

Increased Process Understanding for QbD by Introducing Universal Detection at Several Stages of the Pharmaceutical Process

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ABSTRACT

A new initiative has been mandated by the FDA to improve product quality and increase process understanding during development and production. Quality by Design (QbD) has several major components that have the potential to revolutionize the way in which pharmaceutical products are produced and then tested. The new mandate increases the emphasis on stages defined as risk points in the process, and reduces the emphasis on final product testing. Implementing QbD involves understanding the different aspects related to product variation which include process variables, API variables, and excipient variables. Appropriate metrics of these variables, through the use of new analytical techniques, is an important step towards the implementation of QbD. This study examines several risk concerns in the drug development process which cannot be adequately analyzed via traditional HPLC detection methods. Charged Aerosol Detection® (CAD®) is a newer universal detection technology which has been shown to offer high sensitivity, wide dynamic range, and response independent of chemical structure. Several novel HPLC-CAD methods were developed to examine excipients/surfactants, lot-to-lot variability, extractables and leachables, reaction monitoring, salt stoichiometry, and product degradation. For example, measurement of the lot-to-lot variability and characterization of common excipients/surfactants, including Tween 80 by HPLC-CAD, revealed a significant number of components and possible impurities as well as variability in overall sample composition. The use of newer technology, such as the CAD, in the development process will provide increased sensitivity over traditional techniques (low wavelength HPLC-UV or ELSD) allowing for better process control, and therefore, higher quality products.

INTRODUCTION

Quality by Design was first introduced into the drug development process in 2002 by the FDA and then fully discussed in their guidance *Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach*, released in 2004. The mandate looks for a dramatic shift in the development and quality testing of pharmaceutical products from a reactive to a proactive process approach.¹

The goal of QbD is for manufacturers to have a better understanding and control of their entire process which reduces the need for excessive final product testing and regulation. This process control and knowledge then allows for easier scale-up and successful development of the product.

QbD implements three key regulator concepts.²

- Process Analysis: Identifies variable parameters and focusing on what should be measured or monitored.
- Process Analytical Technology (PAT): Looks at automating traditional techniques and also implementing new technologies to monitor variable and obtain results for an active process.
- Risk-Access variables: Emphasis on the order and importance which should be placed on variables in the production process.

Figure 1 illustrates how QbD helps the individual development and final process components fit together to form the overall process understanding and product knowledge that will lead to consistent quality in the final product.³

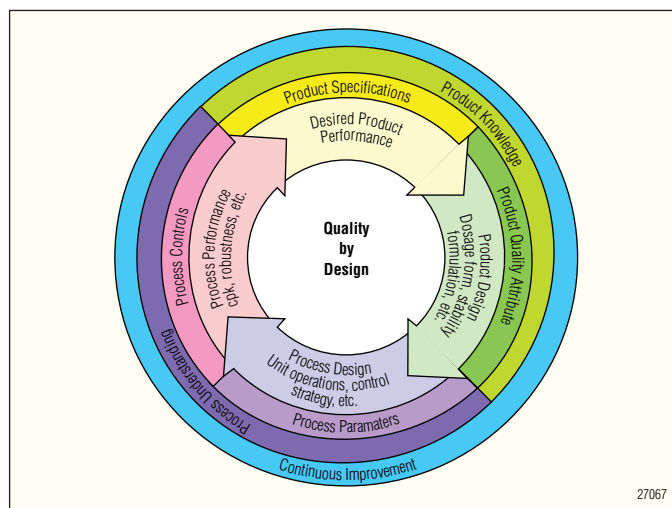


Figure 1. Quality by Design. Figure used with the permission of Moheb M. Nasr, Ph.D.

