QUALITY BY DESIGN IN TDS DEVELOPMENT: BENEFIT OR BUREAUCRATIC BURDEN?

In this article, Petra Botzem, Senior Technician in R&D, and Thomas Hille, PhD, Director of R&D, both of LTS, discuss the Quality-by-Design approach to the development of transdermal drug delivery systems as laid out in ICH guideline Q8. The authors describe the key aspects of identity, purity and strength before applying this knowledge to outline how such a development cycle would work in practice.

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INTRODUCTION

The aim of pharmaceutical development is to design a quality product and its manufacturing process. With reference to ICH guideline Q6A, the quality of a product is characterised by identity, strength, purity and its reproducible manufacturing process. These same quality requirements were already established in the historical monographs of both the German pharmacopeia (DAB) and the United States pharmacopeia (USP) using different words that hold similar meanings: Identification, Assay and Impurities.

Furthermore, other statements taken from the guideline are commonly cited when seeking to understand a product's quality, for example the statements that "Quality cannot be tested into products" and "Quality should be built in by design".

This understanding can be gained through prior knowledge or formal experimental design, which seems, at first, in opposition to the famous statement made by W Edwards Deming:

"In God we trust, all others bring data!"[1]

However, the US definition of "prior knowledge" is different from that given by the European Union. The US FDA states that prior knowledge may only be gained from experimentation and never by education alone. 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.

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It is also worth noting at this stage that the pharmaceutical industry itself has neither the capability nor the authority to enforce legally binding requirements upon its constituent companies. Therefore, the guidelines referenced are merely that, non-binding descriptions of how to go about the business of pharmaceutical development. That being said, they do provide the basis for the present unified development standards, and thus non-compliant companies will experience difficulties operating within the industry.

Finally, this article will not describe the design space for a manufacturing process itself (due to the similarities with process qualification, US, or process validation,

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Petra Botzem
R&D Senior Technician
T: +49 2632 99 2293
E: petra.botzem@itslohmann.de

Dr Thomas Hille
Director of R&D
T: +49 2632 99 2437
E: thomas.hille@itslohmann.de

LTS Lohmann Therapie-Systeme AG
Lohmannstraße 2
56626 Adernach
Germany

ltslohmann.de

non-US), but rather will deal exclusively with the establishment of the design space, including relevant documentation, with a focus on transdermal delivery systems (TDS).

IDENTITY AND PURITY

At present, there are no guidelines defining criteria to test identity when following a quality-by-design (QBD) approach. However, such an approach might be of interest to justify changes at 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 lifecycle, of a product can be achieved (e.g. by utilising pure drug substances and excipients in relevant specifications). The relevance of using pure excipients will be demonstrated with the aforementioned 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 a critical factor when considering 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 a critical impact due to the risk of microbiological contamination 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 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 derivatives) may prove critical to the stability of TDS, but require the following adequate countermeasures to be applied:

- Inert gas flushing in the production.
- Relevant specifications of excipients (e.g. peroxide value in resins, oleic acid and PVP or residuals of initiators, or radical starters, in a polymer as mentioned prior).
- Use of antioxidants in optimal concentration, which can be found by experimentation in the design space.[2]
- Sealing TDS products in airtight sachets.
- Avoidance of light exposure during the manufacturing or storage of intermediates.

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STRENGTH

A parameter and its optimisation are quite different in TDS in comparison to all other dosage forms. As an example, a high proportion of the drug substance in the TDS is not absorbed, but is instead retained in the TDS during and after application, which yields assay and delivery rates that are not identical, hence the unusual nature of the TDS's strength parameter, and the optimisation thereof. In general, it is justified to state that the excess drug substance acts like an enhancer, because a certain part of it is necessary to enable transdermal absorption, even though it is not absorbed. Nevertheless, the demand from health authorities to specify assay within 95-105% of the label claim is difficult to justify.

Optimisation of the utilisation of the drug substance is a major goal for QBD as applied to TDS. This means the TDS drug content should be as low as possible whilst still achieving efficacy. This approach is not only important for economic reasons, but in regards to aspects of safety, sustainability and inhibiting narcotic abuse. In general, drug substances in TDS are very potent, meaning they are toxic, expensive and, in some cases, controlled substances (e.g. buprenorphine, methylphenidate, fentanyl and testosterone).

As well as the quality parameters, it is strongly recommended that two requirements of ICH Q8 concerning the selected dosage form are considered: 1) that the type of dosage form selected is suitable for the intended use, and 2) that it is suitable for patients' needs. Please note that here the term "selected dosage form" does not refer to the selection of a TDS in a general sense, but rather the specific type of TDS, such as a liquid-filled reservoir system, matrix system (with or without a rate-controlling membrane) or micro reservoir system. Furthermore, the drug substance can be dissolved or dispersed within the polymer, where dispersion can mean either in 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 physicochemical properties of the drug substance. In the case of liquid-filled reservoir systems or matrix systems, the drug is dissolved during manufacture and particle size is only important for the rate of dissolution during production, affecting only the rate of dissolution, not the solubility.

