VARIABILITY OF EXCIPIENTS: Xylose in microcrystalline cellulose

Compatibility of excipients with other excipients and the active pharmaceutical ingredient is typically established during early formulation development. In real-time and accelerated stability programs the ability of excipients to provide their intended functionality throughout the intended drug product shelf life and the influence of a variety of environmental factors is demonstrated. However, for various reasons the potential impact of batch-to-batch variability of excipients is too often ignored; because of time constraints, costs, the unpredictability of variability, lack of useful data and knowledge, unawareness, or because of logistic reasons.

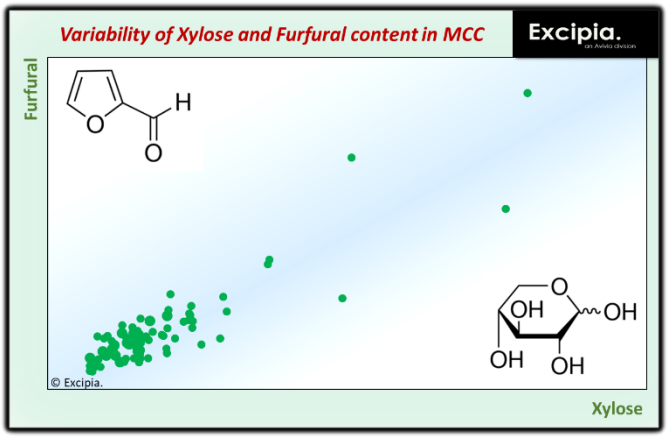
Many excipients are natural, naturally derived or semi-synthetic excipients derived through chemical processing of animal, vegetable, or mineral sources. Variability is introduced by inadequate and fluctuations in specifications of starting materials; species of crop, seasonal and different regional provenance can have a remarkable impact. Also, process technology, process parameters and even operator actions may contribute to batch-to-batch inconsistency of the same material. In addition, when different manufacturers produce the same excipient, batch versus continuous processing, the scale and/or location of manufacturing can lead to variability.

Excipia.
Within Excipia we have setup numerous analytical procedures to reveal and compare the 'hidden features' of all kind of excipients. With the Excipa knowledge platform we can help customers investigate batch to batch product performance variations, implement excipient related Quality by Design (QbD) approaches, perform competitor research and analysis like quantitative deformulation, monitor manufacturing process optimization or site changes, and select excipient batches to improve drug product performance without the need to change a registered product formulation.

For example, over the years we collected about one hundred Microcrystalline Cellulose (MCC) samples from various suppliers and grades, and analyzed these for properties like molecular weight distribution, chemical composition, purity and chemical reactivity. MCC is present as filler in more than 50 percent of all marketed tablet formulations. It is made by processing raw cellulose or 'wood pulp' from trees, which is rich in hemicelluloses; polysaccharides that contain many different sugar monomers. Depending on the tree species and natural variability, the ratio the monosaccharides xylose, mannose, galactose, rhamnose, and arabinose in hemicellulose may vary. As expected, we identified significant variation in composition and purity of MCC, not only between manufacturers, but also between batches of the same brand. Our analytical methodologies expose concealed excipient characteristics and hidden relations that are not listed on any product certificate of analysis.

Xylose and furfural in MCC

For MCC we found a relationship between the measured absolute content of xylose and the total amount of the highly reactive aldehyde **furfural**. Furfural is a specific degradation product of 5-carbon sugars (pentoses) like xylose and often found to adversely affect the stability of drugs. In the analyzed MCC batches we observed for both xylose and furfural a wide concentration range of about **10 to 15 times** the minimum value**.** Particularly for sensitive or low dose drug formulations, selection of the right MCC batch might be a cost-efficient way to improve product performance.



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