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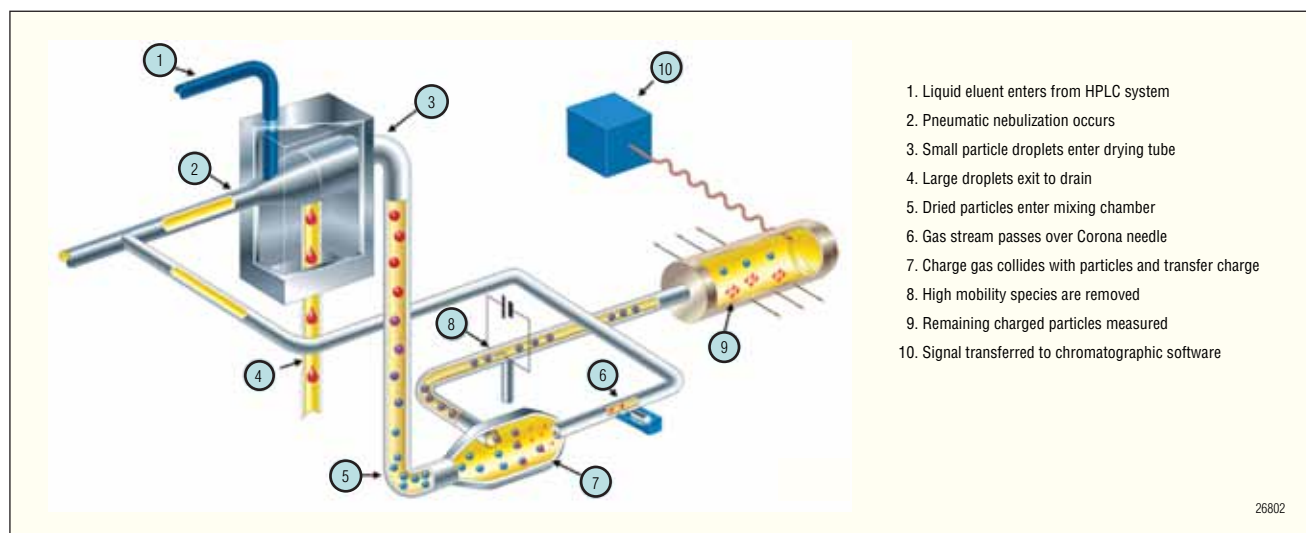


Figure 2. The liquid eluent from the HPLC column enters the Corona.

Two of the major shifts as a result of the introduction of PAT by the FDA change the thinking on analytical test methods.

First manufacturers are to continue to improve their process using new technologies. This is in contrast to the regulations when not operating under the QbD requirements where extensive documentation and filing with the FDA is required for changes to release test methods.

The second is the push for in-line or at-time-of-production testing of Critical Quality Attributes (CQAs) over traditional final product testing of a batch.

The Corona[®] CAD and Corona *ultra*[™] are mass sensitive detectors which use a proven nebulization and charge transfer technique described in Figure 2. They work with standard HPLC and UPLC techniques respectively to detect semivolatile and nonvolatile compounds down to low nanogram on column quantities.

The different applications presented here are of relevance to several potential risk points that are common to the drug development process. In these examples the development of methods using CAD enables the analysis of compounds that contain weak UV chromophores and may have been overlooked by traditional techniques.

LOT-TO-LOT VARIABILITY

UPLC Method Conditions:

Column: Acquity UPLC[®] BEH C18, 2.1 × 50 mm, 1.7 μm
 Column Temp: 40 °C
 Injection Volume: 1 μL
 Mobile Phase A: Water
 Mobile Phase B: Acetonitrile
 Gradient: See Table
 Detector: Corona *ultra*, Filter = Med, Range = 200 pA

Time (min)	%B	Flow Rate (mL/min)
0	6	0.5
1	12	0.6
3	17	0.6
10	20	0.6
18	26	0.6
18.5	66	0.6
23.5	80	0.6
24	6	0.5

2 Increased Process Understanding for QbD by Introducing Universal Detection at Several Stages of the Pharmaceutical Process

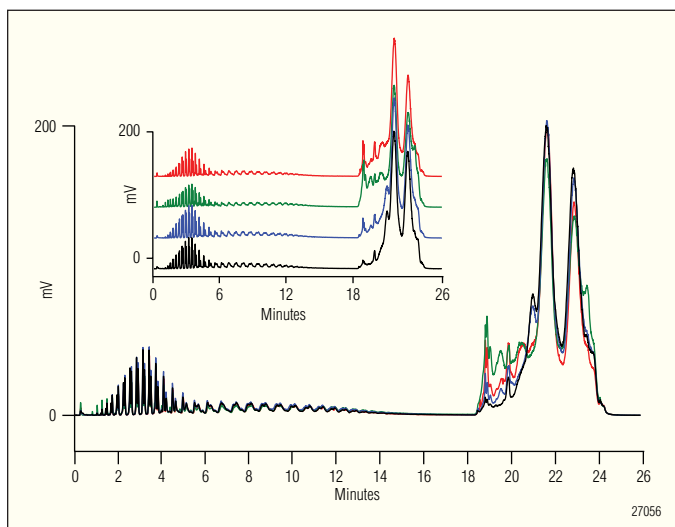


Figure 3. Overlay of 1 μ L injections of four commercially available Tween 80 products at \sim 30 mg/mL each in deionized water (30 μ g on column). (Inset) Expanded view of stacked plots. Red - Tween 80 Sigma P1754, Green - Tween 80 Sigma P-8074, Blue - Tween 80 Fluka 93780, Black - Polysorbate 80 Fluka 59924.

