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Drug safety, drug quality, drug analysis

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Abstract

Controlling and minimizing the side effects of drugs are the key issues in assuring the safety of drug therapy. Since side effects are inherent properties of the drug material, these cannot be influenced by drug analysts. At the same time drug analysts play a predominant role in assuring the quality of bulk drug materials and drug formulations and this is also closely related to the safety issue. The three main attributes of drug quality are identity, strength and purity. Of these, in the case of bulk drug materials, purity is of prominent importance: by the identification (structure elucidation) and quantitative determination of the impurities and degradation products, the risk of their contribution to the side effect profile of the drug materials can be avoided or at least controlled/minimized.

The development in the field of chromatographic and spectroscopic methods in the last decades has led to changes in the philosophy, structure and requirements in the monographs of drug materials in the principal pharmacopoeias. Although the approaches of the European and US Pharmacopoeias are somewhat different, a common feature is the shift of focal point toward purity tests. In contrast to this, relatively few changes are observable in the field of the assay methods for bulk drug materials: non-selective titrimetric and spectrophotometric methods are still widely used. Since the results of these do not contribute to the safety issue, the omission of these tests and substitution by the "mass balance" concept is recommended.

The effectiveness of the tendency of replacing non-selective methods by selective ones (mainly HPLC) is also questionable. The reason for this is that due to the limited precision of the HPLC assay the drug content obtained by the mass balance concept is a much better quality control attribute for bulk drug materials than that obtained by HPLC.

It is recommended that classical assay methods (including HPLC) be used in exceptional cases only and the time and energy thus spared be used for more important impurity-related issues that directly contribute to the safety of drug therapy.

Keywords: Drug quality; Drug safety; Drug purity; Drug analysis; Assay

1. Introduction

1.1. Aims and scope of drug analysis

The aims and scope of drug analysis can be summarized in one sentence as follows:

"The aim of drug *analysis* (with emphasis on industrial drug analysis) is the analytical investigation of

- bulk drug materials,
- the intermediates of their syntheses,
- products of drug research (potential pharmacons),
- drug formulations,
- the impurities and degradation products of drugs,
- biological samples containing the drugs and their metabolites.

with the aim of obtaining data which can contribute to

- the high *quality*,
- the maximum efficacy and
- maximum *safety* of drug therapy and
- the maximum economy of the production of drugs [1]."

This sentence contains the three main issues incorporated in the title of the paper: *safety, quality* and *analysis* of drugs. The aim of this paper is to describe the author's views on the correlation of these with the eyes of a pharmaceutical analyst, i.e. how to optimize the contribution of analytical chemistry in assuring maximum safety of drug therapy. The scope of the

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paper is restricted to bulk drug materials with small molecules: biomacromolecules and drug formulations will not be dealt with.

1.2. Drug safety

The Food and Drug Administration (FDA), one of the flagships of the drug safety issue describes its own role regarding the safety of drug therapy as follows: "... FDA... requires that drugs... be proven safe and effective." "...FDA... must determine that the drug produces the benefits it is supposed to without causing side effects that would outweigh those benefits [2]."

The *efficacy* of drug therapy depends mainly on pharmacologists, biologists, biochemists, synthetic chemists, and clinicians taking part in the development of the drug. Although the role of pharmaceutical analysts is not negligible even in this field, they can only indirectly contribute to the success of drug research aiming at introducing new, highly effective drugs into the therapy [3].

So much the greater is the importance of the activities of analytical chemists in *safety* issues. The definition cited above shows that the safety of drug therapy mainly depends on the *side effect profile* of the drug. As it is known, side effects are inherent properties of the drug material. The examination of the ratio of their beneficial actions and the risks caused by the side effects is the duty of pharmacologists, toxicologists, clinicians and registration agencies before making decision about the introduction of a new drug: analytical chemists do not play any role in this decision.

On the other hand physiologically active impurities and degradation products can contribute to the side effect profile. Avoiding or at least minimizing this contribution is a key issue in assuring the reproducibility and safety of drug therapy. In addition to toxicologists, process chemists, formulation scientists and regulation agencies, analytical chemists play a predominant role in this by controlling the quality (purity) of the drug material.

