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Analytical Methods Needed for Combination Pharmaceutical/Medical Devices

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The demand for sophisticated drug delivery has led to the development of many innovative combinations of pharmaceuticals and medical devices across a broad range of therapeutic areas. While these combination pharmaceutical/medical devices (CPMDs) have the potential to fulfill major unmet medical needs, they also present unique challenges in development and approval. One of these challenges is the development and validation of analytical methods to assess the potency, purity and stability of the pharmaceutical component of the combination device. Additional product-specific analytical methods, such as uniformity or release rate from a drug coated device, will also be needed to support the development of CPMDs.

It is important to note that there are two options for the submission of a CPMD to the U.S. FDA. A CPMD can be treated as pharmaceutical and thus filed as a new drug application (NDA), or it can be treated as a medical device and thus filed as a 510(k) application. Regardless of the filing pathway, the analytical method development and validation are basically the same and are required during product development.

This paper provides an overview of the typical analytical methods that are needed to support a CPMD. One specific CPMD, the metered dose inhaler, is not included because of its unique and specific requirements.

Analytical Methods for Assay, Related Substances and Degradation Products for the Pharmaceutical Component of a CPMD

There are three goals for these methods: to assay the drug content, to measure for known related substances and to

detect degradation products of the drug. Like the analytical methods for more traditional pharmaceuticals, the predominant instrumentation for these methods is high-performance liquid chromatography (HPLC)-UV, with one method usually able to accomplish all three tasks. The main difference between analytical methods for CPMDs and traditional drug product formulations like oral or parenteral dosage forms is in the sample preparation. The sample preparation is unique and specific to the CPMD, but usually involves complicated multi-step procedures. Based upon the CPMD, sample preparations of CPMDs often involve extensive extraction for complete recovery of the drugs. In addition, depending upon the size of the CPMD and the location of the drug, the CPMD may need to be disassembled or reproducibly cut, which can be a significant challenge when the CPMD is made from hard plastics or metals.

If the method is intended to be used as a stability indicating method, a forced degradation study should be done. When designing a forced degradation study for a CPMD, the potential for the device to contribute to the drug degradation or to degrade itself, leading to detectable degradation products, needs to be considered. The type of CPMD will determine if the forced degradation study is done on just the drug, on the fully assembled CPMD or on a combination of the drug and the parts of the device with direct drug contact. It is recommended to include the components of the CPMD that have direct drug contact in the forced degradation study.

Once developed, the analytical methods need to be validated according to the ICH Harmonised Tripartite Guideline, Validation of Analytical Procedures: Text and Methodology (ICH Q2(R1)). One important additional consideration for validation of methods for a CPMD compared to traditional

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pharmaceutical drug products is ruggedness. In the ruggedness validation experiments, additional challenges should be added to evaluate ruggedness of the sample preparation. These experiments will vary depending upon the CPMD, need to be appropriate for the sample preparation and include challenges to each critical step.

Residual Solvents Methods for a CPMD

If organic solvents are used in the assembly of the CPMD, the finished CPMD will need to be tested for these residual solvents. A common example would be if the drug is sprayed onto part of a medical device during the assembly of the CPMD. In this case, the solvents used in the spraying process would be considered residual solvents.

The residual solvents methods need to be developed and validated in accordance with USP <467>. One important additional consideration for residual solvents for a CPMD may be the need for additional sensitivity. Because these residual solvents may be important parameters in developing the process to manufacture the CPMD, the methods may be needed to reach sensitivities as much as 10 fold lower than the required specification to assist in development of the manufacturing process. Once the methods have been validated, residual solvents testing can be done as part of release testing or as part of the process validation.

Analytical Method to Evaluate the Drug Release/Elution from a CPMD

If the CPMD is not intended to mechanically infuse the drug into the patient but instead the drug is intended to passively diffuse into the patient, then analytical methods designed to measure the rate of drug release or elution are needed. To perform this experiment, the CPMD is placed in an appropriate media designed to model the target tissue. The analytical method is then used to measure the increase in drug concentration in the media over time. The instrument conditions used are usually similar to those used for the assay; however, more sensitive methods may need to be developed if the release of drug is expected to be slow. The method will need to be validated similar to an assay method with special consideration to sensitivity and additional ruggedness testing for the sample preparation factors that might impact the release rate.

