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Quality by Design: A New Era in the Pharmaceutical Product Development with Minimum Mistakes and More Effectiveness

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ABSTRACT

Since the Associate in Nursing Era of analysis, the pharmaceutical industries have mature up with several advanced techniques for developing quality product style F&D yet as R&D Departments, etc. The margins of such advances are discovered in developing a quality product with a high level of reliableness. The multifunctional factorial style assists directly within the safety, effectiveness & quality of the developed product. Style of Experiments (DoE) may be a technique for developing an Associate in nursing experimental matrix style that needs specific inputs, measurable outcomes, weighted interests & expertise in reviewing the output. The reward is that the action of "Accuracy," wherever you'll attain all product specifications & process objectives. The standard on purpose (QbD) is meant to grasp "Why the approach is enforced," & the planning of Experiment (DoE) is meant to grasp "How to implement the approach." The set up of action of DoE relies on four main divisions; Scoping, Screening, Optimizing & Robust. The primary three divisions foot-dragging method information & the last division foot-dragging method Confidence. This paper summarizes the thought of "How" to produce a master link in Quality Target Product Profile (QTPP) & conjointly to stress the acceptance of Advance Pharmacy observe expertise (APPE) in alternative Pharmaceutical Domain.

INTRODUCTION: *[1-3]*

The concept of Quality by Design was made to light by Joseph Juran in the automotive industry. In the year, 2004, Janet W. defined the word Quality. The fundamental and vital thought behind QbD is that quality should be "built-in by design not tested in" to processes optimization strategies by a systematic approach and proper implementation to create a thorough initiative which understands the responses of quality of the system to particular variables and acknowledge the usage of a control strategy to continuously ensure quality. QbD alludes to a new way to deal with product advancement that could increment and improve proficiency, give administrative alleviation and adaptability, and offer significant business benefits all through the item life cycle. The point of Pharmaceutical improvement is to plan a quality item and its assembling procedure to reliably convey the expected performance of the product. The data and information picked up from pharmaceutical improvement studies and assembling experience give logical comprehension to help the foundation of the design space, specifications, and manufacturing controls.

Benefits of QBD: [4-6]

1. Eliminate batch failures
2. Minimize deviations and costly investigations
3. Avoid regulatory compliance problems
4. Organizational learning is an investment in future
5. Better development decisions
6. Empowerment of technical staff

Opportunities: *[7-8]*

1. Efficient and flexible system
2. Increase manufacturing efficiency, reduce costs and project rejections and waste.
3. Build a scientific knowledge base for all products.
4. Scientific problems can be better interacted.

