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

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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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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

Table 1
Example of General Elements of QTPP and CQAs for a Conventional Cream Formulation

QTPP	Target	CQAs	Justification
Dosage form	Cream	–	–
Route of administration	Topical	–	Local administration avoiding systemic side effects
Dosage strength	% w/w	–	–
Dosage design	Oil in water emulsion cream with API dispersed in the cream base	–	–
Appearance	White smooth cream with dispersed API	–	–
Identification	USP <621>/Eur. Ph. 2.2.29	–	–
Assay	80%-90% of the saturation concentration in the solubilizing phase	Yes	To set up the dose that will ensure drug availability to promote therapeutic effect
Impurities	USP <1086>/Eur. Ph. 5.20	Yes	Should be maintained below set limits to ensure safety and efficacy of formulation
Uniformity	USP <905>/Eur. Ph. 2.9.40	Yes	To assure consistency of the delivery system performance
API particle size	USP <429>/Eur. Ph. 2.9.31	Yes	Smaller size facilitates drug permeation
API crystallization	USP <854>/Eur. Ph. 2.2.24		Impact on formulation uniformity and stability
pH	USP <791>/Eur. Ph. 2.2.3	Yes	Impact on physicochemical stability
Viscosity	USP <911>/Eur. Ph. 2.2.9	Yes	To increase drug residence time at the site of application and consequently its action duration/To ensure drug release
Oil droplet size	USP <776>/Eur. Ph. 2.9.37	Yes	Impact on release/permeation behavior
In vitro release profile	*In vitro* Release Testing Guidance	Yes	To assess formulation delivery performance for enhanced therapeutic efficacy
Preservatives content	Consult USP <51>/Eur. Ph. 5.1.3	–	–
Microbial limits	USP <61>/Eur. Ph. 2.6.12	Yes	Must be maintained below the specified limits to ensure formulation safety and stability
Residual solvents	USP <467>/Eur. Ph. 5.4	–	–
Stability	ICH QI A	Yes	Quality requirement
Container closure system	Appropriate for the dosage form	–	To ensure target shelf-life
Package integrity	Compatible	–	–

API, active pharmaceutical ingredient; EE, encapsulation efficiency; Eur. Ph., European Pharmacopeia; PDI, polydispersity index; USP, United States Pharmacopeia.

solution is yielded and a higher thermodynamic activity is achieved, increasing the driving force drug diffusion from the formulation.[27-32]

Compatibility among excipients and drug(s) must be evaluated to anticipate any stability failures and possible incompatibilities in the final formulation.[19] These studies are imperative in the drug product development process because the acquired information from compatibility data is applied to select the suitable excipients, to ensure active substance stability, to understand degradation products and its formation pathway, and to investigate reaction mechanisms, which help to prevent unexpected hurdles and identify stable storage conditions.[33]

In the pharmaceutical technological field, there are different accepted methods for drug and excipients compatibility analysis. The accelerated stability test is the most common to evaluate chemical compatibility for topical formulation development.[34]

In the sections that follow, the choice of excipients, their concentration, and characteristics that can influence the drug product performance are discussed as well as their corresponding functions.

Choice of the Oily Phase

External emulsions comprise oily compounds as active substance carriers. There are different oily excipients suitable to use in cream formulations. Saturated and unsaturated fatty acids/fatty acid esters,[35] hydrocarbons, and polyols can constitute the oily phase, also functioning as penetration enhancers, and consistency or viscosity modifiers. Therefore, the selected oily excipients may also influence cream viscosity, drug solubility, physical stability, drug release performance and transport into the skin. Controlling emulsion consistency will ensure cream spreadability, but it needs to be slimy enough to form a continuous film over the skin.[36]

Thickeners and Emulsifying Agents

The physicochemical principles underlying emulsion formulation and stabilization are extremely complex. When 2 immiscible liquids are mechanically mixable without any interfacial stabilization, both liquids will form droplets, which rapidly flocculate (aggregation of dispersed droplets), coalesce (aggregation of flocculated droplets with possible oily and water phases separation), and form a creamy layer (dispersed phase droplets on the top of the continuous phase).[37,38] Physical stability is determined by the ability to mitigate these physical instability phenomena, and it may be accomplished by increasing the viscosity of the continuous phase, reducing the droplet movement rate of the dispersed phase, or decreasing interfacial tension between both phases by an emulsifier addition.

