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Pharmaceutical Analytics at the Department of Pharmacy ETHZ

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Abstract. Description of some research activities in Pharmaceutical Analysis, Irradiation of Pharmaceutical Drug Substances, Developement of Monographs on Pharmaceutical Substances for the European and Swiss Pharmacopoeia.

In our view pharmaceutical analytic means how to obtain, to treat and to interpret analytical data about drugs and drug systems in order to develop new analytical strategies to reach more precise and accurate information concerning the 'true' state of the investigated system. The results from our analytical investigations have a direct and important influence on the security of drug systems in human medicine. They may preserve the patient from undesirable side effects on health, induced by application of unqualified drugs. Our research activities have a worldwide effect because most of the analytical investigations are carried out in collaboration with international authorities (European Pharmacopoeia Commission and WHO) and with different international pharmaceutical industries.

Two main fields of interest of our group should be pointed out and discussed in detail:

1. The Investigation of the Effect of Ionising Radiation (γ-Rays and 10-MeV Electronbeam) on Pharmaceutical Drug Substances and Drug Products

In line with our research collaborations with different pharmaceutical companies we are involved in many problems that can be easily formulated but are hard to solve analytically.

The most frequently encountered question of a manufacturer is as simple as follows:

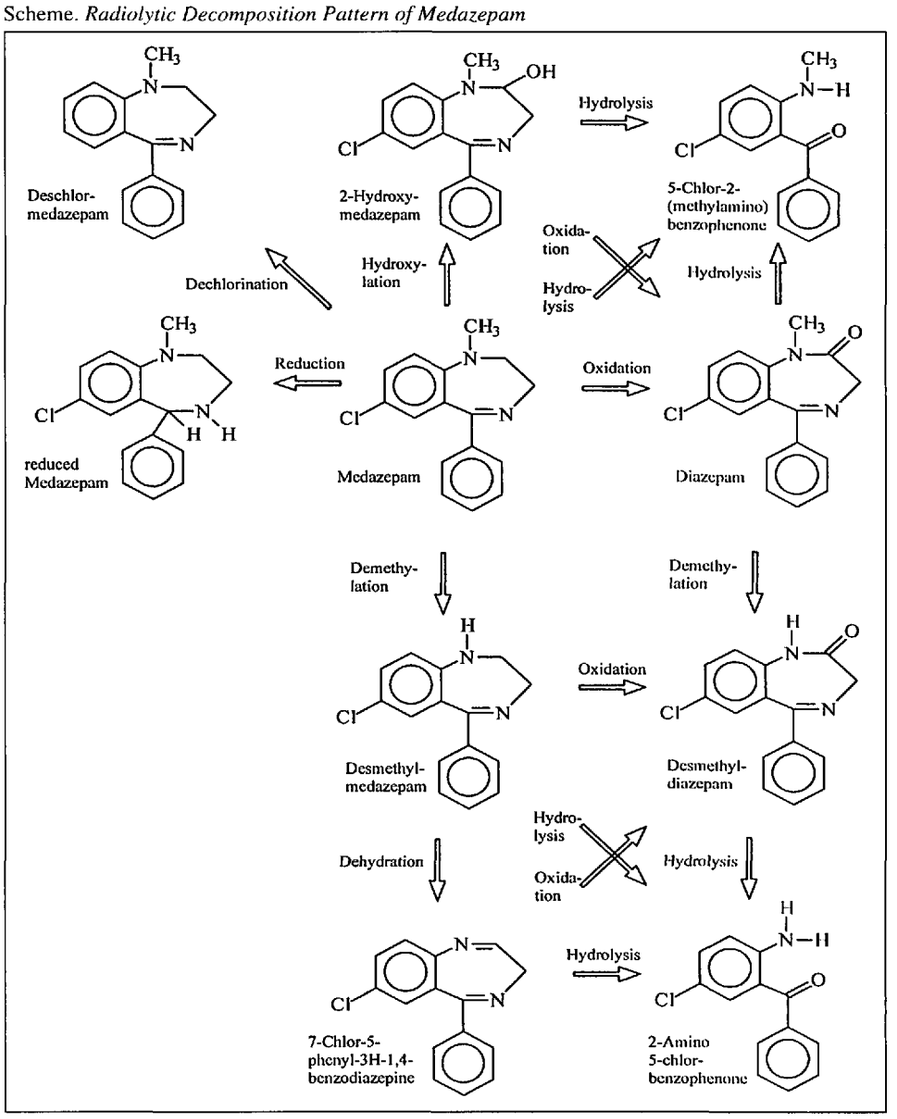
Is it possible to perform γ-sterilisation of a drug or its application form with an energy dose of 25 to 50 kGy without causing any fundamental change of their specifications?