5. Confirm consistent data and Incorporate risk management.

The current scenario in the Pharmaceutical Industry: *[9]*

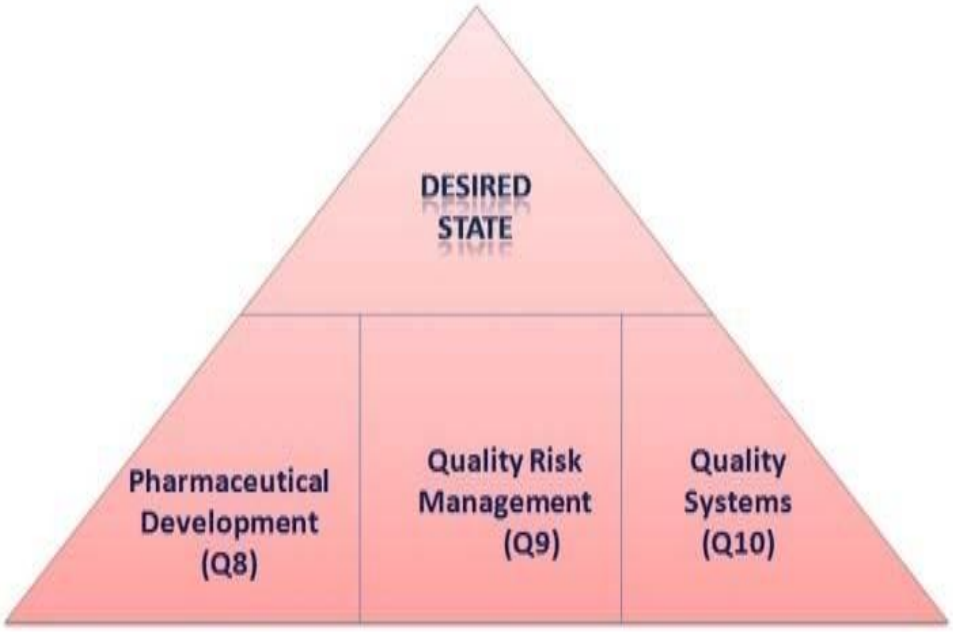
1. Charges of revalidation of products

2. Primary means of control on product manufacturing

3. Incapability to understood reasons for failures and not predicated scale-up issues

ICH GUIDELINES LIKE Q8, Q9, Q10: *[10-14]*

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are the basis of QbD.



ICH GUIDELINES

BASIS OF QbD:

➢ **ICH Q8 Guidelines (Pharmaceutical Development):**

It acknowledges developing and manufacturing a product while taking into consideration quality risk management and Scientific Principles application.

According to the ICH Q8 annex, QbD defines as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Two important prospects under this guideline are Design Space & PAT. Design space is the concept that ensures quality by material attributes and process parameters while PAT is analyzing, controlling, and designing manufacturing through timely measurements in process of raw materials with determining its critical quality and performance attributes.

- **ICH Q9 Guidelines (Quality Risk Management):**

It states about primary tools that occurred in risk assessment along with general guidance. It functions in industries to evaluate the risk factors in the processed products based on scientific information and examine the risk to patients.

Two main principles are outlined for it, in which first is examination and evaluation of risk should be based on a scientific basis which leads to patient's protection and safety and second is documentation informal way to ensure the level of risk under quality risk management system.

- **ICH Q10 Guidelines (Pharmaceutical Quality System):**

The concept of Q10 guidelines is based on ISO which includes cGMP regulations and complements Q8 & Q9. It discusses the comprehensive and wide-ranged model for effective quality in Pharmaceuticals.

The system has 04 major aspects like process performance and product quality monitoring system, corrective action and preventive action system, a change management system, Management review of process performance and product quality.

Table No. 1: Comparison between QbT AND QbD [15]

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical	Systematic; Multivariate experiments
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process Control	In-process testing for go/no-go; offline analysis wide or slow response	PAT utilized for feedback and feedforward at real-time
Product Specification	Primary means of quality control; based on batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate product and end-product testing	Risk-based; controlled shifted upstream, real-time release
Lifecycle Management	Reactive time problem and OOS; Post-approval changes needed	Continual improvement enabled within design space

Conventional Product Development	QbD Approach (Ideal)
Quality assured by end-product testing and inspection and mainly an empirical approach.	Quality built into product & process by design, based on scientific understanding and a systematic approach.
Data-intensive submission – disjointed information without "big picture"	Knowledge rich submission – showing product knowledge & process understanding
Specifications based on batch history	Specifications based on product performance requirements
"Frozen process" disallowing changes	The flexible process within the design space, allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on formulation and process robustness – understanding and controlling variation

