A risk-based and patient-centric approach to pharmaceutical product development: Rheology as a critical quality attribute

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ABSTRACT

The need for a risk-based and patient-centric approach to pharmaceutical product development not only results from an increasing product complexity, but also from frequently occurring drug shortages and recalls. For suspensions for parenteral dosing, their rheological behaviour is a critical quality attribute (CQA) in this approach. Flow properties, such as viscosity and thixotropy of these products, directly impact on the patient through product quality and patient compliance.

INTRODUCTION

The risk-based and patient-centric approach builds upon the quality by design (QbD) concept that originates from post-war Japan[1]. The approach uses risk assessments as a decision making tool and defines the end goal in terms of patient needs.

QbD is based on the hypothesis that unsuccessful products on the market are failing because of their faulty design. The focus on quality is therefore already implemented during the initial conceptualization of a product. Quality is the suitability of a product for its intended use[2]. The main idea is to build this quality into the product by design[1,2]. The start of product development is established by a predefined end in terms of patient needs. The QbD concept starts with the end and keeps the end in mind throughout the product development process.

Within the risk-based approach, risk assessments are used to facilitate the decision making[3,4]. Risk management was implemented in many different fields and industries and it took a long time before being applied in the pharmaceutical world[5]. This might be partially due to the pharmaceutical world's inherently conservative nature, and partially due to the specific nature of the pharmaceutical risk: the patient.

THE NEED FOR A LEAN APPROACH

In 2004, the FDA initiated a revolution in the pharmaceutical industry by announcing the need for modernization in their report "Pharmaceutical cGMP for the 21st century"[5,6]. Shortly thereafter, ICH guidelines ICH Q8 (Pharmaceutical development)[2], Q9 (Quality risk management)[7] and ICH Q10 (Pharmaceutical quality system)[8] were published facilitating QbD in product development. Additional guidelines (ICH Q11 and ICH Q12) followed, with the aim to endorse the implementation of the QbD approach. Today many pharmaceutical companies are engaged in the QbD approach to product development, realizing the need for QbD[9].

The complexity of the drug product design is increasing[3,4]. This complexity can arise from the combination of ingredients, the analytical methods for characterization,

the manufacturing process, the need to modify the drug release profile in the body upon administration or a combination of these. As the complexity increases, it takes more time and effort to review the quality of these pharmaceutical products. This results in long time lines for the products to reach the market and the treatment of patients is delayed. Moreover, it takes additional manpower to review cumbersome applications arising from complex products.

Additionally, there have been alarming shortages and unprecedented recalls of drugs from the market putting pharmaceutical quality on the radar[5].

These points illustrate the need for lean improvement of pharmaceutical quality and the QbD approach fits this very purpose.

THE ADDED VALUE OF QbD

Advantages of QbD next to an enhanced pharmaceutical quality product include:

1. QbD helps a scientist to document and organize the scientific work.
2. Through risk-assessments being utilized as a tool for decision making, QbD facilitates alignment within a team.
3. By documenting the scientific justification of the risk-based decisions, QbD results in a knowledge database.
4. QbD makes the product development process transparent and facilitates transfer of analytical methods and manufacturing processes highly needed within the globalized pharmaceutical manufacturing world.
5. Through a transparent, systematic and scientific approach, QbD aids communication within the project team, towards the peers and to the regulatory authorities. The end result is a smoother review and approval towards a faster availability of new medicines for the patient.

QbD ROADMAP

QbD is a systematic approach to product development resembling a roadmap, as it is composed of pre-defined elements executed in a fixed order (Fig 1). The QbD roadmap helps the pharmaceutical scientist to work systematically, cover the scientific aspects of every item without losing focus of the things that matter and keeps the patient in mind. Pharmaceutical scientists need help as product development is of a multidisciplinary nature and putting a product on a market is a tedious process under tremendous time pressure.

The roadmap starts with the patient, and the overall objective is to meet patient needs in having medicines that are safe, effective, patient-compliant, affordable and available.

From understanding the patient needs, the quality target product profile (QTPP) is established. QTPPs translate the patient needs into the desired product performance at a holistic level. QTPP items include the dosage form, the delivery system, the route of administration, the dose strength(s), the release profile, packaging, storage conditions and regulatory compliance.