It has been described a direct relationship among cream viscosity and the viscosity of its continuous phase, but it is also possible to improve its apparent viscosity by increasing the concentration of the dispersed phase or reducing mean droplet size during homogenization process. A high apparent viscosity is imperative to retard the movement of dispersed phase droplets, keeping an emulsion physically stable.[36]

Thickeners are important excipients with impact on cream viscosity and, consequently, on skin retention of the topical dosage form and on drug penetration. Thereby, it is crucial to carry out *in vitro* skin permeation studies to assess formulation release behavior. For example, the inclusion of methylcellulose and paraffin reduces dispersed droplets mobility in an o/w emulsion and in a w/o emulsion, respectively.

Apparent viscosity can be also controlled by the homogenization process. This unit operation allows the reduction of droplet size and thus increases their number and surface area, increasing cream viscosity.

The inclusion of emulsifying agent(s) is also imperative to assist the emulsification process during cream manufacturing and to ensure emulsion physical stability during the product shelf life. When an emulsion formulation is developed, the type of emulsifying agent (anionic, cationic or nonionic), hydrophilic-lipophilic balance (HLB), log *p*, and concentration are fundamental aspects

to be considered in the emulsifier selection. Although this task seems to be limitless, there are some guidelines that may help in their correct choice. First of all, the use of pharmaceutically approved excipients will reduce regulatory justification periods. Emulsifier agent nature is extremely important for emulsion stabilization and generalization; ionic surfactants are used in o/w emulsions, whereas nonionic surfactants can be used in both o/w and w/o formulations. Essential information is provided by HLB system, a useful method for calculating the relative emulsifier amounts necessary to produce the most physically stable emulsion. Each surfactant is associated to an HLB number (usually between 0 and 20), representing the relative ratio of surfactant lipophilic and hydrophilic proportions. Emulsifiers with high HLB values (hydrophilic or polar proprieties) enable to develop o/w emulsions, whereas surfactants with low HLB values (lipophilic or nonpolar characteristics) allow to formulate w/o emulsions.[36]

Physical stability of semisolid formulations can be assessed through different analytical methodologies. Microscopic examination, centrifugation tests, and viscosity analysis are essential techniques performed for this purpose.[36,39,40]

Preservatives and Antioxidants

Oils and fats used in emulsion formulation are susceptible to oxidation by atmospheric oxygen or the action of microorganisms. The atmosphere oxidation results in degradation products which confer unpleasant cream characteristics. The resulting instability can be prevented by introduction of excipients with antioxidant properties. The selection of the antioxidant and its concentration can only be determined by testing its effectiveness on the final product, according to pharmacopoeial information. Their efficiency depends on its compatibility with other excipients and on its oil/water partition coefficient.

Oxidation from microbiological source influences the physicochemical properties of the emulsion, such as color and odor changes, hydrolysis of fats and oils, pH changes in the aqueous phase, and breaking of emulsion. Emulsions with aqueous continuous phase nature are more susceptible to microbial contamination. Therefore, it is required to include antimicrobial agents (preservatives) to prevent any microorganism growth. A preservative suitable for an emulsion must present wide spectrum of bactericidal activity, low log *p*, compatibility with other excipients, stability, and effectiveness over a wide range of pH and temperatures.

Buffer Agents

To provide chemical stability and to ensure physical compatibility, it is necessary to include buffer agents, but these electrolytes have to be carefully added to avoid undesirable effects on physical stability (e.g., rheological behavior).[36,40]

All components are related to the requirement that formulation must be capable of delivering the correct amount of drug to the therapeutic application site, be free from microbial contamination, and physically unchanged since the manufacturing day.