1.3. Drug quality

The definition of drug quality in a FDA-ICH (International Conference on Harmonisation) document [4] is as follows: "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity." Of the three attributes improving the reliability of the *identification* tests used to be of great importance in the early period of pharmaceutical analysis when identification was based on specific colour reactions. Nowadays, however, infrared spectroscopy and/or chromatographic retention matching with reference standards create a firm basis for identification not necessitating further developments. *Strength* is of course an important quality attribute of drug formulations. It is, however of practically no importance in the case of bulk drug materials, i.e. it is not important whether the active ingredient content is, e.g. 98.5 or 99.5% within the acceptance criteria (typically 98.0–102.0% or even stricter.) The only important point potentially influencing drug safety is the quantity, nature and composition of (100 − active ingredient content)% = impurities. With other words this means that of the three attributes in the FDA/ICH definition *purity* is of prominent importance (in the majority of cases the only really important quality attribute.)

1.4. Drug purity

Of the three types of impurities listed in the ICH Guidelines [5], i.e. (1) organic impurities; (2) inorganic impurities; (3) residual solvents, (2) and (3) are easy to control. The number of toxic metals and solvents that may occur in bulk drug substances is limited. Their toxicity is well characterized and the limits set up in the above-mentioned guidelines and in the pharmacopoeias guarantee that these cannot contribute to the side effect profile of the drug.

So much the more problematic is the potential contribution of organic impurities to the side effects of bulk drugs. The impurity profile of drugs depends on the synthetic route, the origin and purity of the starting materials and reagents, method of purification and storage conditions: various kinds of impurities can originate from differences and changes of these factors. (*Note*: the author of the present paper criticised the official classification [5] of organic impurities and recommended a modified classification better reflecting the chemistry behind the occurrence of the impurities [6].) As a consequence of the uncertainties outlined above, in the overwhelming majority of cases the pharmacopoeias do not specify the impurities in the high-performance liquid chromatographic (HPLC) and thin-layer chromatographic (TLC) purity tests; these are expressed as the main component neglecting the differences in their responses. Of course this can be source of uncertain, moreover sometimes erroneous results. This is why impurity profiling, i.e. analytical activities the aim of which is the detection, identification/structure elucidation and quantitative determination of impurities are key issue in modern pharmaceutical analysis. This creates the basis for the successful application of the principles outlined in the FDA/ICH documents [5] for controlling the limits of individual impurities taking into consideration the toxicity of the impurity and the daily dose of the drug thus greatly contributing to the safety of drug therapy.

The importance of impurity profiling is well reflected by the fact that in the recent years four books [7–10], book chapters [11–14], a special issue in *Trends in Analytical Chemistry* covering (a) general aspects, (b) degradation-related impurities, (c) volatile impurities, (d) TLC aspects, (e) genotoxic and carcinogenic impurities, (f) HPLC aspects and (g) the role of off-line NMR [15], another one in *Advanced Drug Delivery Reviews* with papers on various analytical aspects [16], several review papers dealing with general [17–21], HPLC [22], HPLC–MS [23–25] capillary electrophoresis (CE) and related techniques [26,27], and CE-MS [23], chiral CE [28] aspects and innumerable ordinary papers have been published on this subject. Impurity profiling is a hot topic, indeed, in contemporary pharmaceutical analysis!

2. The safety issue and the pharmacopoeias

2.1. Historical overview

Pharmacopoeias are traditionally considered to be the safeguards and guarantee for the quality of drugs. As shown in Table 1, the principal national pharmacopoeias (and in addition that of the author's country) were first published at various times in the 19th century. Due to the globalisation of the pharmaceutical market, the pharmacopoeias of the countries in the European Union are now under the umbrella of the European Pharmacopoeia (Ph. Eur.) [29], moreover further harmonisation of these standards has been in progress since 1990 among Ph. Eur., the United States Pharmacopoeia (USP) [30] and the Japanese Pharmacopoeia (JP) [31] in the framework of the International Conference on Harmonisation (ICH).

Table 1 the mission of pharmacopoeias is ". . .to maintain and improve health. . .by disseminating authoritative standards. . .for medicines. . ." [30]. It has to be added to this quotation that the pharmacopoeias are not only disseminating the standards but can be considered to be flagships of the drug quality issue by setting these standards. These standards should (or at least ought to) reflect the state-of-the-art of the possibilities represented by the current state of analytical chemistry. The tremendous development in analytical instrumentation enables drug analysts to contribute at a higher level and more effectively to the continuously increasing demands as regards the safety of drugs than in the era of classical analysis.