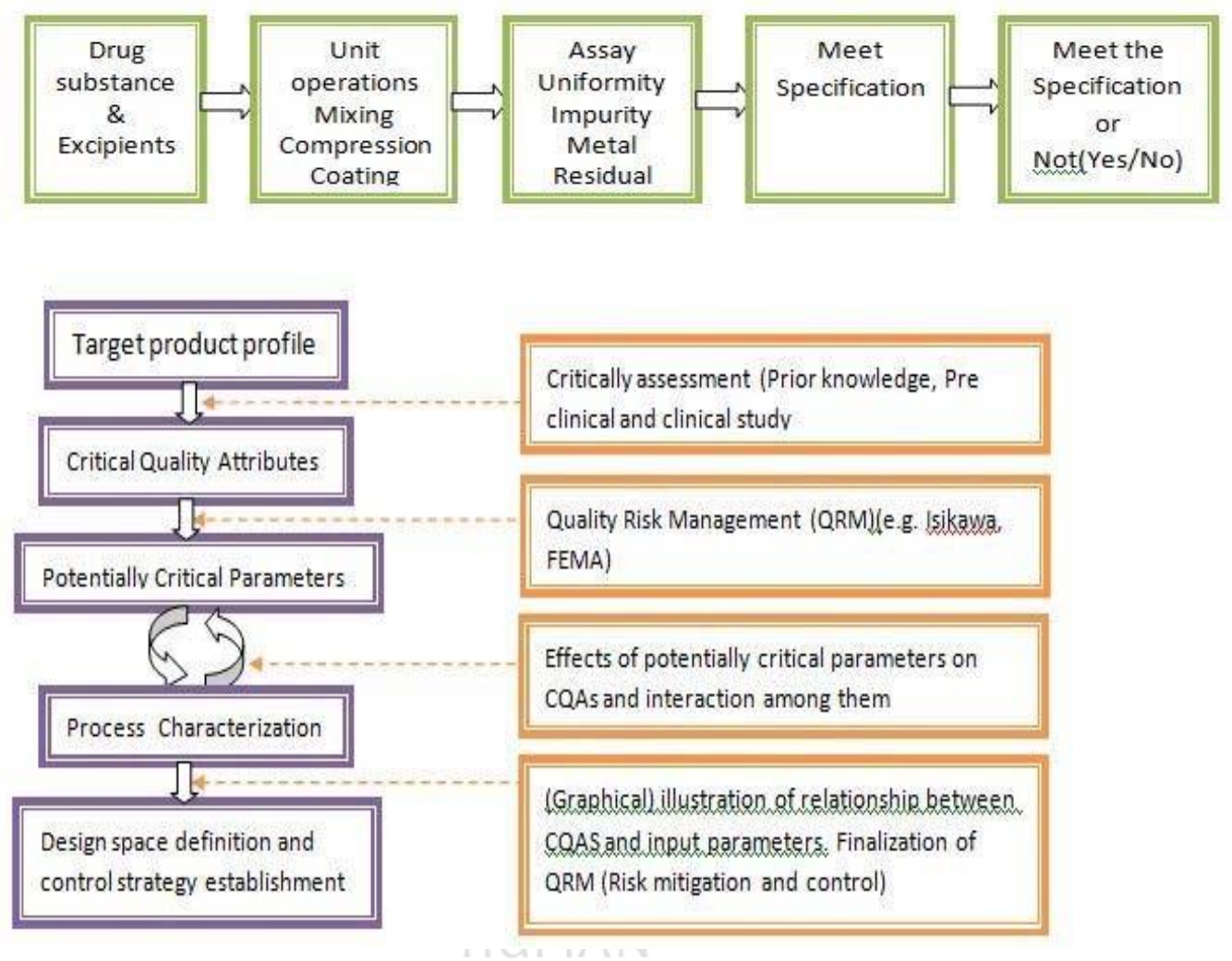


Figure No. 1: Flow-chart of QbT

KEY ASPECTS OF QbD: *[16-23]*

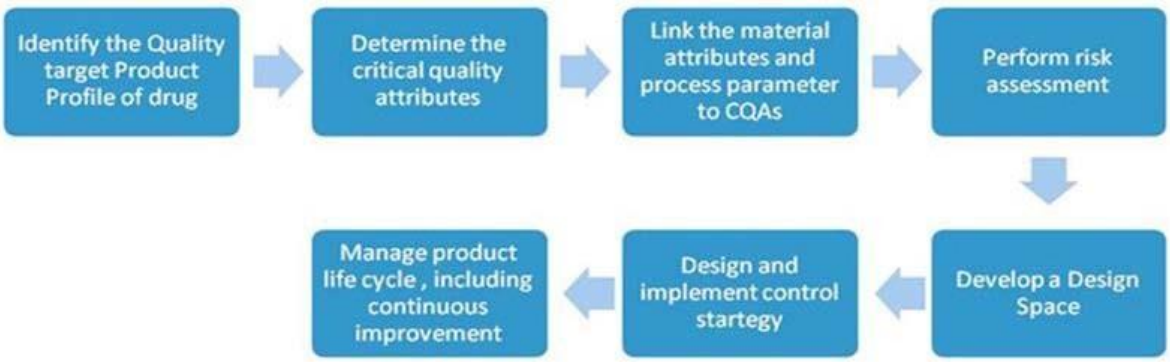


Figure No. 2: Key aspects of QbD

➢ **Identifying Quality Target Product Profile (QTPP):**

It is an overall summation of quality characteristics and attributes which will assure drug safety and efficacy which is achieved ideally for the drug product. The basis of design for the product developed is done by targeting the product's quality.