EXCIPIENTS

UPLC Method Conditions

- Column 1: Acquity UPLC BEH C18 2.1 \times 50 mm, 1.7 μ m
 Column 2: SeQuant ZIC[®]-pHILIC, 4.6 \times 150 mm, 5 μ m
 Flow Rate: 0.6 mL/min
 Detector: Corona *ultra*
 Mobile Phase A: 200 mM Ammonium formate pH = 3.2, acetonitrile, methanol, isopropanol (15:75:5:5)
 Mobile Phase B: 200 mM Ammonium formate pH = 2.75, acetonitrile, methanol, isopropanol (50:25:20:5)

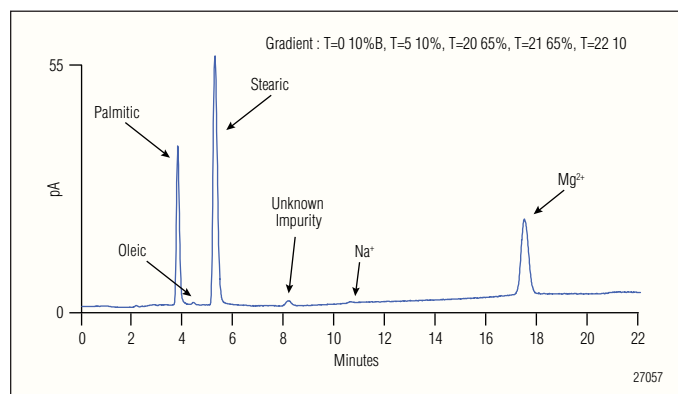


Figure 4. A combination of reversed-phase and HILIC mode chromatography was used to analyze the excipient magnesium stearate (Aldrich, Technical Grade - 65% stearate, 25% palmitate) (10 μ L of 1.1 mg/mL standard; 11 μ g on column). This approach can be used to resolve simultaneously stearic acid, other fatty acids, cations, and impurities.

SALT SELECTION

- Column: Dionex Acclaim[®] Trinity[™] P1, 3.0 \times 50 mm, 3 μ m
 Flow Rate: 0.8 mL/min
 Mobile Phase: Acetonitrile / 120 mM ammonium acetate pH = 4.8 (30 mM total buffer strength) (75:25)

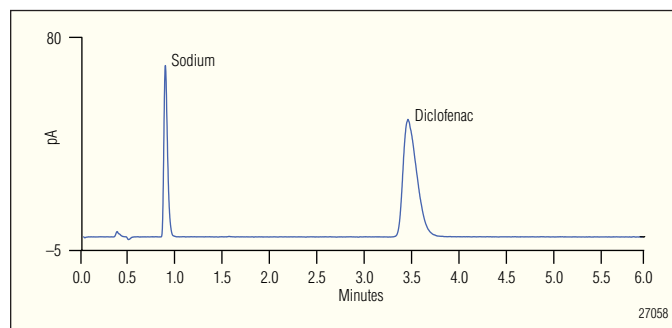


Figure 5. Simultaneous analysis of the API (Diclofenac) and its counterion salt (sodium) in under 5 min using the nanopolymer silica hybrid column technology and charged aerosol detection.

REACTION MONITORING

- Column: Supelco Analytical Astec CHIROBIOTIC[™] T, 4.6 \times 250 mm, 5 μ m (supplied through Sigma Aldrich)
 Mobile Phase: Ethanol:HPLC grade Water 1:1
 Flow Rate: 1 mL/min
 Injection Volume: 3 μ L

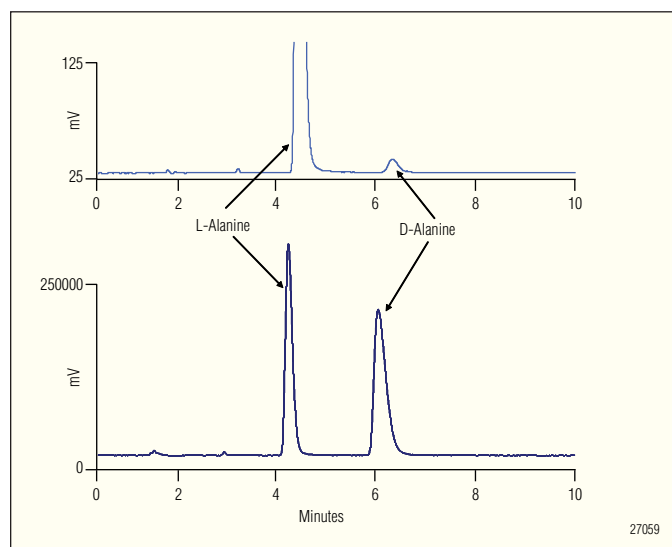


Figure 6. Chromatographic separation of alanine enantiomers. Bottom trace DL alanine (1 μ g on column). Top trace 1% D in L-Alanine (\sim 7.5 μ g on column).

