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Quality by Design in the Development: Benefit or Bureaucratic Burden?

An Essay about ICH Guideline Q8 with Focus on Transdermal Delivery Systems Development

The industry cannot enforce any legally binding requirements for a systematic approach to pharmaceutical development. Therefore, the referenced guideline **ICH Q8** is rather a descriptive guideline on how the chapter **pharmaceutical development** (e.g. 3.2.P.2 of registration files) should be written. That said, a unified standard for the principles of development is clearly defined and without **design space and its documentation** registration relevant data for 3.2.P.2 cannot be provided for registration files.

Key words

- Quality by design approaches in the development of TDS
- General aspects according to ICH guideline Q8
- Establishment of the design space
- Documentation of the design space

For easy identification, the referenced technical terms of the guideline Q8 are highlighted in bold.

The aim of pharmaceutical development is to design a quality product and its manufacturing process. With reference to ICH guideline Q6A, **quality** of a product is characterised by **identity, strength, and purity** (as defined) and its reproducible manufacturing process.

These same quality requirements were already established in the historical monographs of the German pharmacopeia DAB (DAB) and USP monographs using different words that hold similar meanings: Identification, Assay and Impurities. Furthermore, other statements of the guideline are commonly understood. For example, the statements that '**quality cannot be tested into products**' and '**quality should be built in by design**' which means by:

- **Understanding of the development**
- **Drug substance and excipients in relevant specifications**
- **A defined manufacturing process!**

This understanding can be gained by prior knowledge or formal experimental design, which seems on the first view in opposition to the W. Edwards Deming statement:

"In God we trust, all others bring data!"
Deming, W.E. The New Economics For Industry, Government and Education. Cambridge, MA: MIT Press, 1993

However, the US definition of "prior knowledge" is different from the European understanding of this term. The FDA states that prior knowledge can only be gained by experiments and never by education.

Taking the costs of development into account makes the statement remarkable **that the level of knowledge gained, and not the volume of data, provides the basis for science-based submissions.**

Finally, this article does not describe the design space for **a manufacturing process** (since such an approach is comparable to the US process qualification (PQ) or validation process outside the US), but deals exclusively with the establishment of the design space, including its documentation, for development of transdermal delivery systems (TDS).

The article is subdivided into two parts detailing how a design space approach may be applied to development of finished product TDS with relation to 1) identity and purity and 2) strengh.

Identity and Purity

So far, there are no guidelines defining criteria to test **identity** by following the **QbD** approach; however, such an approach might be of interest to justify changes of manufacturing sites. For example, this is especially true for excipients used in TDS such as pressure-sensitive adhesives or liners.

Furthermore, it is obvious how **purity** within the specification and also throughout the **life cycle** of a product can be achieved (e.g. by utilising pure drug substances and excipients **(2.1.2 Excipients) in relevant specifications)**. The relevance of using pure excipients will be demonstrated with an important TDS ingredient, the pressure-sensitive adhesives. Pressure-sensitive adhesives contain monomers and initiators which are critical impurities in polymers ("critical" in the sense of quality-affecting impact on the final product).

Residuals of initiators (or radical starters) in a polymer are critical for the purity of the drug product TDS. They can initiate a radical degradation of the drug substance during the manufacturing or storage of the TDS.

Furthermore, non-hazardous excipients (e.g. water) can have critical impact due to the risk for microbiological contamination **(2.5 Microbiological Attributes)** or hydrolysis of the drug substance when applied transdermally. For these reasons, the use of polymers dissolved in organic solvents rather than aqueous polymer dispersions is preferred for the manufacture of TDS, to minimise the potential risk (the growth of germs is unlikely in organic solvents).

The use of oxygen- or light-sensitive substances (e.g. nicotine, buprenorphine and nifedipine) or excipients used as tackifiers (e.g. oleic acid or abietic acid derivative) may prove critical for the stability of TDS, but adequate countermeasures can be applied:

- Inert gas flushing in the production, but additionally:
- Relevant specifications of excipients (e.g. peroxide value in resins, oleic acid and PVP or residuals of initiators (or radical starters) in a polymer, see above).
- Use of antioxidants in optimal

concentration, which can be found in experiments in the **design space**[1].
- Pouch in tight sachets **(4. Container Closure System)**
- Avoidance of light exposure during the manufacturing or storage of intermediates

Strength
A Parameter and its optimisation Quite Different in TDS in Comparison to All Other Dosage Forms.

A more or less high amount of the drug substance in the TDS is not absorbed, but will be retained in the TDS during the application period, which yields assay and delivery rates that are not identical. Therefore, the parameter strength and also its optimisation are quite different for TDS when compared to all other dosage forms. In general, it is justified to state that the drug substance acts like an enhancer, because a certain part of the drug substance is necessary to enable the transdermal absorption, even though not absorbed!