QTPP is "a prospective description of the quality characteristics of a drug product which, taking into consideration the protection and feasibility of the drug product, can preferably be accomplished to ensure the desired quality." The QTPP is an integral aspect of the QbD strategy and forms the basis for the design of the generic product. A quantitative alternative for facets of therapeutic safety and effectiveness is the QTPP. It is performance based not mechanism base.

QTPP should only include the performance of the product relevant to the patient. For instance, if the particle size is crucial to the dissolution of a solid oral substance, then dissolution but not particle size should be included in the QTPP. A critical material attribute would be particle size and would thus be included in the description and control strategy of the process.

➢ **Identification of Critical Quality Attributes (CQA):**

CQA is physical, chemical, biological, or microbiological characteristics that provide desired product quality within a commensurate range and limit. These attributes are related to excipients and drug materials, intermediates which are involved in-process materials, and drug product.

➢ **Quality Attributes important to Performance of Drug Product:**

From a clinical view, the most important aspect of product development is its safety and efficacy. For instance, drug dissolution or drug release, polymer concentration, and viscosity, glass transition temperature (Tg), etc. can either be substituted for clinical performance for an oral product.

➢ **Quality Risk Assessment:**

A Key role of risk assessment is to predict the sources of variations during the manufacturing process to obtain the desired product quality. This is to identify which material attributes and

process parameters will be beneficial or will affect CQAs. This is an implemented control strategy for the desired quality.

➢ **Critical Process Parameters (CPP):**

CPP is any measurable operating parameter or output material attribute that should be controlled to have the desired quality and process consistency. CPP is defined as any measurable input (attribute of the input material or operating parameter) or output (attribute of the process state variable or output material) of a process step that needs to be controlled to achieve the desired quality of the product and uniformity of the process. Each object will be a parameter of a method in this view.

We suggest that the process parameter be understood to apply to the operating parameters of the input (mixing speed, flow rate) and the variables of the process state (temperature, pressure).

Table no 2: Process parameter and materials attributes associated with wet granulation.[24]

Sr. No.	Variables	examples
1.	Drug Materials	Particle size, Amt., Moisture contents, etc.
2.	Drug Excipients	Excipient quantity, particle size, etc.
3.	Granulation Operating Variables	Impellor speed, Granulation time, Binder rate, etc.
4.	State Conditions	Temperature & Power Consumption
5.	After Granulation	Blend uniformity, Agglomerate size, flow properties, etc.

Parameters or variables are critical when they cause product failure in realistic changes to meet QTPP. So, one has to consider any changes either small or large as it counts as a risk factor. Thereby, 1st step in classifying variables is POS (potential operating space) which determines the range of interest.

➢ **Design Space:**

It is defined as the multidimensional combination of material attributes as well as process parameters that have been verified and explained to the commensurate quality of the product. Working within it considers not a change but movement out of it, start regulatory post approval change process. It is a theme to regulatory assessment and approval which is a proposal by the applicant.

"The multidimensional combination and interaction of input variables (e.g. content attributes) and process parameters that have been proven to provide quality assurance" is the current concept of design space. This concept originated from early ICH Q8 draughts where "the developed set of process parameters that have been shown to provide quality assurance" was identified as design space.