The manufacturer expects the answer YES or NO, with a scientific prove of the reasons leading to the decision.

The analytical problems arising from γ-irradiation of drugs with high energy doses like 25 kGy are very complex and often unusual, since by-products might have been formed that are very different from those derived from conventional degradation mechanisms. Theoretical considerations are helpful, but in all cases a lot of experimental work has to be carried out [1].

Therefore, the analytical strategy for testing irradiated compounds concerning their content and their impurity profile is as follows: Many different analytical methods have to be screened in order to be sure, that no radiolyticly generated by-product has escaped detection. The pharmacopoeias of the different countries, although indicating valuable starting points for the analysis must be extended by additional

Scheme. *Radiolytic Decomposition Pattern of Medazepam*



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tests. Furthermore, it has to be taken into account that the non irradiated substance itself is 'impure' and its known composition is, therefore, taken as a 'quasi-standard' and compared with the irradiated substances [2].

This procedure leads to different decision situations.

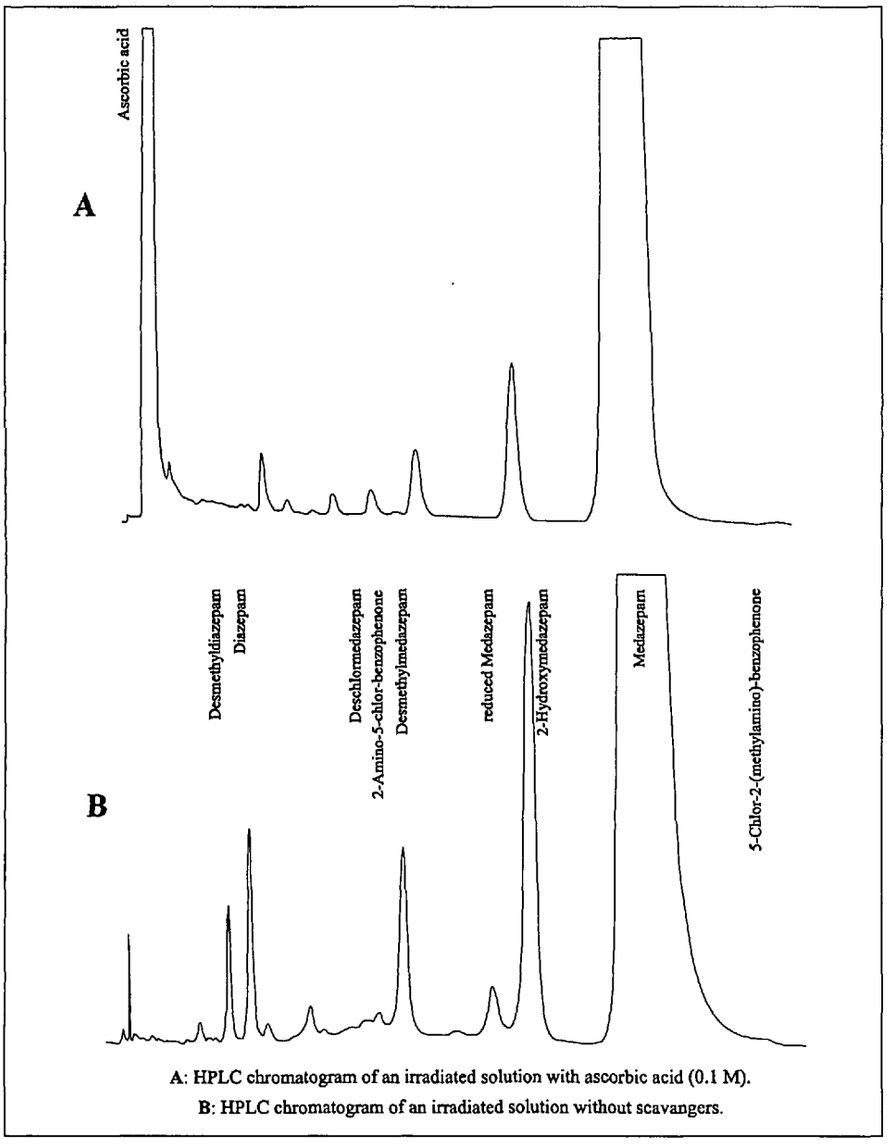
If one or more applied methods indicate a significant difference between the non irradiated and the irradiated compound regarding the content and/or the impurity profile, the substance is classified to be not stable to γ-irradiation. Due to the amount of the generated radiolytic by-products in general the following decision levels are reached:

