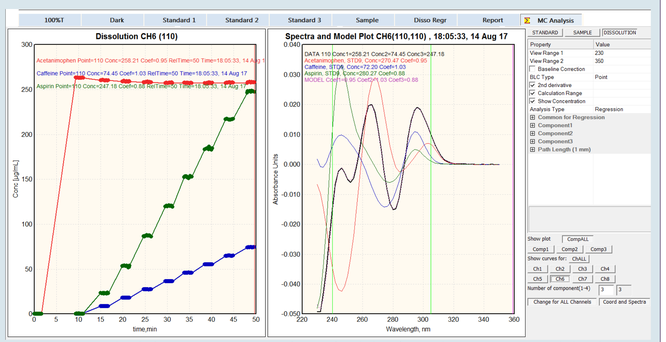

Figure 6. On the left: concentration of AAP (red dots) was kept constant while aliquots of CFN (blue dots) and ASP (green dots) were added. On the right: 2nd derivative spectra of standards (AAP - red, CFN – blue, ASP - green), a spectrum of a mixture at a particular time point (black) and a model spectrum (purple dashed line).

Dissolution of Excedrin Caplets

The dissolution of Excedrin® caplets were performed in 4 vessels of Erweka dissolution bath. Figure 7 shows dissolution profiles while Table 3 summarizes the error analysis between expected and measured concentrations for all APIs.

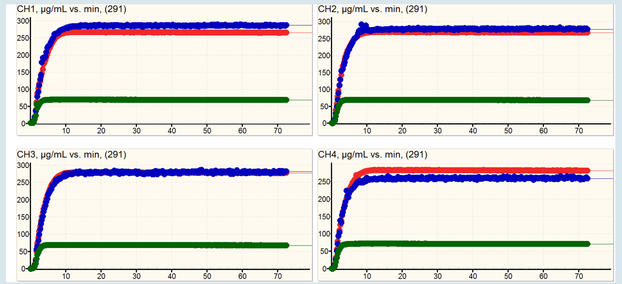

Figure 7. Concentration (µg/mL) versus time (minutes) measured in real time for AAP (red), ASP (blue) and CFN (green)

Table 3. Summary of dissolution results showing averages for 4 replicates.

Component	Dose, mg	Expected Concentration, µg/mL	Determined Concentration, µg/mL	Difference (%)
Acetaminophen	250	277.8	273.1 (+/-7.6)	-1.7%
Aspirin	250	277.8	275.5 (+/-11.5)	-0.8%
Caffeine	65	72.2	68.6 (+/-1.4)	-5.0%

CONCLUSIONS

Dissolution profiles of three individual components of OTC drug Excedrin® Migraine were **successfully characterized** using multi-component regression analysis implemented in **AuPRO software** version 6.0.

The **difference** between expected and measured concentrations was **within 5%.**

The conducted study demonstrated **ability of fiber optic platform** to perform **dissolution monitoring of multi-active drug products** *in situ* with **no need for HPLC**.

Time and cost of the **combination drug product development** can be significantly **reduced**.

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