From the QTPP, the critical quality attributes (CQAs) are derived, capturing the patient needs in greater detail. CQAs are the measurable physical, chemical, biological and microbiological attributes of the finished and intermediate products.

When within predefined specifications, CQAs ensure QTPP that meets patient needs. A suitable analytical method for characterization of each CQA is the basis of scientific understanding of its relation to the patient.

CQA's are rated on their criticality for the patient using a risk-based approach. Risk assessments are based on the prior knowledge of related products and the

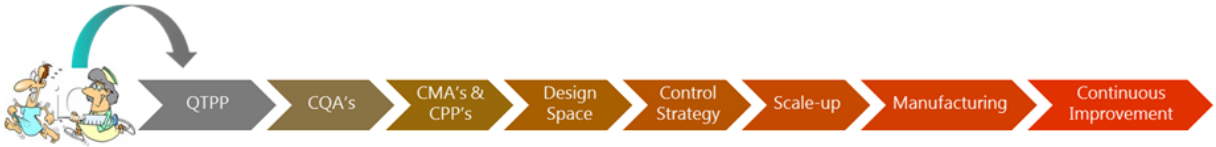

Figure 1. The QbD roadmap helps the pharmaceutical scientist to focus on the patient.

scientific knowledge from the public domain. The choice between qualitative and quantitative risk assessment is determined by the number of the attributes and the level of ranking detail that needs to be acquired. The elaborative nature of quantitative risk assessments, such as failure mode and effects analysis (FMEA), is not in proportion to the added value to the end objective and is therefore not preferred over qualitative risk assessments, e.g. risk ranking and filtering. Both qualitative and quantitative risk assessments need a justification of the levels of criticality.

RHEOLOGY AS A CQA

Rheological characterization is an essential part of the scientific understanding of pharmaceutical suspensions for parenteral dosing. Control of the flow behaviour of suspensions is essential for generating a high quality product. Colloidal suspension rheology can be used to study the effect of multiple critical attributes of these suspensions, such as viscoelastic properties, particle size and shape, agglomeration, flocculation, resuspendability and injectability. They are critical for the manufacturability, ease of administration, pharmacokinetics and stability of the product.

Product quality

Rheological properties are critical in every process step where shear is applied. Basic steps of the manufacturing process are called unit operations. Unit operations applying forces to decrease the particle size are wet ball milling (WBM) and high pressure homogenization (HPH). The unit operation used for transport of material is filling. Effectiveness and robustness of these unit operations is influenced by the rheological behaviour of the formulation.

Wet ball milling

WBM is used to physically decrease the particle size of suspended solids based on principles of comminution. A large frictional impact of the grinding media on the movable suspension ensures particle disruption. During WBM, the movable liquid is decreasing with the increased surface area of decreased particle size`, resulting is an increased viscosity[11]. Scientific understanding of this unit operation can be accomplished by characterizing the viscosity and hereby the particle size evolution of the milled suspension.

It is known that the particles in suspension during WBM have a tendency to re-flocculate and agglomerate[12]. Suspensions with larger-scale agglomerates exhibit higher viscosity[13]. Moreover, a flocculated suspension has thixotropic properties[12]. Viscosity and thixotropy characterization using process analytical tools (PAT) can be used as quantification of the quality of the suspension and the effectiveness of milling in terms of particle size decrease, agglomeration and re-flocculation.

Milling time is influenced by the viscosity. It is therefore expected that keeping the viscosity of the milled suspension at the optimum level will lead to an improved grinding effect and a smaller particle size. This opens new perspectives of process optimization.