Nevertheless, the demand of health authorities worldwide to specify an assay with a 95–105% label claim is difficult to justify.

Optimisation of the utilisation of the drug substance is a major goal for **quality by design** applied to TDS. This means the TDS drug content should be as low as possible and not higher than necessary.

This approach is not only important for economic reasons,but also regarding aspects of safety, sustainability and avoidance of narcotic abuse. In general, drug substances in TDS are very potent substances, which means they are toxic, expensive, and in some cases controlled substances (e.g. fentanyl, buprenorphine, ritaline or testosterone).

It is strictly recommended to consider, besides the quality parameters, two requirements of ICH Q8, which are that the **type of dosage form selected is suitable both for the intended use** and also **for patients` needs.**

Please note that the term “selected dosage form” does not mean TDS, in general, but rather a TDS selected from the group liquid-filled reservoir system, matrix system with or without rate-controlling membrane or micro reservoir system. Furthermore, the drug substance can be dissolved or dispersed within the polymer, whereas dispersion can mean either in the form of a supersaturated solution (e.g. suspension), or crystals.

Besides optimisation of the assay, the clear definition of the **type of dosage** form helps to recognise the relevance of the physico-chemical properties of the drug substance (2.1.1 **Drug Substance ... properties that might need to be examined include solubility, water content, particle size crystal properties ...).** In the case of liquid-filled reservoir systems or matrix systems, the drug substance will be dissolved during the TDS manufacturing and particle size is only important for the rate of dissolution during production. It affects only the rate of dissolution, but not the solubility.

According to the European understanding, the Noyes und Whitney equation can be regarded as **prior knowledge**; however, some health authorities will request supportive experimental data.

In addition, the requirements TDS have to fulfill besides quality parameters (mentioned in the guideline Q8, PART II as **patients` needs and the intended product performance)** are different from those of other dosage forms. The simplicity of the answer to define the main features of a TDS might sometimes be surprising, as requirements are so simple that developers just forget them. Therefore, it is strongly recommended to point out that a TDS has to adhere to the skin and to deliver the drug substance transdermally over an application period of one or even more days. Afterwards, the TDS has to be removed without any adhesive residuals and – even more important – removal must be painless for the user!

For completion, it is necessary to define that reversible adhesion is the tendency of two dissimilar surfaces to stick to one another by wetting both surfaces with a liquid or a polymer in its rubbery state. In the field of transdermal application, one surface is human skin, the other the backing layer of the TDS.

Both requirements for the TDS are fulfilled by the one essential excipient, including its essential property, which is the pressure-sensitive adhesive polymer building the matrix of TDS. One of the most unique physical properties that defines a polymer is its glass transition temperature, t_g, which directly correlates with its mechanical property. In case the tg of the polymer is lower than room temperature RT (t_g < RT) it acquires rubber-like characteristics, surfaces can be wet, and the polymer acts as an adhesive. Polymers exposed to temperatures below their specific t_g become hard and brittle and are no longer adhesives. Due to the decreased motion of the polymer chains, the diffusion of the drug substance in relevant amounts is not sufficient and transdermal absorption is impossible.

This introduction was required to work out the main items of the approach, how to optimise the assay of the drug substance with systematic and targeted experiments by taking input factors into account. If it is accepted that just a certain amount of the drug substance in TDS can be utilised via transdermal absorption, then it becomes obvious that optimisation of the drug substance assay means an optimisation of the transdermal absorption. This is because the higher the relative amount of drug substance is absorbed transdermally, the lower the absolute drug substance assay in the TDS. When planning experiments within the design space, **prior knowledge** can be applied, but should not be taken schematically 1:1.

According to Hadgraft[2] and Davis 'vehicles' containing the drug substances in the form of supersaturated solutions have a clear advantage for transdermal drug application compared to drug solutions at or below its concentration of saturation cs.

They emphasise the relevance of drug substances` 'thermodynamic activities' over their concentrations, and justify this hypothesis as follows, starting with Higuchi`s modification of Fick`s diffusion law:

$$F = D \times C_{skin} / L$$

where:

F: Flux/ area
D: Diffusion coefficient of the drug substance in the stratum corneum
L: Effective thickness of the stratum corneum
cskin: Concentration of the drug substance in the outer layer of the stratum corneum

Furthermore, they define:

$$c_{skin} = c_{vehicle} \times P_c$$

where:

$c_{vehicle}$: Concentration of the drug substance in the vehicle (which means in the TDS) and

P_c: Partition coefficient of the drug substance vehicle / stratum corneum

Under stable equilibrium conditions, flux will be at a maximum, when the outer layer of the skin is saturated and, by definition, this will occur when the TDS matrix is also saturated with the drug substance.