Analytical Method to Evaluate Uniformity

For CPMDs where the medical device is coated with a drug or drugs, the uniformity of this coating will need to be evaluated. Similar to the drug release methods, the instrument conditions used are usually those used for the assay; however, more sensitive methods may need to be developed depending upon the intended level of drug in the coating. In addition, the sample preparation will need to be adjusted so that samples are taken from all areas of the device to ensure uniformity of the coating. In some CPMDs where the device is not a simple geometric shape, the surface area coated from the different sections of the device will need to be included in the determination of the level of the drug in the coating.

Analytical Methods for the Analysis of Leachables from the CPMD

Leachables (a.k.a. migrants) from the medical device need to be considered when the drug is in direct contact with the medical device during the intended shelf storage, when the CPMD is intended to be surgically implanted or when the CPMD will have direct patient contact for an extended period of time. For these types of CPMDs, two types of studies are performed. The first study is a forced extraction study on just the medical device and the second study a migration study on the entire CPMD.

In a forced extraction study, the medical device is extracted with two solvents at an elevated temperature. Usually the drug is not included in the forced extraction. The extraction solvents are selected so that one mimics either the drug formulation or the intended patient tissue that the CPMD will contact, and the second solvent is selected to represent a “worst-case scenario” condition based upon either the drug formulation or the intended patient tissue. The sample extracts are analyzed by mass spectrometry (gas chromatography, liquid chromatography or inductively coupled plasma (GC-MS, LC-MS and ICP-MS respectively)) to attempt to identify all possible organic and inorganic extractables.

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Analytical methods are then developed that can detect the extractables observed in the forced extraction studies as leachables in either the drug product or a model solvent that mimics the intended patient tissue. Analytical methods for leachables need to be extremely sensitive and usually require MS detection. An additional challenge commonly arises when the drug product is present at concentrations significantly higher than the levels required for detection of the leachables. In this case sample preparation steps and method adaptations need to minimize the interferences from the drug. Once developed, the analytical methods need to be validated before proceeding to the migration study. The validation of the methods should be similar to validation of a method for related substances but allowance may be needed to reach the required level of sensitivity.

The migration study is the second study where the leachables (a.k.a. migrants) are monitored. When the risk of leachables is deemed to be highest from the drug being in direct contact with the medical device during the intended shelf storage, the leachables should be evaluated as part of the stability study to determine the shelf life. When the risk of leachables is due to the CPMD being surgically implanted or from direct patient contact, a simulated migration study is performed. In this case the CPMD is exposed to a model solvent that mimics the intended patient tissue at 37° C for an appropriate length of time determined by the intended use. In both studies, previously validated analytical methods are used to evaluate the leachables entering the drug product or the model solvent.

Other Analytical Methods

Since many types of CPMDs are in development with many unique critical features, analytical methods may be required to measure qualities specific to a given CPMD that are expected to be critical to function properly. In this case the analytical method will need to be developed to address a specific attribute of the CPMD.

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These methods will still require validation even when few of the standard validation parameters apply. In this scenario, the validation should address at a minimum reproducibility and ruggedness. Ruggedness testing should include all method parameters that could impact the reported result.

Conclusion

As diverse and ingenious CPMDs continue to be developed, analytical methods that can be used to support the development and ensure the quality of these products are needed. A thorough understanding of the CPMD is critical to ensure that the analytical methods are monitoring the proper attributes of the CPMD and the analytical chemist may need to be creative in developing methods and preparing samples to support these important therapeutic advances.

About the Author

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Kurt L. Moyer has more than 23 years of pharmaceutical development experience spanning all areas from discovery support to marketed products. His primary expertise is in the areas of bioanalysis, extractables and leachables, method development and validation, identification of impurities and metabolites, and GLP/GMP compliance. He also has extensive experience with drugs for anticoagulant and cardiovascular therapies. In addition, Dr. Moyer provides NSF Health Sciences clients with project management that is designed to accelerate the development process. Prior to joining NSF Health Sciences, Dr. Moyer served as a Senior Research Investigator for Sanofi Aventis and a Research Scientist for the DuPont Pharmaceutical Company. Dr. Moyer received his Ph.D. in biochemistry from Villanova University.

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