High pressure homogenization

HPH pumps a suspension with a constant flow and under high pressure through a narrow gap valve. Particles are subjected to high mechanical stress of twisting and deformation, as a consequence of depressurization, cavitation forces and applied high shear stress. As a consequence the particle size decreases. With the understanding of the influence of HPH on the steady-state shear and time-dependent rheological parameters of suspensions, the HPH unit operation can be optimized and scaled up[10]. Rheological parameters, such as the apparent viscosity and shear stress, are defined by the suspended solid particles and

the liquid matrix of the suspension, as well as the interactions between them. If the liquid is a Newtonian fluid, upon dispersion of a sufficient quantity of particles, it will become a Herschel-Bulkley fluid[10]. For a suspension with the particle size between 10 and 1000 μm, Brownian motion is negligible, thus hydrodynamic forces govern its rheological properties, and the product can be classified as a non-colloidal dispersion. A model can be generated using for example apparent viscosity and shear-stress as a function of applied HPH pressure. The generated model is a tool for optimization and scale-up of this unit operation. However, products that, are colloidal dispersions, have different rheological properties and colloidal forces need to be taken into account as being determining of the rheological behaviour. Consequently, a different model applies for process development and optimization.

Filling

Filling is a unit operation that utilizes shear forces to deliver a consistent homogeneous content into primary packaging. Primary packaging is the layer of packaging that comes in direct contact with the product. Consistent flow is critical in establishing a uniform dosage form and ensures that the delivered dose is within the therapeutic window upon administration. This applies particularly to single dose packaged products.

Unit operations using pumps for material transport heavily rely on a uniform flow of materials. The choice of the pump and the tubing across production scales will determine the shear forces applied to the product. Evaluation, understanding and control of the flow behaviour will hereby enable scalable, robust and reproducible unit operations. Shear forces of these unit operations can be quantified, which gives opportunity to evaluate, understand and optimize flow behaviour off-line. It also opens possibilities for a comparison of different equipment (scales) and for a realization of a model for scale-up.

Patient

Rheological behaviour of pharmaceutical suspensions is a CQA through its impact on the patient. It determines the route of administration and choice of the delivery system.

Drug administration

Viscosity of ophthalamic and parenterally dosed drug dosage forms is critical for patient compliance in terms of pain, discomfort and duration of administration. Highly viscous drugs are uncomfortable or painful upon administration due to the viscosity difference with the fluids at the administration site. For example, the application of ophthalmic products with a viscosity higher than the viscosity of the tear fluid, is experienced as discomfort. Highly viscous injectables dosed intramuscularly are painful due to physical intrusion of the muscle tissue. Injectability of more viscous drugs requires increasing the size of the needle, leading to a more painful administration. In addition, a high viscosity of the dosage form increases the time of administration and hereby prolongs the pain of drug delivery. For suspensions that need to be injected through a very thin needle into a muscle for example, shear thinning is a pre-requisite for injectability or substantial force is needed for injection, leading to damage of the muscle tissue. Shear thinning enables faster administration of highly viscous products, resulting in less painful administration and an improved patient compliance.

Dissolution profile

The viscosity of the suspension medium of an injectable intramuscular oily suspension for example, may influence the dissolution rate by affecting the mobility at the molecular level[10d]. Viscosity of for example oil within the dosage form could therefore be used to control the release in the body upon intramuscular administration.

If scientifically understood, it is possible to carefully control the dissolution by modifying the viscosity and hereby avoid side effects and / or decrease the frequency of administration. Reduced administration frequency improves patient compliance and reduces in many cases the costs to health care providers. Rheological characterization can lead to scientific understanding of in-vivo shear forces upon administration and their influence on the release of the active compound in the body. Furthermore, viscosity modifiers can be used to tailor the dissolution media and develop a discriminant in vitro dissolution method for in vitro product optimization.

CONCLUSION

Rheological behaviour is a CQA in the development of pharmaceutical suspensions for parenteral dosing because it directly impacts the patient. Flow behaviour during unit operations, where shear is applied, determines the quality of the final product. Viscosity and thixotropy characterization can help generating understanding of the quality of the suspensions by discriminating between the agglomerates and flocculates versus non-agglomerated and non-flocculated suspension. This understanding can lead to an improved control of the suspension stability. Viscosity of an injectable product determines the amount of pain upon administration, and flow behaviour of a topical ocular product determines the amount of discomfort. Shear thinning is a important property of a formulation as it ensures a comfortable application. A correctly adjusted level of product viscosity can decrease side effects and reduce frequency of administration. It can also be used to tailor a discriminant in vitro dissolution method towards formulation development and in vitro – in vivo correlation. Availability of a suitable analytical method and the understanding of the patient needs are hereby important.

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