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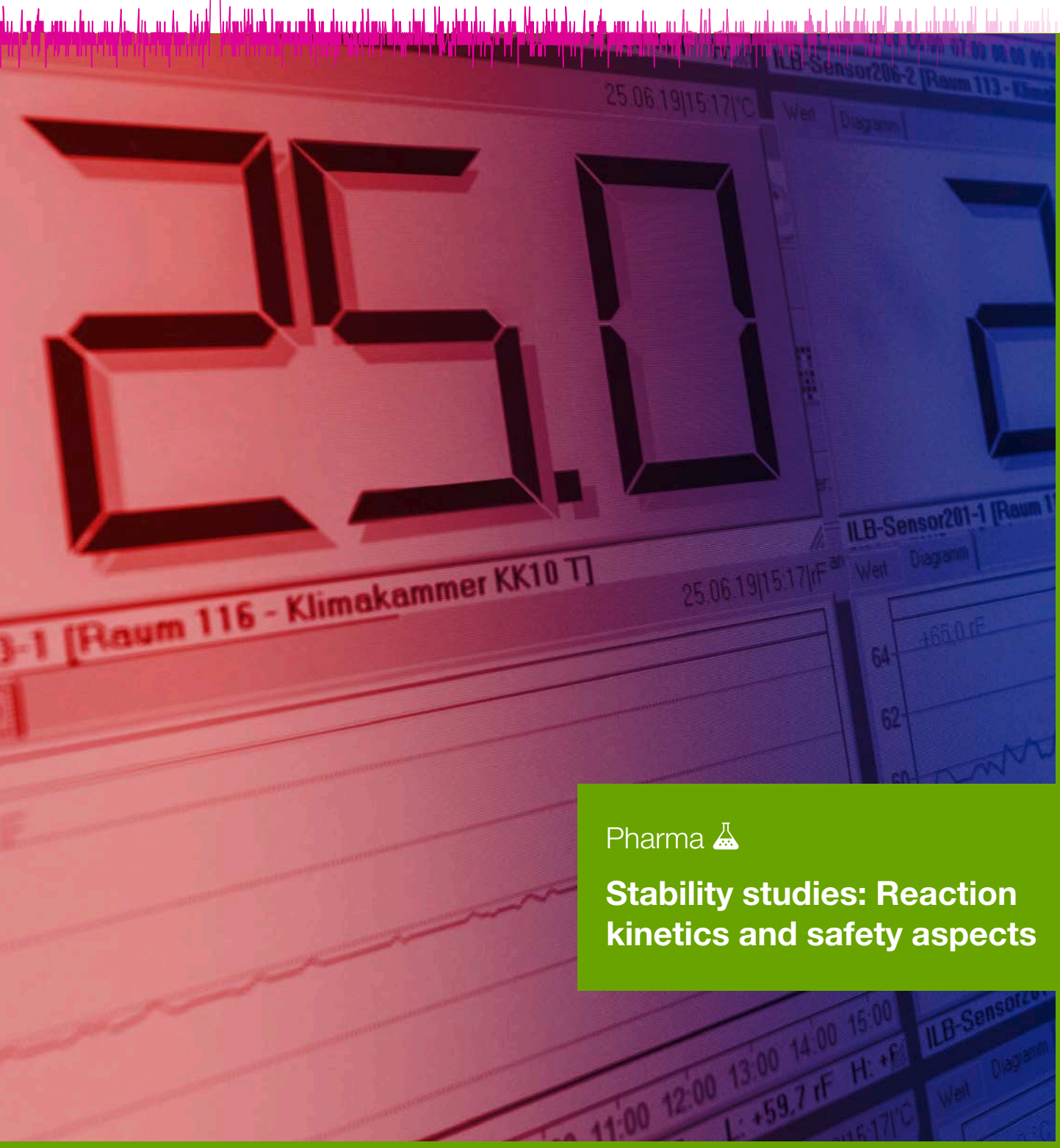

Pharma

Stability studies: Reaction kinetics and safety aspects

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For many, the careful arrangement of the pharmaceutical travel kit is part of the preparation for the summer holidays. It is often asked whether the quality of the pharmaceuticals suffers from the „stress of travel", such as high humidity or tropical temperatures, and whether this affects the shelf life of the products. Similar considerations are taken into account by pharmaceutical manufacturers in the development of pharmaceuticals in the context of stability studies.

Regulatory framework conditions

The general aim of a stability study is to determine the shelf life of a pharmaceutical on the basis of experimental data and to define an expiry date. The necessary steps are shown in diagram 1.

The regulatory framework for the collection of stability data is laid down in the Q1A - Q1E quality guidelines of the ICH (International Conference of Harmonization). For example, for climate zones I and II (including North America, Japan and Europe) and III, IVa and IVb (including a large proportion of Asian and African countries), the following representative storage conditions are defined with regard to temperature and humidity[1]:

- Conditions climate zone I & II: 25 °C/60 % RH
- Conditions climate zone III, IVa, IVb: 30 °C/75 % RH

Depending on the data available and the application (initial registration, follow-up study, product development or transport simulation), the duration of stability studies ranges from a few weeks to several years[2].

Reaction kinetics

Particular care is required in the planning of stability studies for products containing active substances with limited shelf life or requiring high safety precautions. A good example of the former is the active substance phenylbutazone, which is used in veterinary medicine as an antirheumatic agent. (see 2)

1 Process steps in the planning and execution of a stability study.

1. Step

Definition of specifications

concerning microbiological, physical and chemical product quality (e.g. API content, degradation products, total bacterial count, pH value)

2. Step

Definition of analytical methods for product quality control

Development and/or validation respectively verification of suitable analytical methods. For example HPLC or GC procedures for determining the content of APIs.