ADHESIVE

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

For completeness, reversible adhesion is defined as 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, the pressure sensitive adhesive polymer building the matrix of the TDS. One of the physical properties that defines a polymer most uniquely is its glass transition temperature

(Tg), which directly correlates with its mechanical properties. When the Tg of a polymer is lower than room temperature RT (Tg < RT), it acquires rubber-like characteristics, its surface can be wet and the polymer acts as an adhesive. Polymers exposed to temperatures below their specific Tg become hard and brittle and are no longer adhesive. Due to the decreased motion of the polymer chains the diffusion of the drug substance in relevant amounts is not sufficient and thus transdermal absorption of it is impossible.

SUPERSATURATION

Armed with this knowledge, it is now possible 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 only 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 that is 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.

According to Hadgraft and Davis,[3] "vehicles" containing the drug substances in the form of supersaturated solutions have a clear advantage for transdermal drug application compared with drug solutions at or below its concentration of saturation c_s. They emphasise the relevance of drug substances' "thermodynamic activities" over their concentrations, and justify this hypothesis starting with Higuchi's modification of Fick's diffusion law:

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

Where:

- F = flux/area
- D = diffusion co-efficient of the drug substance in the stratum corneum
- L = effective thickness of the stratum corneum
- c_{skin} = concentration of the drug substance in the outer layer of the stratum corneum.

Furthermore, they define:

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

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Where:

- $C_{vehicle}$ = concentration of the drug substance in the vehicle (which means in the TDS)
- Pc = partition co-efficient of the drug vehicle/stratum corneum.

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

In that stage the calculation can be written as the equation:

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

That means that the higher the partition co-efficient of the drug substance vehicle/stratum corneum, the lower the drug substance c_s in the vehicle (i.e. the TDS). Consequently, the amount of drug substance absorbed transdermally depends on its concentration at saturation, but neither on its actual concentration nor, even more remarkably, on its absolute content.

Therefore, Hadgraft and Davis support the utility of supersaturated systems for the development of TDS, meaning that TDS containing the drug substance above its c_s, which can be described with the inequality:

$$c_{vehicle} > c_s$$

Without reflection, this explanation permits 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 a TDS 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 product's lifecycle and patients' needs have not been considered, as supersaturated systems have the tendency to crystallise during the product's shelf life, and adherence to the skin after 24 hours or longer must be assured. What does it matter if, by obtaining the highest possible thermodynamic activity, the TDS does not stick? Bridging the gap between an optimised flux and skin adhesion of TDS is precisely the challenge, whilst in parallel ensuring that drug substance crystallisation in the polymer should is avoided.

TDS DEVELOPMENT

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

First of all, the drug concentration at saturation has to be determined. This parameter depends upon 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 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 main focus on the flux and adhesion properties (output parameter). The drug substance can have either a positive (by reducing the glass transition temperature) or a negative (by reducing the wetting properties of the surface) impact on the adhesion strength.

In parallel, monitoring the *in vitro* dissolution is recommended, 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 the temperature of the storage conditions will expedite crystallisation, as higher temperatures increase the velocity of diffusion and decreases the viscosity of the polymers.

After identifying the optimal polymer type, experiments with polymers of different relative viscosity have to be performed. In linear polymers (e.g. in polyacrylates or polyisobutylenes) 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 the 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 these experiments is to provide knowledge as to 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 process qualification approach towards documentation in the QBD approach. This means that a protocol approved prior to any experimental activities should be followed, i.e. expectations fixed prior to any experiments followed by a comparison between said expectations and experimental results. Such an approach 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 title of the article, the provoking question had been raised as to whether the QBD approach is just a further bureaucratic burden in scientific research. In fact, the very opposite is true; ICH guideline Q8 is of great benefit, describing well-established development strategies and providing a well-structured content a platform for controlled and organised development, not only for TDS but across the full spectrum of pharmaceutical development.

ABOUT THE COMPANY

LTS Lohmann Therapie-Systeme (LTS) is a pharmaceutical technology company that develops and manufactures innovative drug delivery systems such as transdermal therapeutic patches (TTS) and oral thin films (OTF) for the pharmaceutical industry. LTS's innovation model consists of both partner-funded and self-funded initiatives, currently encompassing more than 20 marketed products and a deep and diverse pipeline targeting multiple disease indications. LTS maintains its leading position through the continuous refinement of its core TTS and OTF technologies and by advancing emerging drug delivery technologies, including Micro Array Patches for the transdermal delivery of large molecule, biological actives. Founded in 1984, LTS operates today from two sites in Andernach (Germany) and West Caldwell (NJ, US), with a representation in Shanghai (China).