In that stage, the calculation can be written:

$$c_{s\ vehicle} \times P_c = \text{constant}.$$

That means that if the partition coefficient of the drug substance vehicle/ stratum corneum is higher, the lower the drug substance concentration of saturation cs in the vehicle (that means in the TDS!) is. Consequently, the amount of drug substance absorbed transdermally depends on its concentration at saturation, but neither on its concentration nor (even more remarkable) on its absolute content!

Therefore, Hadgraft and Davis support the utility of supersaturated systems for the development of TDS; that means TDS containing the drug substance above its concentration of saturation c_s, which can be described as:

$$c_{vehicle} > c_s$$

Without reflection, this explanation allows the conclusion that it only needs the determination of the lowest c_s of a drug substance in different polymers, followed by the manufacture of TDS with a high amount of the drug substance in the respective polymer and a high drug loading. As a consequence, this approach results in a TDS with a maximum of thermodynamic activity and the utmost utilisation of the drug substance, however:

So far, **the life cycle and patients` needs** of a TDS have not been considered, as supersaturated systems have the tendency to crystallise during the shelf life, and adherence to the skin after 24 hours or longer has to be assured.

What does it matter if the highest thermodynamic activity is obtained, if the TDS does not stick?!

Bridging the gap between an optimised flux and skin adhesion of TDS is exactly the challenge,

whereas in parallel drug substance, crystallisation in the polymer should be avoided.

Based on this information, a systematic development of a TDS essentially consisting of an acrylate copolymer matrix and a drug substance will be outlined, which conforms to ICH guideline Q8. Acrylate copolymers have been chosen because they are still the most important pressure-sensitive adhesives today. In general, the following explanations are also relevant for poly isobutylenes and poly siloxanes.

First of all, the drug concentration at saturation has to be determined. This parameter depends on the chemical structures of the monomers – the dissolution is allocated in the oscillating polymer side chains – rather than the molecular weight distribution influencing the viscosity and, as a consequence of this, rate of diffusion, the glass transition temperature and lastly the adhesion properties of the pressure-sensitive polymer.

After the determination of the c_s value, the so-called systematic targeted experiments (**design space**) in the form of binary blends consisting of drug substance and polymer will be performed. Starting with the defined c_s, the test series will be continued by increasing the drug substance content (**input parameter**) gradually (c_s + x % drug substance in the polymer matrix) with a main focus on the flux and adhesion properties (**output parameter**), because the drug substance can have either positive (by reducing the glass transition temperature) or negative (by reducing the wetting properties of the surface) impact on the adhesion strength.

In parallel, it is recommended to monitor the *in vitro* dissolution, because crystallisation can be the root cause for decreasing of the dissolution. The binary mixtures have to be stored under accelerated conditions (e.g. 40°C) as increasing of the storage conditions will expedite crystallisation, as higher temperature increases the velocity of diffusion and decreases the viscosity of polymers.

After identifying the optimal polymer type, experiments with polymers of different relative viscosity have to be performed. In linear polymers (e.g. in poly acrylates or poly isobutylenes) dynamic and complex viscosities correlate, because both depend on the molecular weight distribution (as long as the polymers will not be further cross-linked after polymerisation). The relative viscosity will be tested in polymer solutions of defined solid content (e.g. 2 %) because content of solids and the molecular weight distribution also have an impact on the viscosity. Therefore, the viscosity allows an indirect determination of the molecular weight distribution.

The aim of the experiments is to provide knowledge of whether the viscosity of 2 % (w/w) polymer solution impacts the adhesion properties of the binary mixtures and whether the viscosity is sufficient to stabilise the supersaturated solution. A stable supersaturated solution will avoid any drug substance crystallisation or, in case of individual crystals, indicate whether an impact towards the *in vitro* dissolution can be observed.

Finally, due to the similarity of process qualification/validation and the QbD approach, it might be reasonable to adopt the PQ approach towards documentation in the QbD approach. This means to follow a protocol approved prior to any experimental activities, since expectations fixed prior to any experiments followed by a comparison between expectations and results, because that demonstrates that the developers understand what they are doing, even if no specifications can be set in the very early phases of research and development.

Conclusion

In the headline, the provoking question had been raised as to whether the QbD approach is a further bureaucratic burden in scientific research. In fact, the very opposite is right, because ICH guideline Q8 is of benefit in describing well-established development strategies and providing – due to its well-structured content – a platform for controlled and organised development, not only for TDS.

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