3. Step

Determination of the framework

Storage conditions, storage duration, test times, batch selection and container/closure system are determined depending on the climatic zones relevenat for the product and the data already available

4. Step

Execution of the stability study

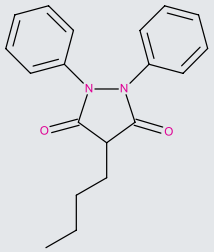
Sample storage and analysis at times specified in step 3

5. Step

Evaluation of stability data

Determination of shelf life and expiration date on the basis of the data obtained.

2 Chemical structure of phenylbutazone



It is known that chemical reactions are temperature-dependent and that this dependence is not linear according to the Arrhenius equation:

$$k = A \cdot e^{-\frac{E_A}{R \cdot T}}$$

Based on the Arrhenius equation and by conducting stability studies at different temperatures, the reaction kinetics can be determined and a deeper understanding of the degradation reactions in the preparation can be gained. In addition, the data obtained in this way enable reliable determination of the storage temperature and the respective shelf life. Figure 3 shows the phenylbutazone content of a semi-solid preparation as a function of time and storage temperature.

The data show a zero-order degradation reaction, whereby it should be noted that the respective initial concentrations are comparable and the proportions of degradation products are presumably relatively low. In general, reaction rates depend on the concentration of the reacting substances and increase with it (keyword collision theory). In the concrete example, any dependencies of the initial concentrations of the educts which would lead to higher reaction orders are negligible. With the help of the experimentally determined data, the velocity constants of the degradation reaction can be approximately calculated as a function of the temperature (**Table 1**).

This database enables the shelf life of the preparation to be determined at different storage temperatures, whereby it should not be forgotten that the active ingredient content is not the only limiting factor. In the concrete example, a shelf life of 24 months at 5°C and 12 months at 25°C could be defined. In addition, the measurement results can be used to develop an emergency plan in the event of a cold room failure or a cold chain interruption, for example during transport.

Safety aspects

In addition to active substances with a limited shelf life, another critical point in stability studies should not be underestimated, namely the storage of hazardous substances or preparations containing in particular volatile and flammable components. In such cases, special measures must be taken on the basis of a risk analysis (e.g. FMEA) in order to reduce the hazard risk for humans and the operation to a minimum (**Table 2**).

3 Phenylbutazone content in % of the expected value.

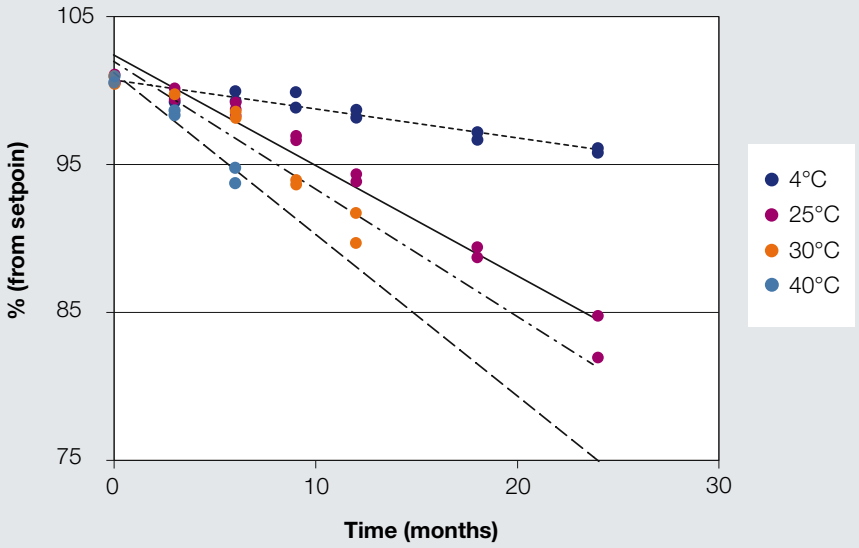


Table 1: Speed constants (Arrhenius equation) as a function of temperature.

Temperature	Temperature	1/Temp.	k (slope)	ln k
°C	K		Zero order reaction	
4	277	0.00361011	0.1945	-1.63732312
25	298	0.0033557	0.7449	-0.2945053
30	303	0.00330033	0.8617	-0.1488481
40	313	0.00319489	1.0917	0.08773611

Table 2: Overview of hazards and possible risk reduction measures.

Risks	Measure
- Formation of explosive atmosphere by propellant gases (e.g. aerosol cans) - Risk of suffocation due to propellant gases (e.g. aerosol cans) - Formation of flammable vapour-air mixtures by (easily) combustible solvents	- Use of tested packaging units (tightly closing containers) - Gas sensors for flammable gases and vapours (e.g. infra-red gas transmitters) - Monitoring measurements (e.g. mass loss) - Avoid ignition sources near the ground (e.g. electrical switches, power sources)

Conclusion

Planning and conducting stability studies requires both detailed product knowledge and indispensable analytical and regulatory know-how. In addition, rooms with appropriate temperature and humidity conditions as well as adequate security systems must be available. □

References

1. *https://www.pharmaguideline.com/2010/12/different-climatic-zones-for-stability.html*
2. *Stabilitätsprüfung in der Pharmazie (Stability testing in the pharmaceutical industry), Wolfgang Grimm et al., 3rd edition 2011, Publisher: Editio Cantor-Verlag.*

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