ABOUT THE AUTHORS

Petra Botzem is a Senior Technician in the LTS R&D department, possessing a wealth of experience in the development and scale-up of TDS and oral thin films. She handles manufacturing site changes concerning inactive ingredient, as well as the tech transfers processes for final dosage forms. Ms Botzem's experience has been gained working at the manufacturing sites of LTS in both Europe and the US. Furthermore, Petra is the co-inventor on several patents.

Thomas Hille is a pharmacist and achieved his PhD in Natural Science at the University of Bonn. He is a Director of the LTS R&D department and has developed TDS from lab formulation all the way through to final product, resulting in international registrations and product launches across five continents. Dr Hille holds several international patents for TDS formulations and manufacturing processes, especially for TDS containing narcotics.

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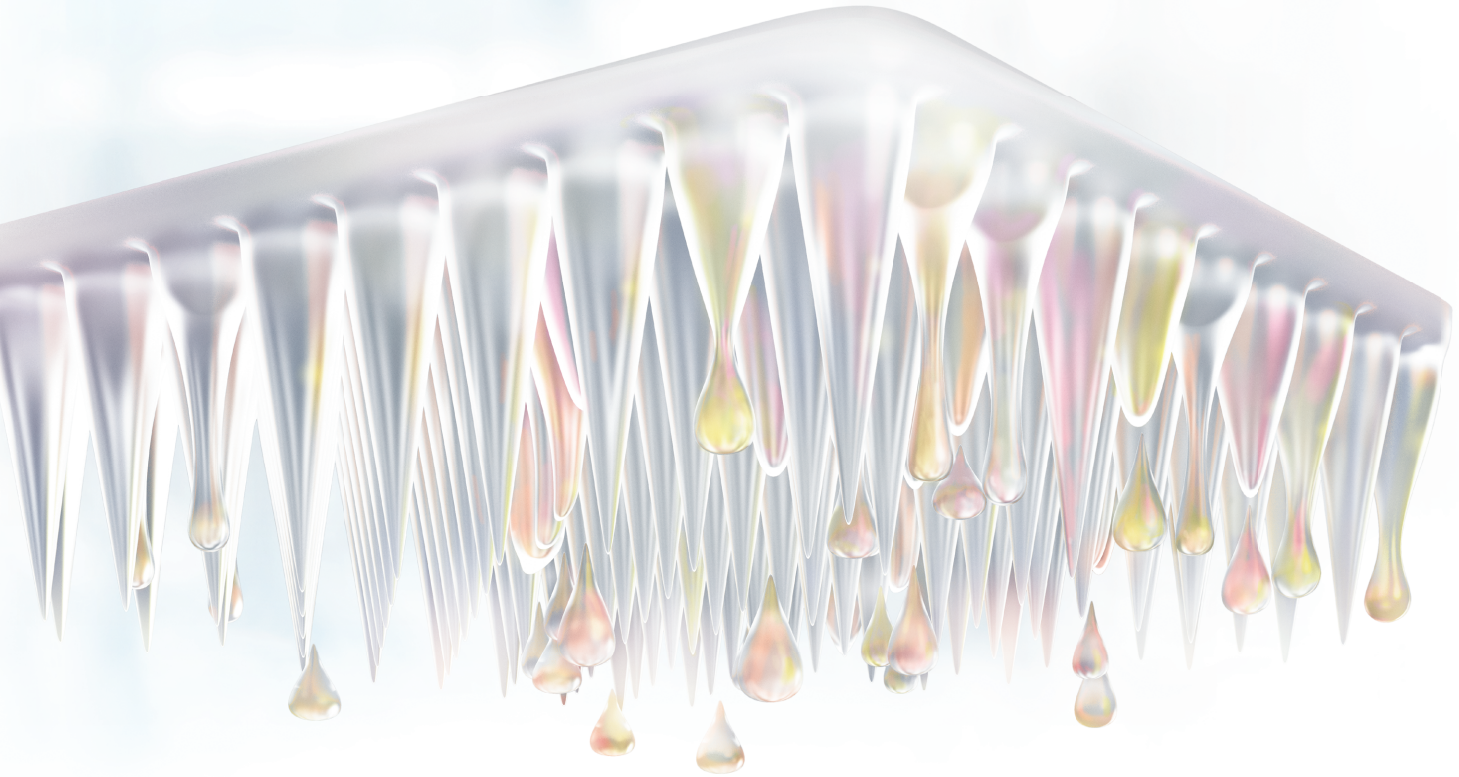

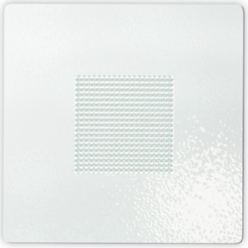

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