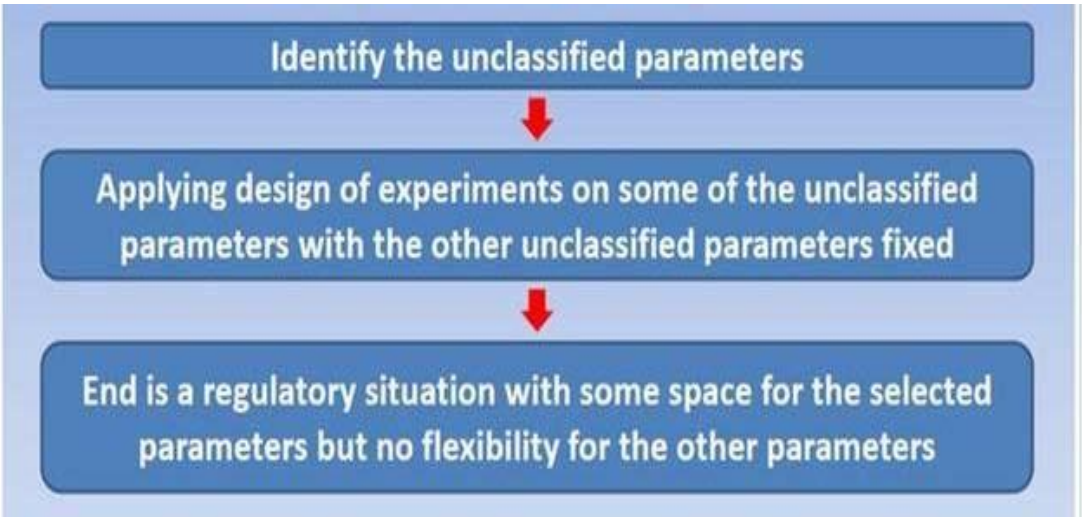


Figure No. 3: Space Steps

Design of Experiment: *[25-30]*

DOE is an effective method for the preparation of experiments to evaluate the data collected and produce accurate and objective results. A formal, coordinated method for determining the relationship between factors influencing a process and the performance of that process is known as the Design of an experiment.

The candidate can choose to conduct pharmaceutical production experiments that can lead to an increased understanding of product efficiency over a broader variety of content properties, manufacturing choices and process parameters. The inclusion in this chapter of this additional

information provides an opportunity to demonstrate a greater degree of understanding of production processes and process controls.

The design space is set up by this scientific understanding. There are opportunities to develop more responsive regulatory approaches in these cases, such as to facilitate: risk-based regulatory decisions (reviews and inspections); production process changes, without further regulatory review, within the permitted design space defined in the dossier; real-time quality monitoring, leading to a reduction in the release testing of end goods.

Benefits of DoE: *[31]*

DoE is used to determine the causes of variance in the response, find conditions under which the optimum response (maximum or minimum) is obtained, evaluate responses at various levels of regulated variables, and build a model for predicting response.

Control Strategy: *[32-36]*

It includes input material controls, process controls and monitoring, design space surrounding ones or multiple unit operations, and/or ultimate product specifications provides to ensure quality consistency. The ultimate product is assessed by various quality assurance tests to see that their product is according to their willingness and desire.

Input material controls, process controls, and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to guarantee consistent quality may be part of a control strategy. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their exhibit batch process.

By assessing whether they meet specifications, the finished drug products are tested for quality. Also, producers are generally expected to perform extensive process tests, such as uniformity of the blend or hardness of the tablet. It is also not allowed for manufacturers to make adjustments to the operating parameters (a large number of UPPs) listed in the batch report or to make any process changes without the FDA filling in the supplements.

DERMATOLOGICAL SEMISOLID DOSAGE FORMS: *[37]*

The main challenging work semisolid dosage form in the QbD approach is to select CQAs which further determines QTPP. By making changes or altering formulation variables and

process parameters, one can change the CQAs of marketed products. Mainly, Particle size, pH, rheological characteristics and microbial contamination plays a major role in efficacy, safety & quality of dosage form.

QAs of Topical Dosage Forms: *[38-42]*

QAs which affect the pharmaceutical, therapeutic and perceptive presentation of dosage formulation is known as Critical Quality Attributes (CQAs). We have put forth some key points of QAs which have appreciable impacts on the quality, safety & efficacy of the ultimate product.

1. **Particle size:** It is a vital element and key attribute in semisolid dosage form especially when API is suspended in the formulation. It may vary through aggregation, polymorphism, and phase separation over product's shelf life which leads to variation in bioavailability due to which it gets impact over the perception of products like smoothness and grittiness which determines patients compliance and acceptance.