Process Design and Development

Since a formulation cannot become a product without a process, process and product design and development cannot be separated. Process design is an initial phase of the process development and should include all factors that need to be considered in cream production, such as equipment, material transfer, and manufacturing variables. Therefore, process selection depends on the product design and material properties. Once process design and development has been concluded, preliminary studies are conducted in accordance to the cream QTPP, product, and process knowledge.

To produce the intended quality product, a series of unit operations are accomplished throughout the cream manufacturing process. A unit operation involves physical or chemical changes while process parameters are referred to the input operating parameters (e.g., speed) or variables associated with a specific operation (e.g., temperature).

Manufacturing Process

In cream formulation production, the first mechanical process carried out is the mixture of both the aqueous and oily phases by adding the dispersed to the continuous phase or of the continuous to the dispersed phase. Sometimes, o/w emulsions are prepared through the phase inversion technique, in which the aqueous phase is slowly added to the oily phase. Initially, a w/o emulsion is formed, but as further aqueous phase is added, the emulsion inverts to form an o/w emulsion. It should be evaluated the effect of the order of addition and the rate of addition on the drug product quality attributes.

Prior to mixing, different excipients are dissolved in the phase in which they are soluble. The initial mixing temperature of both phases should be high enough to ensure intimate liquid mixing and avoid premature solidification of the oily phase by the colder water. Aqueous phase should be warmed to a temperature slightly higher than the oily phase.

Some active pharmaceutical ingredients can be dissolved at high temperature and recrystallized during the cooling stage. In this case, the active substance can be carried to the cooled down cream base via a powder eduction system or through a slurry addition and simultaneously mixed into the cream base, thus preventing the recrystallization problem. The stage to introduce the active substance into the semisolid mixture may be critical and should be identified.[20,39]

The next step in cream production is the homogenization stage. Agitators, mechanical mixers, rotor stators, homogenizers, or ultrasonic devices could be employed to ensure uniform excipient dispersion and droplet size reduction. To remove cream air pockets, a deaeration via vacuum with low-speed mixing may be turned on to the system. Homogenization time and vacuum pressure are significant process variables that can affect physical stability (e.g., coalescence of droplets, phase separation) and homogeneity. During cream process development and manufacturing, time, temperature, and mechanical energy are high-risk variables of the homogenization equipment that must be controlled to produce consistent quality.

Furthermore, as cooling rate can influence the final product quality, different cooling rates after melting, mixing, and homogenization steps should be additionally investigated as process variables.

Visual inspection is a useful and simple confirmatory test to ensure solid dissolution or uniformity system before proceeding to the next step. Microscopic visualizations should be also performed to select homogenization speed and time, so as to enable proper incorporation of the active substance into the base and conform the microscopic appearance, including drug particle size and droplet size.[14,41]

Risk Assessment

Based on prior knowledge, an initial risk assessment is performed to identify and prioritize potential high-risk variables that may influence identified cream CQAs. The outcome of this procedure is to determine which material attributes and process parameters are critical and which ones need to be experimentally