If we compare the changes within half a century by comparing, e.g. USP 16, published in 1960 with the currently official USP 30 (2007), some conclusions can be drawn:

- The structure of the monographs for bulk drug materials is more or less the same: *description, identification, physical constants, impurity-related tests, assay*.
- As already mentioned, classical colour tests for the *identification* are being step-by-step replaced by infrared spectroscopy and chromatographic retention matching with reference standards.
- The greatest development is observable in the field which is of immense importance from the point of view of drug safety, i.e. in the field of *impurity-related tests*. In 1960 HPLC did not yet exist and TLC was at its beginnings. For this reason impurity-related tests were restricted to tests such as residue of ignition, loss on drying, completeness, colour and clarity of the solution, chloride, sulphate, heavy metals, easily carbonizable substances, range and sharpness of the melting point, etc. It is needless to say that these tests did not characterize the purity of the drug material at a sufficiently high level and hence only very moderately contributed to the safety of drugs. The development in this field in the last few decades has been very rapid and substantial. Thanks to the development in chromatographic technology, the overwhelming majority of monographs in modern pharmacopoeias contain chromatographic (usually HPLC or TLC) tests suitable for the characterisation of the impurity profile of the drug material.
- The picture as regards the development of assay methods is not as clear as with the impurities. The discussion of this will be the subject of Section 2.2 in this paper.

Table 1
Principal pharmacopoeias

Pharmacopoeia	First volume	Present volume
United States	1820	United States Pharmacopeia (USP) 30, 2007
Europe	1964–1971	European Pharmacopoeia 5, 2007
United Kingdom	1864	British Pharmacopoeia (BP) 2007
France	1837	Pharmacopée Française 10, 2005
Germany	1872	Deutsches Arzneibuch (DAB) 10, Nachtrag 8, 2005
Italy	1892	Farmacopea Italiana XI, 2002, Suppl. 1, 2005
Hungary	1871	Pharmacopoeia Hungarica VIII, 2003–2006
Japan	1874	Japanese Pharmacopoeia XIV, 2001, Suppl. 2006

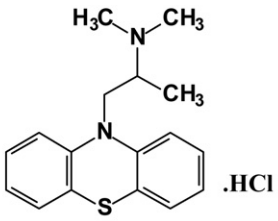
2.2. Assay methods for bulk drug materials in pharmacopoeias

2.2.1. Definition

The definition of *assay* in ICH documents [32] is as follows: "Assay: To provide an exact result which allows an accurate statement of the content or potency of the analyte in a sample." The following sections will show how the requirements in this definition are fulfilled in the current pharmacopoeias.

2.2.2. Non-selective methods

Reflecting the state-of-the-art of analytical chemistry in the late 1950s and early 1960s, the principal methods in USP 16 [33] were titration and ultraviolet-visible spectrophotometry (the latter being often based on colour reactions). Although these are non-selective methods, i.e. the majority of the potential impurities are likely to contain the same moieties on which the methods are based as the drug itself: acidic or basic functional groups and chromophores, respectively, these methods are still widely used in the pharmacopoeias. The share of titration methods in the current USP and Ph. Eur. is about 40 and 70%, respectively, while the same figures for UV spectrophotometry are about 10% in both pharmacopoeias; the role of outdated colorimetric methods has decreased substantially. To illustrate how minimal the changes have been in these fields, the case of promethazine hydrochloride is mentioned. The assay method of this classical drug material in USP 16 was titration by acetous perchloric acid after the liberation of the free base by the classical mercury(II) acetate method [34]. The method in USP 30 [28a] is the same the only "differences" between the two texts being that the same indicator in USP 16 is named methylrosaniline chloride and in USP 30 crystal violet and the solutions should be titrated to green [33] or blue [30a] colour. Ph. Eur. titrates the protonated base with 0.1 M sodium hydroxide in ethanolic medium using potentiometric endpoint detection [29a]. Fig. 1 shows the formulae of promethazine hydrochloride with its named impurities in Ph.



Promethazine hydrochloride

Named impurities in European Pharmacopoeia 5

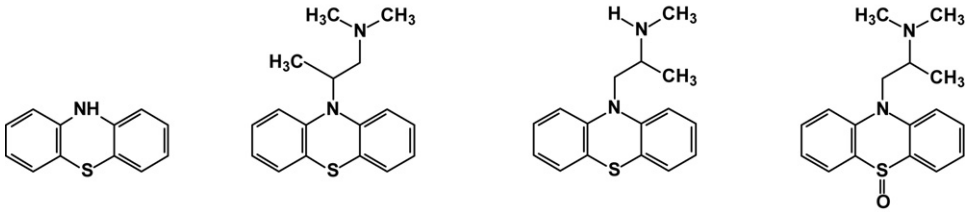


Fig. 1. The formulae of promethazine hydrochloride and its named impurities in Ph. Eur. 5 [27a].

