Journal of Pharmaceutical Sciences xxx (2018) 1-10

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

A Tutorial for Developing a Topical Cream Formulation Based on the Quality by Design Approach

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ARTICLE INFO

Article history:
Received 9 April 2018
Revised 7 June 2018
Accepted 12 June 2018

Keywords:
quality by design
quality target product profile
critical quality attributes
critical material attributes
critical process parameters

ABSTRACT

The pharmaceutical industry has entered in a new era, as there is a growing interest in increasing the quality standards of dosage forms, through the implementation of more structured development and manufacturing approaches. For many decades, the manufacturing of drug products was controlled by a regulatory framework to guarantee the quality of the final product through a fixed process and exhaustive testing. Limitations related to the Quality by Test system have been widely acknowledged. The emergence of Quality by Design (QbD) as a systematic and risk-based approach introduced a new quality concept based on a good understanding of how raw materials and process parameters influence the final quality profile. Although the QbD system has been recognized as a revolutionary approach to product development and manufacturing, its full implementation in the pharmaceutical field is still limited. This is particularly evident in the case of semisolid complex formulation development. The present review aims at establishing a practical QbD framework to describe all stages comprised in the pharmaceutical development of a conventional cream in a comprehensible manner.

Introduction

Over the last decades, our understanding about physicochemical properties of topical formulations and their excipients, result in the ability to develop physical, chemical and biologically stable products. To design and develop a successful pharmaceutical dosage form for skin delivery, preformulation and formulation studies require particular considerations. Moreover, the knowledge of skin barrier structure and drug permeation properties is essential for a rational progress in the development of topical formulations.

Dosage forms for topical application are intended to produce the required therapeutic action at specific targets in the skin with the least probable adverse effects.[1,2] Topical formulations can be easily administered and transported, and are used for the treatment of several disorders. For any topical formulation, the onset, rate, and extent of therapeutic response depend on the efficiency of sequential processes: release of the active substance from the dosage form, penetration/diffusion of the drug through the *stratum corneum* (SC), and other skin layers, before producing the pharmacological effect. These different processes are variables which result in formulation safety and efficacy differences.[3] There are several topical formulations available in the market; however, semisolids (e.g., ointments, creams and gels) are the most commonly used for this purpose.[4]

Included in the latter category, conventional creams/emulsions represent a promising pharmaceutical vehicle for skin drug delivery despite their thermodynamic instability and complex formulation remaining a challenge for pharmaceutical technology.[5] Depending on the physicochemical properties, desired site of action, and drug delivery strategies, drugs incorporated into semisolid products can be applied for different purposes. A cream is a semisolid emulsion containing one or more active substances, dissolved or dispersed, and may be defined as a biphasic system in which the dispersed or internal phase is finely and uniformly dispersed in the continuous or external phase. According to the dispersed phase nature, it is possible to acquire an oil-in-water cream (o/w) or a water-in-oil cream (w/o).[4,6]

Besides the several aspects taken into account in cream product design, during the whole process, it is imperative to preserve a high quality level. Thereby, in cream research and development, the application of a systematic approach is demanded to avoid product rejections during manufacturing and to achieve regulatory approval.

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https://doi.org/10.1016/j.xphs.2018.06.010
0022-3549/

Over the years, pharmaceutical industries have spent significant efforts to ensure product quality, to achieve regulatory compliance, and to yield pharmaceuticals as cost efficient as possible. Therefore, they perform sophisticated processes and technologies that require steadiness among scientific progress and operational complexity. Nonetheless, such processes do not present a rational understanding of critical variables and control strategies, which is imperative to ensure the product quality.[7]

In this context, the U.S. Food and Drug Administration has highlighted Quality by Design (QbD) as current Good Manufacturing Practices initiative for the 21st century. The emergence of this approach has added a new dimension to pharmaceutical development and manufacturing.[8-10]

The implementation of the QbD approach includes the definition of the quality target product profile (QTPP) and critical quality attributes (CQAs) of drug product, the accomplishment of risk assessment (International Conference on Harmonisation [ICH] Q9) to identify critical material attributes (CMAs) and critical process parameters (CPPs), the definition of a design space through design of experiments (DoEs), the establishment of a control strategy, and the continual improvement and innovation throughout the product life cycle.[11]

As mentioned in the Q8 guideline, the aim of the pharmaceutical development based on a QbD approach is to design a successful product and its manufacturing process according to the intended quality performance. During product development, a detailed identification, understanding, and control of critical variables, with their optimal operating range definition, will enable to yield a product with the required quality profile. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide an enhancement of scientific understanding. Greater product and process understanding is also crucial for more flexible regulatory approaches. The degree of regulatory flexibility relies on the level of scientific knowledge provided in the registration dossier.