DEGRADATION STUDIES

Column:	Agilent Zorbax Eclipse XDB, C18, 4.6 × 100 mm, 1.8 μm
Mobile Phase A:	0.2% Pentafluoropropionic acid in DI water
Mobile Phase B:	Methanol
Gradient:	See table
Pre-column Temp:	55 °C
Post-column Temp:	25 °C
Detector:	Corona <i>ultra</i>
Nebulizer Temp:	25 °C
Filter:	High

Time (min)	% Mobile (Phase B)	Flow Rate (mL/min)
0.0	10	1.5
0.3	10	1.5
2.5	60	1.3
4.5	60	1.3
5.5	10	1.5
8.0	10	1.5

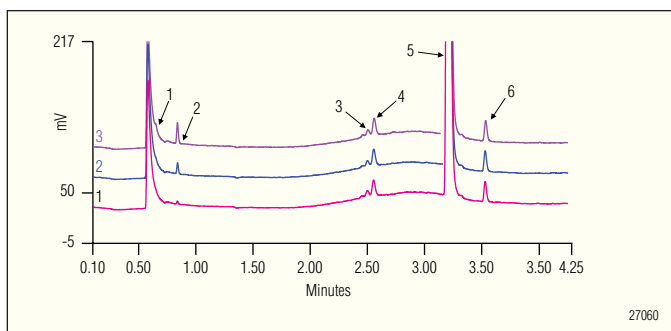


Figure 7. Forced degradation chromatograms for amikacin (~ 5 μg on column) heated at 80 °C in autosampler vial. The black (bottom) trace is T=0, the blue (middle) trace is T=10 min, and the purple (top) trace is T=20 min.

Peak Identification: Peak 1 located within the void, and Peak 2 at 0.6 min, are potential degradation products that are only formed upon prolonged heating (purple trace). Peaks 3, 4, and 6 are unknown impurities. Peak 5 is the amikacin.

EXTRACTABLES AND LEACHABLES

Column:	MD 150 × 3.2 mm, 3 μm
Column Temperature:	40 °C
Mobile Phase A:	Water
Mobile Phase B:	Acetonitrile
Gradient:	10% to 30% B over 15 min, hold for 5 min 30% to 10% B over 5 mins
Flow Rate:	0.6 mL/min
Injection Volume:	10 μL
Corona:	100 pA,
Filter:	None

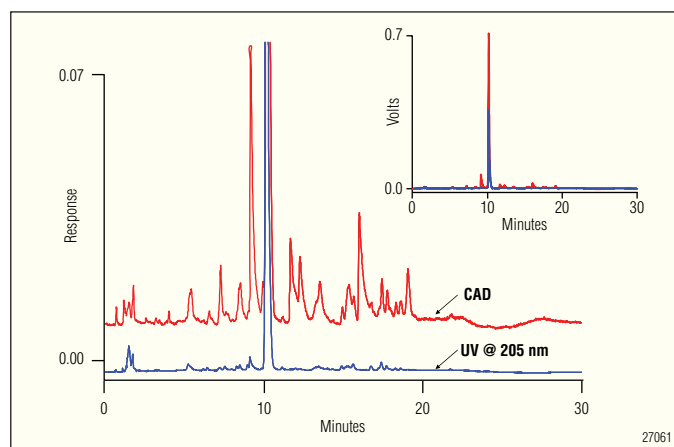


Figure 8. Analysis of Wheaton 13 mm snap-on natural rubber stopper from Fisher (06-447C). Stoppers were placed in a vial and extracted via ultrasonication for 2 h. The extraction solvent was 6 mL IPA. The extracts were directly injected on column without dilution. Inset: Chromatogram full-scale.

DISCUSSION

This poster illustrates how the CAD can assist in QbD functions at a various stages of product development.