Eur. [29a]. It is evident that with the exception of phenothiazine all impurities are titrated together with promethazine, i.e. the methods are not selective and the assay results are not accurate.

A similar example is levonorgestrel. Its assay in USP 30 is based on UV spectrophotometric measurement of the α, β-unsaturated 3-oxo moiety at 241 nm [30b] while in Ph. Eur. 5 the indirect titrimetric determination of the ethinyl group (after

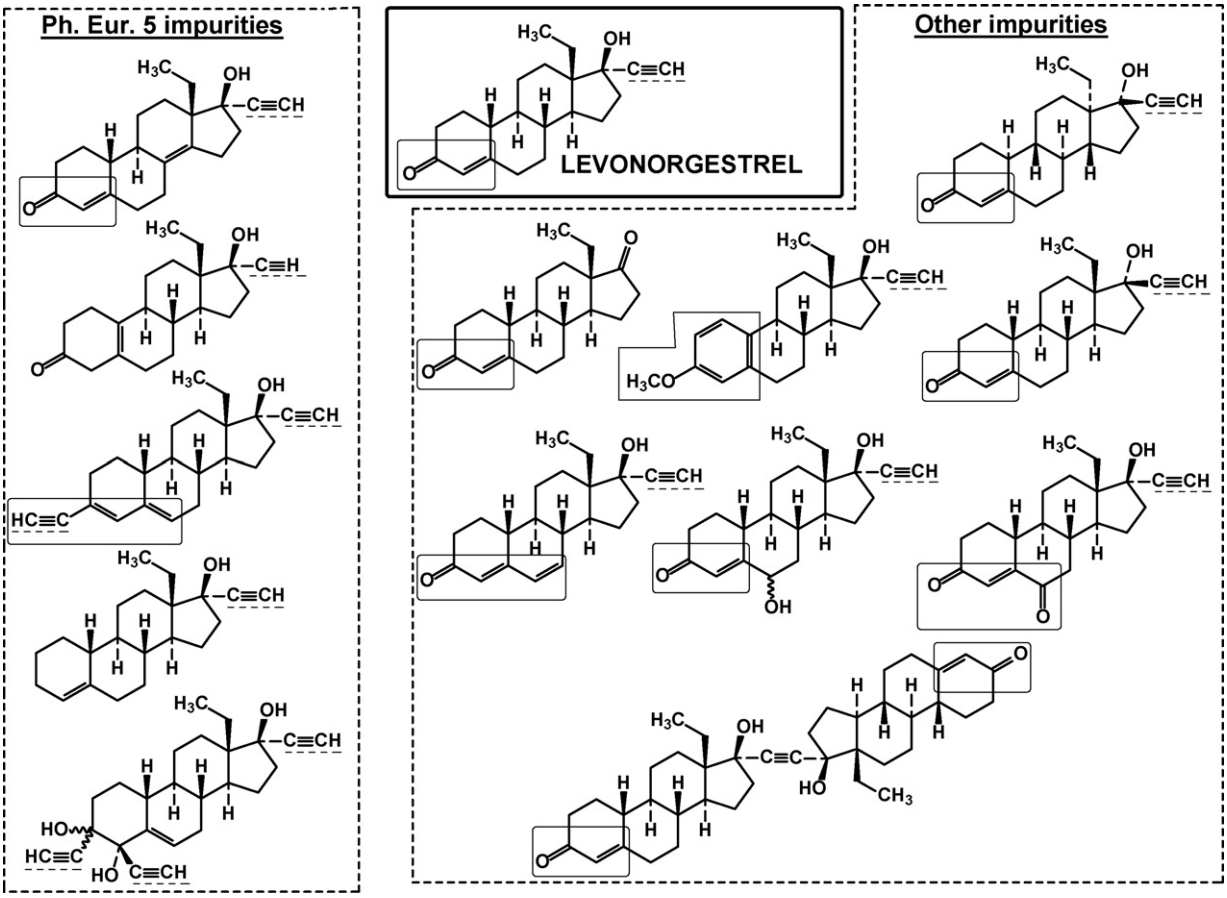


Fig. 2. The formulae of levonorgestrel, its named impurities in Ph. Eur. 5 [27b] and some other impurities [33–37]. *Key*: ▭ UV-active moiety; - - - - ethinyl group.

reaction with silver nitrate) is prescribed [29b]. Fig. 2 shows the formulae of levonorgestrel together with its named impurities in Ph. Eur. 5 [27b] and some other impurities [35–39]. As it is seen, the majority of the impurities contain UV-active groups strongly absorbing at 241 nm and/or ethinyl group(s). This means that the same applies to this case as was described for promethazine.