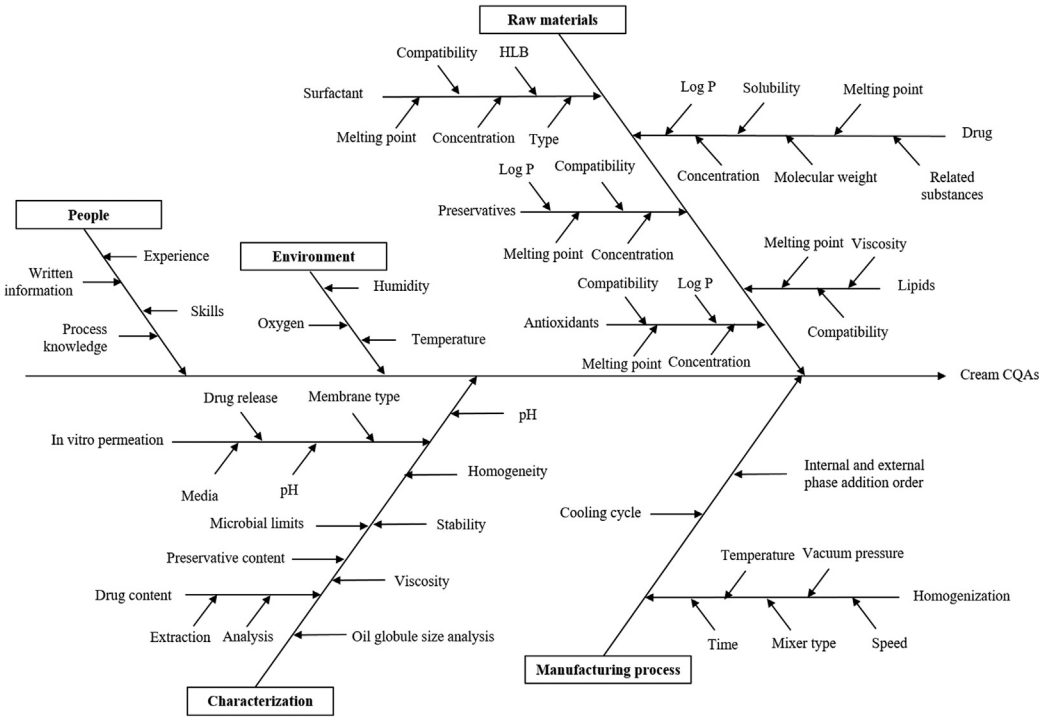

Figure 1. Ishikawa diagram showing critical parameters of a conventional cream pharmaceutical development. Log *p*, octanol-water partition coefficient.

investigated and controlled within appropriate ranges to ensure cream quality.

Using a risk approach, the starting point must be the identification of all material attributes and process parameters that can influence product CQAs and hence generate quality failure. To ascertain which of these parameters need to be further studied and controlled, an Ishikawa diagram is constructed (Fig. 1).[42,43] In addition, a risk estimation matrix (REM) is carried out to prioritize material attributes and process parameters that were demonstrated to be a potential risk factor for cream CQAs (Fig. 2).[44-46]

In pharmaceutical development, risk assessment analysis must be accomplished in early phases, but it is important to be updated at different development stages as further information becomes available and greater knowledge is obtained.[47,48] After risk assessment data analysis, specific parameters are, then, selected for subsequent screening studies (DoEs).

Identification of CMAs and CPPs

In cream development, several variables need to be considered and investigated to reach predefined QTPP. CMAs and CPPs that may specifically influence one or more cream CQAs must be identified to develop an adequate cream formulation (Tables 2 and 3).

Critical variable identification is the preliminary step in the optimization methodology, which is established through a screening process. A screening design is an experimental planning where a relatively large number of factors is simultaneously evaluated using a small number of experiments. During the screening phase, all factors are tested to indicate the most critical ones. These designs enable to detect which variables are responsible for the final product quality to eliminate all those ones which do not play an important role in ensuring quality constancy. Different experimental designs, such as, full factorial, fractional factorial, and Placket-Burman designs are usually used for screening purposes.[18,49-51]

Formulation Optimization

After performing screening experiments, variables that show criticality in the previous phase are also optimized through a DoEs. The optimization stage aids to specify CMAs and CPPs optimal settings, and, ultimately, the definition of design space. Note that any manufacturing process developed within the design space will be regulatory acceptable.

Response surface designs, such as Central Composite Design and Box Behnken are the most usual models to predict the optimal CMAs and CPPs ranges. Currently, some software packages are available to simplify experimental design procedure and assist in results interpretation: MODDE, Design Expert Design-Ease, and JMP.[52-56] The application of the QbD concepts to optimize formulation, single-unit operation, or to the entire manufacturing process, is intended to support end-product quality and real-time release.[11,14]

Formulation Performance Testing

According to the predefined QTPP, cream performance needs to be assessed. There are 3 important CQAs to consider in topical formulation development: formulation stability, drug release profile, and skin permeation behavior.[11,33,57]

Stability Testing

To identify formulation stability issues, formulation stability studies must be performed.[34] This stage aims at developing a stability screen of prototype formulations to select the most promising ones for *in vitro* drug release and permeation testing.