Excipients like Tween 80 and magnesium stearate, which are often used in formulations of many common pharmaceutical products as a tablet lubricant, are often purchased as large bulk batches from manufacturers outside the pharmaceutical industry. Under the new regulations additional scrutiny will be placed on understanding these incoming products and potential risks variability will have on the process.

Figure 3 illustrates the lot-to-lot variability of four commercially available Tween 80. The impact that this level of variability will have on the quality of a pharmaceutical formulation is unknown. However, the ability to see the variability and monitor and understand its impact on the process is important.

Figure 4 illustrates a novel approach to the analysis of magnesium stearate using combined columns and the Corona *ultra* as the detector. The most commonly used excipient was characterized in a 25 minutes using a serial-connected UPLC C18 column and a zwitterionic-HILIC column. This approach enabled the simultaneous measurement of analytes with very different physico-chemical properties e.g., two hydrophobic fatty acids, and one inorganic ion, along with several impurities on a single platform. Typical characterization of these compounds only look at the physical characteristics of the product (e.g., porosity, hardness, wetting) to determine acceptability. The ability to have quantifiable chemical testing of the material may be a better approach to characterize products.

Salt selection and stoichiometry are an important steps in the drug development process. For APIs with ionizable functional groups salt formation can be used to improve the physicochemical properties which can ultimately have an impact on a stability and bioavailability. The ability to monitor salt stoichiometry and an API in a single analysis is shown in Figure 5. This rapid analysis enables facile salt screening and stability testing early in the process, which can save time in needless and costly reformulation.

Enzymatic reactions are commonly used for conversion of racemic amino acids to those which are enantiomerically pure. This process can be expensive and time consuming, and the common methods for analysis of progress lack sensitivity or require time consuming derivatization. Figure 6 illustrates the potential for using CAD to monitor important reactions directly and with a high level of sensitivity. On-line monitoring systems such as the Intergral™ Process Analytical System from Dionex are now being incorporated into the manufacturing process. The inclusion of the Corona CAD to these systems help to automate various monitoring tests at important points of the process.

Product stability information is crucial to produce acceptable shelf life of the final product. The analysis and quantification of degradants is often a difficult step in the analytical process. The degradants are not always able to be identified or do not have commercially available standards. This becomes further complicated when using UV analysis as it often occurs that the degradants and API may have very different absorption spectra. The incorrect choice of wavelength can lead to either an over or underestimation of true content and as a result compromise product quality. The Corona CAD is a mass sensitive detector with response that is independent of chemical characteristics unlike other evaporative technique. Figure 7 is an overlay of an amikacin solution which was analyzed unstressed and then heat stressed at two time points. The time dependent growth of an unknown degradation product was observed at ~0.6 min.

The introduction of undesired materials from a storage container, reaction vessels, or from other contact points in the process can lead to costly and difficult investigations to identify their sources. An experiment was conducted to extract material from a common rubber stopper to illustrate that the CAD was able measure extractables and leachables. The results in Figure 8 clearly illustrate the amount of extractable material detected by the CAD that was not visible with the UV @ 205 nm. The potential risk point could be evaluated early in the process by screening materials with chemicals they will come in contact with and then analyzing these extracts by using a similar method as shown in Figure 8.

CONCLUSION

CAD can be deployed into the development and manufacturing processes to help identify and quantify CQAs. The earlier product variables are identified the easier it becomes to have a higher quality final product and save costs.

Several novel HPLC-CAD methods were developed to examine excipients/surfactants, lot-to-lot variability, extractables and leachables, reaction monitoring, salt stoichiometry, and product degradation. Characterization of these critical components from starting materials, excipients, APIs and counterions, chiral impurity monitoring, product degradation and purity analysis, and possible extractables and leachables was demonstrated on a single HPLC platform and detector technology.

The reproducibility, ease of use, and compatibility make the Corona CAD detector an important complement to traditional UV methodology to obtain key product and process information. This allows for further understanding and continued improvement in the drug development process which is an essential part of QbD.

REFERENCES

1. John M. Kovaleski, Ph.D. Teva Pharmaceuticals USA, Implementation of Quality-by-Design: Industry Perspective, Drug Information Association Annual Meeting 2006.
2. Sandy Weinberg, Ph.D. Quality by Design for Laboratory Automation <http://www.scientificcomputing.com/Quality-by-Design-for-Laboratory-Automation.aspX>
3. Moheb M. Nasr, Ph.D. CDER, FDA, Quality by Design and its Relevance to Dissolution, AAPS Workshop on Challenges for Dissolution Testing for the 21st Century, Arlington, VA. May 1, 2006.

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