1. If the sum of all radiolytic by-products amounts to more than 5%, the substance is not worth further analytical investigations. The answer concerning the possibility of a successful γ-sterilisation is definitely NO. No doubt is possible in this case.
2. If the sum of all radiolytic by-products is within the range of 0.5–2% the structure of the major radiolytic products should be elucidated and the amount of each should be estimated by at least two independent methods in order to prove accuracy and precision. In case the generated radiolytic products are toxic and the irradiated substance could have harmful effects, the decision depends on toxicity measurements whether the substance is to be used for human or veterinary therapy or not. At the same time a likely pathway for the radiation-induced decomposition of the drug substance has to be stated, considering not only the pure compound itself but also the influence of the generally present impurities (by-products from the synthesis, degradation products and, very importantly, the residual solvents) (*Scheme*). The knowledge of the irradiation induced decomposition pathway can lead to modified radiation conditions, *e.g.*, irradiation at lower temperature, change to inert-gas conditions or the use of radical scavengers. If the amount of the radiolytic by-products could be reduced to an acceptable level (Pharmacopoeia/ICH guidelines) by the modifications mentioned above, the answer concerning a successful γ-sterilisation will be YES (*Fig. 1*). After this decision has been made the analytical validation-procedure requires a protocol for quality control along with its well-established rules to create a general prescription for characterisation of the irradiated drug.

If none of the applied methods shows a significant difference between the irradiated and non irradiated substance, and – this is very important – the applied methods are different and relevant to the analytical problem, the answer concerning the possibility of γ-sterilisation is YES.

Unfortunately, in practice this case is quite rare and considering the low energy required for fission of bonds in organic compounds is rather small compared to the irradiation energy, theoretically less probable.

At the present time six drug substances are under study at different stages.



A: HPLC chromatogram of an irradiated solution with ascorbic acid (0.1 M).
B: HPLC chromatogram of an irradiated solution without scavangers.

Fig. 1. *HPLC Chromatograms of 2%* Medazepam *solutions, protected/unprotected*

2. The Development of Monographs on Pharmaceutical Substances for the European and the Swiss Pharmacopoeia

A monograph on a chemical substance is divided in five different sections:

DEFINITION – CHARACTERS – IDENTIFICATION – TESTS – ASSAY

Prior to the preparation of any monograph it is essential to accumulate as much information as possible on the substance in question.

In particular it is necessary to ascertain:

- whether the substance is of natural, synthetic or semi-synthetic origin,
- whether the substance is a mixture or a single entity,
- the method(s) of preparation in detail (method(s) of synthesis, isolation and purification),
- whether there are different polymorphic forms, since the properties of the

substance may vary in accordance with this parameter,
- whether the substance is available in pure enantiomeric form or as a racemic mixture,
- whether there are different hydrates or solvates,
- whether there are different salts.

The substance has to be defined with the greatest possible precision with respect to the above mentioned properties. Some chemical substances, particularly those obtained from raw materials of natural origin and substances produced by fermentation may not be easily separated from certain related substances (*e.g.*, quinin salts). Hence, pharmaceuticals can be categorized as:
- a chemical product when obtained in a very pure state when they can be assayed by a physico-chemical method
- a substance accompanied by a certain proportion of related substances, given an exact definition of the main component only (*e.g.*, neomycin)
- a mixture of several components, sometimes difficult to define, where an overall description may suffice (*e.g.*, nystatin).

The most important step during the elaboration of a monograph represents the choice of the analytical procedure (methods) for identification, purity testing and the assay of a drug substance [3–5]

The most complex and from the analytical point of view the most demanding part of a monograph represents the test section. In designing the purity tests for a monograph on a given material, interest is to be focused on limiting tests for those impurities that could possibly arise during its manufacture, its degradation upon storage, or in case of biological materials, due to adulteration. Whenever possible, products of different origin are to be examined in this respect. Special attention must be paid to impurities that are known to possess or are suspected to have toxic properties or that could appreciable modify the activity and/or stability of the drug substance itself or of other materials with which it is usually associated. It must be recognised, however, that not all impurities can be limited by means of specific tests and that a certain lack of specificity may even be desirable in order to provide some safeguard against the presence of unforeseen foreign substances in a material.