The general conclusions that can be drawn from the facts described above are as follows:

- Titrimetric and spectrophotometric methods are non-selective: although these are rapid, inexpensive and precise methods, their accuracy is low.
- These methods do not meet the criteria of ICH described in Section 2.2.1.
- The assay values obtained by these methods do not characterize the quality of the bulk drug substance and hence are of no (or very limited) value from the point of view of the safety of drugs.
- These methods could easily be left out from the protocol of analysing bulk drug materials without endangering the safety of drugs.

In an earlier publication it was proposed by the author of this paper [40] that non-selective (and as shown later also selective) assay methods for bulk drug materials be replaced by making – when necessary – calculations of the basis of the mass balance principle known mainly from drug distribution, pharmacokinetic and metabolic investigations. It is often used also in drug degradation studies, e.g. [41,42] and for characterizing the quality of reference standards [43]:

$$\begin{aligned}\text{Active ingredient content} &= (100 - \Sigma_{\text{impurities}})\% \\ &= (100 - \Sigma_{\text{inorganic impurities}} - \Sigma_{\text{organic impurities}} \\ &\quad - \Sigma_{\text{volatile impurities}})\%. \end{aligned} \quad (1)$$

2.2.3. Selective methods (HPLC)

Another possibility to solve the problem of the non-selectivity of titrimetric and spectrophotometric assay methods is to replace them by selective methods, i.e. in the overwhelming majority of cases HPLC. Since its first appearance in a pharmacopoeia in 1980 [44] the speed of the propagation of this method in general and at the pharmacopoeia level is unprecedented in the history of pharmaceutical analysis. This is the main method (together with TLC) for the determination of *related organic impurities* and the stability indicating assay method for drug formulations. This greatly contributes to the possibility of improving drug safety. As for HPLC as an *assay* method for bulk drug materials (with a share of about 50% in USP [30] and 15% in Ph. Eur. [29]) the picture is far from clear and positive.

It is evident that a well-designed, carefully optimised and validated HPLC method has sufficient selectivity to furnish accurate assays. However, the limited precision of this method greatly decreases its value as a quality attribute. Due to this limited precision, the HPLC assay is not suitable to play an important role in characterising the quality of bulk drug materials: the author of the present paper proposed HPLC method also to be omitted from the analytical protocol of bulk drug materials replacing it – when necessary – with the mass balance concept (Eq. (1)) [40]. The argumentation for this is described in more detail in the cited paper. In addition to the precision issue here we only mention that HPLC assay is very time consuming, labour-intensive and -expensive. Column conditioning, system suitability tests, and a sufficient number of replicates take according to the most conservative calculation, about half a working day in the course of the assay of a drug material. It is at least questionable if it is worthwhile to spend so much time, energy and money on an analytical investigation that adds very little if any to the safety of the drug.

As for the question of the precision, the author's value of RSD of 0.5–1% for a typical HPLC assay on bulk drug materials was based on estimation only [40] but this was in good agreement with earlier [45,46] and subsequent [47,48] results on similar systems. It has to be noted that another study [49] showed that the precision can greatly be improved by using higher weights of sample and standard.

A real breakthrough in this field was the publication of a paper on this subject quite recently by Hofer et al. [50]. In the course of a systematic study with 21 drug substances an average RSD of 0.61% (range 0.29–1.0%) was found by them with 898 degrees of freedom for the analysis. In the title of this paper the authors raise the question "Is HPLC assay for drug substance a useful quality control attribute?" They demonstrate with experimental results and model calculations that in agreement with the views described in Ref. [40] the mass balance approach is a much better quality control attribute: the assay results are essentially the same but the standard deviations are less by one order of magnitude. This also means that in such a way the number of false out-of-specification results originating from the closeness of specification limits and the standard deviation of the HPLC assay can be greatly reduced.

