Stability Testing of Herbal Medicinal Products

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Introduction

Stability testing is an obligatory requirement in the registration process for all medicinal products, including Herbal Medicinal Products (HMPs).(1) The tests are performed to define storage conditions and the product's shelf-life.(2) For products on the market, the marketing authorisation holder is legally obliged to undertake on-going stability studies to prove that the medicinal product can be used safely over the entire period of its shelf-life.(3)(4)

In many aspects stability testing of HMPs follows the same requirements as stability testing of chemically defined substances.(2) However, some specific characteristics have to be taken into consideration:(5)(6)(7)

- Herbal drugs and preparations (extracts) are the active pharmaceutical ingredient.
- HMPs are complex in nature due to their high number of constituents.
- Constituents belong to different chemical classes with different analytical behaviour.
- Constituents sometimes have very low concentrations in the finished product.

In consequence, analysis of HMPs should consider:

- Different requirements for the different types of extracts.(5)(8)
- **Use of markers for the API**.
- Use of fingerprint chromatograms.
- Special hurdles to take for combination products.(9)

How to find the right marker?

Markers are chemically defined constituents, or groups thereof, which are of interest for control purposes independent of whether they have any therapeutic activity. Therefore, they are used as "Deputy APIs" for an extract and its entirety of constituents. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the HMP if the marker could be quantitively determined in the herbal substance and/or herbal preparations.
The choice of the marker has to be justified.(5)

Finding the "right" analytical marker is a crucial need for stability testing of HMPs.
Typical sources for finding markers are:

- Monographs(8) and drafts (EDQM Pharmeuropa).
- Experience, transfer from other plants/constituents.
- Literature research about known constituents.
- **Scientific research.**

The search for suitable and new marker substances is an important interface between scientific research and the use of the results in HMP-industry´s routine quality control.
The isolation and structure elucidation of chemically defined substances in a plant, drug and/or drug preparation not only helps to better understand the active principle of an HMP. It can enhance analytical quality control. But to utilise results of scientific research on an industrial scale, any new marker should meet certain requirements:

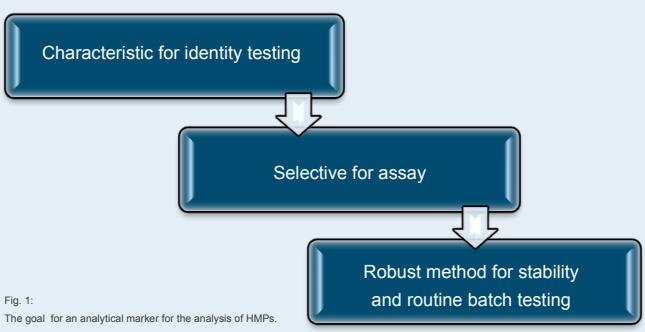

Fig. 1:
The goal for an analytical marker for the analysis of HMPs.

Moreover, for HMP-industry´s routine quality control it is of great importance that the substance is available as reference standard in an appropriate quality, quantity and for a reasonable price.

Case studies

Hops *(Humulus lupulus L., Cannabaceae)*
Xanthohumol is a characteristic constituent of hops. Therefore, it could serve as a suitable marker for identity testing and assay. But due to its lipophilic nature it is rarely detectable in the hydrophilic extracts from hops which are commonly used in HMPs.
Therefore, an alternative marker needs to be defined for testing aqueous extracts and finished products thereof, e.g .the flavonoides *Rutoside* and *Isoquercitrin*.

Feverfew *(Tanacetum parthenium L., Asteraceae)*
Parthenolide is a specific marker for feverfew. But, it is known to be unstable in particular at higher temperature. Additionally, effects of the product's matrix may reduce the stability. If *Parthenolide* is used as a marker to test a product's stability, problems with instability findings and Out-of-specification (OOS) results are more likely to occur.

Birch *(Betula pendula Roth, B. pubescens Erh., Betulaceae)*
Exemplary, for birch only one marker (*hyperoside*) could be installed to verify the traceability in the drug birch leaf, in the drug preparation (dry extract) and in a finished product (here: tablet). The marker shows sufficient stability to prove a shelf-life of at least 3 years for the finished product.

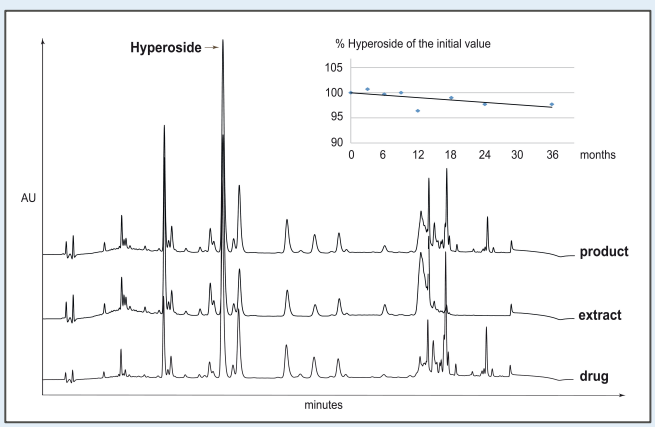

Fig. 2: HPLC chromatograms from birch leaf, extract and finished product, incl. product stability.

Discussion & Conclusion

Scientific research and structure elucidation plays an essential role in finding new markers for established and new herbal drugs and their corresponding HMPs. In order to be applicable for industrial routine quality control, it is necessary to consider the marker´s stability and the traceability in drug preparations (extracts) and if possible product formula-tions. Analytical data should be available and the methods used have to be validated.(10)
Reflecting these requirements, phytopharmaceutical research helps to ensure that herbal medicinal products can be used safely throughout their shelf-life.
An intensive exchange between researchers like PhD students and the pharmaceutical industry strengthens the understanding of the each other´s needs and helps create the basis for a productive cooperation.

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