Although the implementation of the QbD principles is one step forward for conventional solid form development, the case of conventional semisolid forms still remain largely unexplained. This review focuses on QbD approach for the development of semisolid dosage forms, particularly on cream formulations. Employing QbD principles to a complex formulation such as a cream, an effective product development, with an optimized formulation, and a continuous and robust manufacturing process, may be easily achieved. Therefore, QbD approach will provide an opportunity for pharmaceutical companies to improve formulation and manufacturing efficiencies and productivity, with significant reduction in cost production, product variability, defects, and batch rejection, so as to get more flexible regulatory approvals, to decrease postapproval changes and to produce high-quality pharmaceuticals under real-time release.[11-15] Thus, the predicted level established through this system is expected to be a scientific and technological progress for industries and regulatory authorities.

QbD Approach—Cream Development Strategy

Definition of Conventional Cream QTPP and CQAs

The initial step when using QbD-based development is to predefine the final quality profile. QTPP comprises cream quality parameters that should be ideally achieved at the final stage of the product development and production, considering its safety and efficacy.

The second step of the QbD-based development is to identify the critical quality parameters. Derived from QTPP, CQAs are quality attributes that must be studied, controlled, and ensured during cream development and manufacturing to guarantee predefined product quality.[7,11,16-18] An example of cream QTPP and its CQAs is provided in Table 1.

Product Design and Development

Once the dosage form is selected, the drug product development using the QbD approach is initiated. The main purpose of the product design is to develop a robust cream that can achieve the therapeutic objectives and quality attributes, remaining stable over the shelf life.

Drug Substance

The physicochemical and biological properties of the drug substance have a significant effect on drug product performance and manufacturability. Thereby, these properties must be identified to produce the right dosage form and to select the appropriate drug concentration, excipients, and process parameters.

During preformulation studies, drug properties such as solubility, partition coefficient (log p), particle size, pKa, permeability, melting point, and molecular weight need to be identified because of their role on percutaneous permeation.[8,11,19,20]

The quality attributes of drug substance will ensure that the drug product meets its CQAs and must be controlled within the defined specifications.[21]

Excipient Selection

Special consideration needs to be given to excipient selection because of their influence also on the final product performance, manufacturability, and stability. This selection is related to the intended dosage form, route of administration, safety profile, manufacturing process, and regulatory aspects. Excipient nature and concentration will determine drug release from the dosage form, skin barrier features and drug penetration/diffusion, affecting the duration and extent of the therapeutic action at the target skin layer.[22]

In cream formulation, excipients are used to improve drug solubility and to incorporate it at the target concentration (solvents), to control drug release and cream viscosity (thickeners), to improve drug skin permeability (chemical permeation enhancers), to enhance drug and formulation stability (antioxidants, emulsifiers and buffers), and to prevent microbial growth and contamination (preservatives).[23] Acceptable pharmaceutical excipients are listed in international pharmacopoeias for pharmaceutical product development.[4]

At this stage, special consideration must be given to drug solubility because it will dictate the excipient selection because of its impact on diffusion through each skin environment, as well as on release pattern from the dosage form vehicle, final cream uniformity, and stability. If a suitable solvent is selected, to comprise the solubilizing phase of the emulsion system, an excellent skin permeation rate of the drug substance will be provided. According to drug physicochemical properties and dosage form (aqueous or oily solubilizing phase nature), different solvents have to be wisely selected and tested. The equilibrium solubility is defined as the maximum quantity of a drug which can be completely dissolved, at a given temperature and pressure, in a specific amount of solvent. Therefore, for a specific drug substance in the solid form, it is imperative to perform a solvent screening to determine the active equilibrium solubility in each promising solvent and later in the solvent blend/solubilizing phase.[24-26]

Another important parameter to be considered for drug release performance and percutaneous absorption rate assessment is the thermodynamic activity of the drug in the formulation. Once exceeded the solubility equilibrium, a supersaturated