Related substances are known impurities which may be identified or unidentified. They include intermediates and by-products from a synthetically produced organic substance, co-extracted substances from a natural product and degradation products of the substance. This definition does not include other possible impurities such as residual solvents, residues from cells and micro organisms or culture media used in fermentation processes. Related substances can be controlled by various spectroscopic or chromatographic methods or combinations of these. Whichever approach is taken to control the impurities in a drug substance knowledge of the synthetic route and the likely decomposition pathways is essential to develop a test for related substances that is highly discriminatory and that can separate the suspected impurities from the substance itself (*Fig. 2*). In case of different ways of synthesis used by various manufacturers the analytical techniques described must control the major impurities for all syntheses. Detection limits must be established for impurities of known structure. The discrimination power of an analytical impurity test, its repeatability and its reproducibility must be determined by means of collaborative studies. The limits set for the control of impurities will depend on a number of factors including toxicity, route of administration and the duration of treatment of the drug substance. In newly developed drug substances, unidentified impurities are not allowed to exceed the level of 0.1% normally.

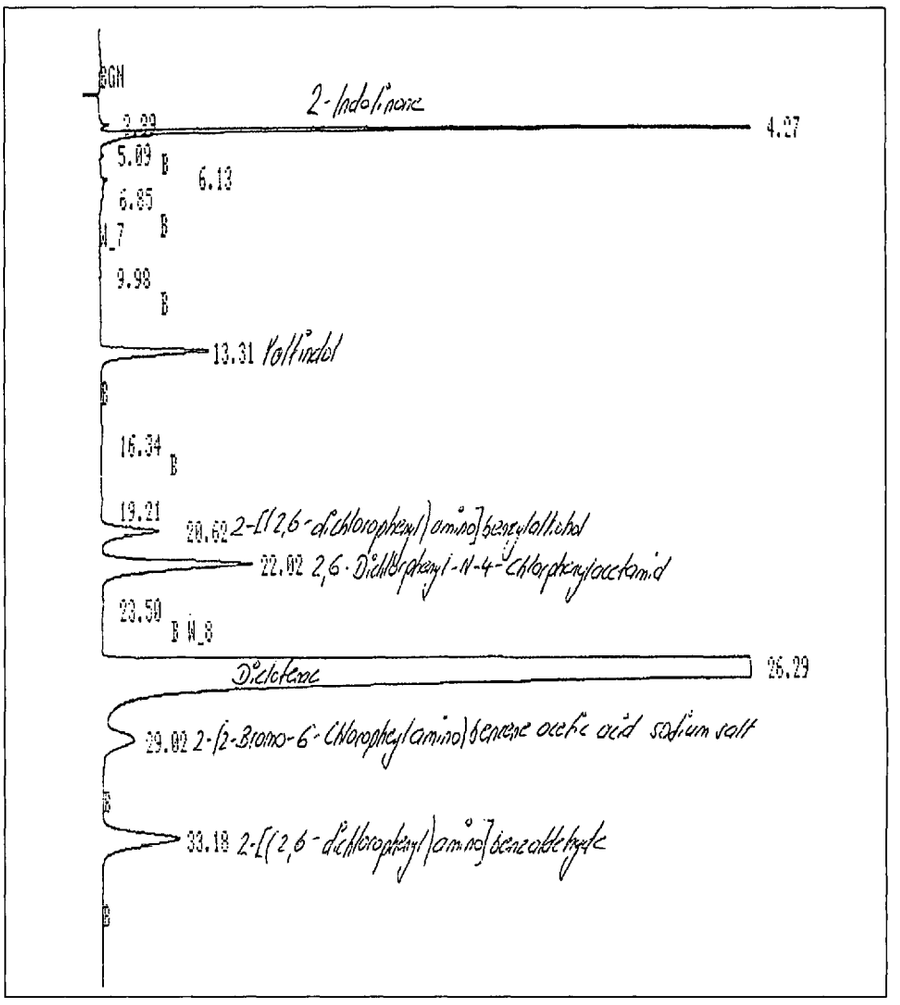


Fig. 2. *Impurity test, HPLC of* Sodium Diclofenac (reproduction of the original document)

At the moment monographs on two new substances for the European Pharmacopoeia and three substances for the Swiss Pharmacopoeia are under study in our group.

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