In Vitro *Release Studies*

The release rate of an active substance from a dosage form is a critical feature for semisolid dermatological products because the active must be released from the vehicle and diffused through the

		Cream CQAs					
		Globule size	Viscosity	Content Uniformity	Stability	Drug release	Permeation rate
Raw Materials	Drug substance: Log P	Low	Low	Medium	High	High	High
	Drug substance: Solubility	Low	Low	High	High	Medium	High
	Drug substance: Molecular weight	Low	Low	Low	Low	High	High
	Drug substance: Equilibrium Solubility and Concentration	Low	Medium	Medium	Medium	High	High
	Drug substance: Melting point	Low	Medium	Medium	Low	High	High
	Oily excipients: Viscosity	Medium	High	High	Medium	High	High
	Oily excipients: Concentration	High	High	High	High	Medium	Medium
	Oily excipients: Melting point	Low	Medium	Medium	Medium	Medium	Medium
	Emulsifying agent: Type	High	Low	High	High	Medium	Medium
	Emulsifying agent: Log P	High	Low	High	High	Medium	Medium
	Emulsifying agent: HLB	High	Low	High	High	Medium	Medium
	Emulsifying agent: Melting point	Low	Medium	Medium	Medium	Medium	Medium
	Emulsifying agent: Concentration	High	Medium	High	High	Medium	Medium
	Preservatives: Log P	Low	Low	Low	Medium	Low	Low
	Preservatives: Melting point	Low	Low	Low	Low	Low	Low
	Preservatives: Concentration	Low	Low	Low	High	Low	Low
	Antioxidants: Log P	Low	Low	Low	Low	Low	Low
	Antioxidants: Melting point	Low	Low	Low	Low	Low	Low
	Antioxidants: Concentration	Low	Low	Low	High	Low	Low
Process Parameters	Active ingredient addition	Low	Low	Medium	Low	Low	Low
	Phases addition order	Medium	Low	Medium	High	Low	Low
	Mixer type	High	Low	High	Low	Low	Low
	Mixing temperature	Medium	High	High	High	Medium	Medium
	Mixing time	High	Medium	High	High	Medium	Medium
	Mixing speed	High	Medium	High	High	Low	Low
	Homogenization time	High	High	High	High	Medium	Medium
	Homogenization speed	High	High	High	High	Medium	Medium
	Vacuum pressure	Low	Low	Low	High	Low	Low
	Cooling cycle	Medium	Medium	Low	High	Low	Low
	Powder eduction rate	Low	High	High	Low	Medium	Medium

Figure 2. Risk estimation matrix presenting initial risk assessment levels of individual formulation and manufacturing parameters: Low, low risk parameter; Medium, medium risk parameter; High, high-risk parameter; Log *p*, Octanol-water partition coefficient.

skin. When a topical formulation is applied to the skin, drug thermodynamic activity must be suitable to ensure an adequate release rate from the final topical dosage form. To characterize and optimize formulation release performance, *in vitro* release tests are performed. In QbD context, it is imperative to select a suitable release study to discriminate differences on cream release rate

Table 2
CMAs of a Cream Formulation

Formulation Components	Parameter Type	CQAs
Drug substance		
Physical attributes	–	–
Log *p*	CMA	Drug release/permeation, stability
Molecular weight	CMA	Permeation
Melting point	CMA	Drug release/permeation, viscosity, stability
Equilibrium Solubility and Concentration	CMA	Drug release/permeation, uniformity, viscosity, stability
Assay	CMA	Content uniformity, drug release
Related substances	CMA	Degradation products
Excipients		
Compatibility	CMA	Stability
Viscosity	CMA	Viscosity, stability
Concentration	CMA	Uniformity, viscosity, stability
Melting point	CMA	Viscosity, stability
Oil/water ratio	CMA	Stability
Emulsifying agent		
Type	CMA	Droplet size, uniformity, stability
Log *p*	CMA	Stability
HLB	CMA	Droplet size, uniformity, stability
Concentration	CMA	Droplet size, uniformity, stability
Melting point	CMA	Viscosity, stability
Preservatives		
Log *p*	CMA	Stability
Concentration	CMA	Stability
Melting point	CMA	Viscosity, stability
Antioxidants		
Log *p*	CMA	Stability
Concentration	CMA	Stability
Melting point	CMA	Viscosity, stability

Log *p*, octanol-water partition coefficient.