2. **Globule size:** It plays a significant role in emulsion dosage forms, especially related to its release properties as well as physical stability properties. Variation in its size affects drug entrapped into the globule, partitioning of active ingredient within different phases of product and then release into the skin. Imbalance in globule size results in creaming, cracking, or phase inversion which leads to the potential failure of the final product. For instance, if the product is packaged into the tube and phase inversion occurs then the oil phase accumulates at the orifice of the tube, causing instability in semisolid dosage form and leads to improper drug consumption in treatment applications. Thereby, it is very critical to prevent phase inversion for commensurate product quality and efficacy. Rate of mixing, temperature, and excipients addition have a foremost impact on manufacturing process parameters.

3. **Polymorphism:** Different physiochemical Properties like stability, solubility, textures, melting points, etc exhibit different forms of polymorphism. Type, grade, and source of excipients utilized in preparing semisolid formulations to lead to polymorphism variation which leads to skin retention and permeation. Its active form is considered as CMA. However, instability in API leads to changes in polymorphism which are disadvantageous to product performance.

4. **pH:** It is an amalgamation of CMAs and CPPs. The solubility of active pharmaceutical ingredients is mainly dependent on pH. So, alteration in Ph in any topical formulation or emulsion type of dosage form affects its product's shelf life and bioavailability. This mainly affects zeta potential due to variation in droplet size and its distribution of emulsion. If Zeta potential decreases, the stability of emulsion decreases as the size distribution of oil droplets, the thickness of the hydrated layer, and electrostatic interaction affects viscosity. Thereby, pH should be limited to minimize the probability of disadvantageous effects on actives. Furthermore, the pH range is adjusted based on the physiology of skin pH in topical dosage forms which assures that product will be stable during their shelf life.

5. **Rheological properties:** Key Q3 attributes are flow properties of semi-solid products. The Viscosity of the Newtonian fluids is independent of the shear rate, so the viscosity remains constant as the shear rate increases, while the viscosity is dependent on shear stress for non-Newtonian materials such as topical semi-solid products. "Unless they have reached a critical stress level called" yield stress, These non-Newtonian materials do not flow. Spreadability and ease of application found a correlation with yield stress point.

Rheological characteristics have a potential for drug release from the formulation, skin penetration, and skin retainment of the topical dosage forms. By characterizing the flow behavior of a topical product, valuable insight about the microstructure of the product can be gained, which can aid in differentiating topical dosage forms. Furthermore, rheological properties affect the consistency, physical features, and efficiency of the formulation that can shift over the shelf. Variations in viscoelastic properties may lead to variations in spreadability of the topical formulation leading to dissimilarity in skin feel. Patients apply topical formulations on their epidermal directly, and so sensorial variables are assumed to have a significance that could directly impact patient compliance. CMSs and CPPs are a combination of the properties of Rheology.

6. **Evaporation of volatile substances:** It is possible to differentiate topical formulations with varying water and volatile percentages into different dosage shape forms. For example, since ointments tend to be kept longer on the skin, low evaporation rates are needed, which can be given by a high content of PEG or mineral oil. On the other side, owing to a greater proportion of water and alcohol, gels evaporate more quickly. Evaporation from a formulation of volatiles such as water and alcohol can lead to stiffening and changes in the microstructure of the formulation. Apart from influencing the composition, solvent

evaporation may also affect the API. Loss of water and volatiles can contribute to changes in the solubility of the active substance in the formulation through evaporation allowing the dissolved substance to become crystallized, thus altering the retention of the skin, thermodynamic behavior, and penetration of the active substance. The proportion of volatile excipients in topical semi-solid products may also be performance-affecting CQAs. CMAs, such as the form and quantity of volatile additives, can also affect evaporation.

7. **Container/closure system:** In multiple dispenser devices, such as barrels, tubes, and different types of pumps, topical semi-solid items are packaged. The selection of an effective container/closure device depends primarily on the type of the dosage and the product's flow properties. Different modes of dispensing of a product may exert different shear forces on the formulation, as explained above, which may affect the microstructure and therefore the product's performance. Moreover, because of their high water content, the risk of bottle contact and consequent deterioration is greater in topical formulations.