3. Conclusions: proposals

As discussed in Section 1, the main aim of drug analysis is to contribute to the improvement of drug safety. Due to the poor selectivity of the titrimetric and spectrophotometric assay methods and the insufficient precision of the selective HPLC method none of these methods can be considered to fulfil this requirement. Although it is evident that realization of the following proposal would require the breakthrough of the walls of century-old traditions in pharmaceutical analysis, the author still proposes (in agreement with Hofer et al. [50]) assay methods to be omitted from the protocol of the quality control of bulk drug materials (small molecules) by replacing them with the mass balance assay. (*Note*: both in Refs. [40] and [50] some cases are listed when assay methods in the classical sense of the word can be still necessary).

In the case of the acceptance of this principle much time, energy and cost could be spared. It is, however, by no means the aim of this paper to propose to decrease the efforts of drug analysts to control the quality of drugs. In contrast, it is our aim to

improve the quality of drugs. However, the author is convinced that the spared time, energy and money could be used much more effectively by concentrating on impurities than by carrying out the more or less obsolete and useless assay tests.

Williams et al. [43] described the possible pitfalls of the mass balance method which they recommended (together with other methods) for the characterisation of the quality of USP Reference Standard materials: "In many cases the chromatographic impurities are unknown, or standards of them are not available. The impurities are then determined by the very risky assumption that the impurities have the same response factors as the main component." Of course the same applies to the application of this principle to ordinary bulk drug materials also.

Some tasks and possibilities to surmount these difficulties are as follows. It is an important task to decrease the relative number of unknowns within the total number of impurities with the aim of controlling and minimizing the presence of impurities with potentially undesirable biological activity. The tendency of Ph. Eur. to list at the end of the monographs possible impurities is useful especially if the list is comprehensive which is not always the case: the number of named impurities varies between 0 and 15. Of course full coverage of all possible impurities on the pharmacopoeia level is possible only in the case of classical drug materials with low molecular weight and limited number of possible synthetic pathways. For larger molecules with complicated structures and several possible synthesis methods only the listing of the most characteristic impurities is possible leaving space to the individual drug companies to fill the gap in their own drug mater files.

It is especially important and desirable that the tendency of Ph. Eur. and USP to increase within named impurities the proportion of specified impurities, i.e. individual impurities with a specific acceptance criterion and with specific methods for their determination is continued. The latter can be an individual method or the application of the method for ordinary impurities (terminology of USP) using suitable response factors in the HPLC (or TLC densitometric) tests. In both cases the synthesis of the impurity is necessary. This can be used as reference standard for developing the specific method or calculating the response factor, thus avoiding the over- or underestimation of certain impurities and also enables the qualification of the impurity.

To reach these goals the following developments in the methodology of drug impurity profiling seem to be desirable:

- Using routinely dual (multiple) purity tests. HPLC is and will certainly remain the principal method for the determination of (related) organic impurities in drugs. However, the simultaneous use of other chromatographic techniques, mainly TLC but also hitherto only scarcely used methods, such as ion chromatography, CE and related techniques may afford useful complementary information on impurities, among them the unwanted enantiomer in chiral drugs administered as the pure enantiomer. These methods could be useful for the detection and quantitation of ionic species such as ammonium, or tetraalkyl-ammonium salts that are not detectable by the presently used HPLC or TLC methods and do not contribute to the residue of ignition thus causing systematic error in using the mass balance principle for the assay.
- Improving the general applicability, sensitivity and selectivity of HPLC detection by more widely using the *MS detector*. The *general applicability* is an important issue, since the detection and especially the quantitation of UV-inactive impurities in UV-active drugs is very problematic using the generally used UV-detectors and this also causes problems in applying the mass balance principle for the assay. Although this problem can be solved also by using evaporative light scattering detectors [51], the use of MS detector in the total ion current mode seems to be necessary even routinely (even if problems may occur also here with poorly ionisable compounds). The availability of relatively inexpensive HPLC-MSD (mass-selective detector) instruments creates the basis for this. The high *sensitivity* of the MS detector is especially useful in those cases when the analytical task is the detection and quantitative measurement of ultra-trace impurities (e.g. signal impurities, genotoxic impurities, etc.). The high *selectivity* of the mass spectrometer as a HPLC detector is very useful in HPLC-UV peak purity studies and in detecting rapidly and routinely changes in the impurity profile of a given bulk drug material.

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