Table 3
CPPs of a Cream Formulation

Risk Assessment	Parameter Type	CQAs
Drug substance addition phase	CPP	Uniformity, particle size
Phases addition order	CPP	Uniformity
Mixer type	CPP	Uniformity, droplet size, stability
Mixing temperature	CPP	Uniformity, viscosity, stability
Mixing time	CPP	Uniformity, droplet size, stability
Mixing speed	CPP	Uniformity, droplet size, stability
Homogenization time	CPP	Uniformity, droplet size, drug particle size, viscosity, stability
Homogenization speed	CPP	Uniformity, droplet size, drug particle size, viscosity, stability
Vacuum pressure	CPP	Uniformity, stability
Cooling cycle	CPP	Uniformity, viscosity, stability
Powder education rate	CPP	Uniformity, drug particle size, viscosity

when variations in formulation and manufacturing parameters of the drug product are applied and assessed.[3,58-62]

Topical formulations release performance is commonly performed by Franz diffusion cells, where synthetic membranes (silicone, polycarbonate, or cellulose) have received distinct attention because of their ability to mimic physiological and anatomical skin conditions. This is a well-established method where a specific dose of formulation is applied on a membrane surface in the open donor chamber of the cell. The diffusion of drug from the topical product across the membrane is monitored by assay of sequentially collected samples from the receptor chamber. The receptor compartment of the Franz cells is filled with a suitable receiver fluid to maintain sink conditions embedded in a water bath at 37°C, so as to ensure a temperature of 32°C at the surface. The receptor chamber content is agitated by small magnetic stirrers, at regular time intervals, and samples of receiver fluid are collected from the receptor compartment, replaced with fresh receiver medium, and assayed by a suitable assay method, such as HPLC. Quantification of the residual drug on the surface of the membrane is also performed.[61,63-66]

In Vitro *Skin Permeation Studies*

Drug absorption depends on some factors, including formulation composition, drug thermodynamic activity, drug physicochemical properties, drug solvent solubility, type and condition of the skin, and intrinsic factors, such as temperature, humidity, and occlusion. When a topical formulation is applied to the skin, the drug diffuses across the formulation, releases from the vehicle, and penetrates into the SC. In topical formulation development, *in vitro* skin permeation studies need to be developed to estimate drug permeation rate from the final product and the time over which permeation occurs.[60]

In this sense, the assessment of permeation behavior is commonly carried out via Franz diffusion cells, in the same conditions of the *in vitro* release studies, but using skin membranes placed between the donor and the receptor compartments instead. Quantification of the residual drug on the surface of the membrane, within the SC, epidermal membrane, and dermis is performed.[24,62,63,67]

Different skin models are reported in the literature. Although human skin is considered the gold standard for permeation measurements,[68] several animal (e.g., pig) and reconstructed skin models have been alternatively proposed.[69] Note that skin treatment and storage conditions need to be described and controlled.[70] According to drug solubility characteristics, different skin models can be used: full-thickness skin, dermatomed skin, and most commonly, epidermal membranes, prepared by heat separation technique.[57] During epidermal membrane preparation, the skin samples are immerged in water at 60°C, and the epidermis is gently separated from the dermis and stored at −20°C. Previously to the experiments, the thawed epidermis is hydrated overnight, in an appropriate solution (e.g., phosphate buffer saline solution, pH = 7.4), in a refrigerator. Skin barrier function and integrity are critical aspects to ensure reliable data, and for this reason, they may be inspected through measuring the transepidermal water loss, the permeation of tritiated water, the electrical resistance, or by visual inspection.[46,57,63,70-72]

Lead Selection

Once such assessments and formulation optimization have been completed, one lead formulation must be selected for full characterization and stability testing.

A comprehensive formulation characterization must be further performed to define provisional product specification and parameter measurement methods. Product performance is monitored by ICH stability tests, to predict the performance of the product over its shelf-life. There are some parameters that must be determined, such as macroscopic and microscopy appearance, odor, assay, active substance crystallization, uniformity, oil droplet size, impurities, preservative content, antioxidant content, pH, rheology, viscosity, microbial quality or microbial limit test, and preservative efficacy test.[4] The lead formulation is then submitted to long-term, accelerated, and real-time stability studies as described in ICH Q1A guideline.[34]

Excipient Quality

The excipient quality attributes must be controlled by appropriate acceptance criteria, according to the established specifications.[21] Selecting specific grade of excipients, for example,

super-refined grade, low aldehyde grade or antioxidant added grade, may be necessary to minimize variations on quality attributes of the final drug product.

Executive Summary

QbD Approach

- An initiative of the U.S. Food and Drug Administration to ensure product quality over the whole procedures established in pharmaceutical development of different dosage forms.
- An optimized formulation and a continuous and robust manufacturing process can be easily achieved, with significant reduction in costs production, product variability, and batches rejection.
- The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide an enhancement of scientific understanding and then regulatory flexibility.

Product Design and Development

- Cream development, as a conventional semisolid form with a complex formulation and critical stability issues, remains a challenge for pharmaceutical technology.
- Different excipients must be carefully selected to develop a formulation that can achieve the therapeutic objectives and quality attributes, ensuring its stability over the shelf life.
- Product design and development according to QbD approach, starts by defining cream QTPP and the respective CQAs.
- An initial risk assessment is performed to establish cream CMAs. Log *p*, solubility, molecular weight, melting point, concentration, compatibility, viscosity, and HLB are the main CMAs of drug substance and excipients.

Process Design and Development

- In cream production, different process parameters must be considered and studied to develop a robust manufacturing process, safeguarding cream quality attributes.
- During process design and development according to QbD approach, variability associated to production process can be finely/comprehensively understood and controlled.
- An initial risk assessment is performed to identify cream CPPs. Phase addition order, temperature, time, and speed of mixture and homogenization procedures are the foremost variables in cream production.

Conclusion

In pharmaceutical development, different strategies can be implemented. In recent years, QbD has received greater attention as an innovative and systematic development approach because it enables designing a robust formulation and manufacturing process to achieve the intended product quality, to help regulators to better understand the adopted development strategy, to decrease development stage costs, and to accelerate the process of product commercialization. Based on prior knowledge about quality risk management, DoEs, and experimental data, QbD plays an important role for pharmaceutical companies and regulatory authorities as it reliably produces drug products with high quality. Besides QbD benefits, its concepts remain ambiguous, resulting in a lack of interest in applying its principles either for innovative or generic product development.

Robust manufacturing of conventional creams, with their complex formulation components, requires a detailed QTPP definition, CQAs identification, and deep understanding of their CMAs and CPPs. QbD aids not only to identify and to understand the critical parameters in cream development but also to assess the interaction among them in achieving the target quality. Therefore, implementing QbD in a cream development, as planning system, can be useful to optimize its formulation and processes parameters, providing fundamental data to understand how to develop an optimal pharmaceutical formulation.

In the new era of massive consumption of generic products, a scientific and technological progress is required. For this reason, it is imperative to evaluate the reference-listed drug (RLD) formulation in a critical manner. This comprises the implementation of QbD elements to ensure similar desired quality attributes to the RLD and to guarantee the successful pharmaceutical and therapeutic equivalence.

In a generic product design and development, under the QbD approach, the information and knowledge generated during this systematic process will be an asset for industries who intend to mimic the RLD. A tutorial document with complete cream formulation guide, such as CQAs, CMAs, CPPs, and design space, will ensure a robust and efficacy generic production according to RLD QTPP. Therefore, in a near future, the implementation of QbD in every stage of cream generic design and development could help in the management of issues to properly ensure both technical and regulatory successes.

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