Product Design and Development: *[43-50]*

1. **CMAs:** API and excipient qualitative and quantitative data are known to be raw material attributes. Choosing a proper API source is the most important aspect of food production. To determine the optimal type of salt and polymorphic type of the API, to assess its purity and consistency, to define its storage temperature and shelf life, and to understand its stability under various processing conditions, pre-formulation studies need to be carried out. The API grade affects its physicochemical characteristics. Having different polymorphic forms, for example, is one of the effects of using various API grades, which can affect the final formulation's quality attributes. The selection of the source of the active substance is therefore essential for the development of pharmaceutical formulations.

2. **CPPs:** All factors, including equipment, facilities, material transfer, manufacturing variables, and QTPP, should be considered to design an optimal manufacturing process. The three major variables in the manufacturing of semisolid formulations are mixing / homogenization time, mixer type, temperature, and mechanical energy input. To generate batches of consistent consistency, the process parameters using these related variables must be defined and carefully monitored.

3. **Temperature Control in the process:** Choosing the right processing temperature range is important not only for preserving the stability of materials but also for dissolving and

dispersing active ingredients and excipients. The temperature variation can have a significant impact on the end product's quality. For example, a batch's heating or cooling rate may affect the quality of the topical semi-solid substance. During manufacturing, excess heating can lead to ingredient degradation, while inadequate heat can cause substance failure due to problems with drug solubility. The schedule for temperature changes must be closely calibrated to the appropriate operation, as extreme or rapid cooling will lead to solubilized ingredient precipitation or crystallization or changes in viscosity.

4. **Type of Mixer:** A stainless steel jacket tank with an agitator is the most widely used production tank in the pharmaceutical industry. The homogeneity of the product will be affected by the shape, capacity and ability to maintain the desired temperature of the tank. In order to give a consistent distribution of the active ingredient in a batch, it is also important to use the right combination of tank, mixer blade, and formulation. For example, in the case of extremely viscous goods, the mixer should have lightweight scraper blades to separate materials from the internal walls of the tank and redistribute them into the center for mixing. The use of hard plastic blades such as Teflon blades, which cause minimal damage to the tank walls, is recommended by the FDA. A mixing validation procedure is carried out on the chosen tank and mixer to ensure the uniformity of the final product.

5. **Speed & Time at mixing:** These two factors are critical parameters that need to be accurately controlled when manufacturing semi-solid products with suitable mixers with programmable logic controllers. Low shear mixing is typically required for manufacturing gels to maintain the product's viscosity, while emulsification typically requires high shear rates to achieve optimum droplet size and dispersion. The minimum needed time to dissolve the ingredients and the maximal mixing time before which the product's viscosity decreases (causing product failure) should be established to maximize the mixing time. The structural breakdown of polymeric gels, marked by a dramatic decrease in emulsion viscosity, can be caused by over-mixing. Mixing speed and time is also a CPP that can impact the QAs of the finished product.

6. **Homogenization:** Emulsion homogenization contributes to decreases in the size of oil globules and helps to spread globules evenly. Homogenization time is a CPP that may affect a formulation's physical stability. Furthermore, excess homogenization can heat the bulk and cause thermolabile active instability. However, insufficient homogenization may result in

insufficient aqueous and oily phase mixing, leading to microstructure differences or even phase separation of the semi-solid product.

7. **Milling:** Milling is a process of reduction in the particle size of solid ingredients that may have a significant effect on the breakdown of the ingredients and have an effect on the viscosity of the final formulation. The nature of the particles to be milled and the particle size proposed guide the mill choice. The bulk density and particle size distribution can be influenced by the type of mill used. The scale of the mill should be big enough to de-lump the whole batch in a fair period of time to prevent the drying of constituents during the process.

8. **Risk Assessment and Risk Control:** Variations in raw material supplies and proposed production methods are known to be risk factors that may influence the essential quality attributes of the formulation and ultimately cause product failure in topical semisolid formulations. The probability and possible severity of these risk factors and subsequent failure modes should be established to establish action plans towards the CMAs and CPPs, contributing to the mitigation of the risk factors.

SUMMARY

One of the fastest-growing product markets worldwide is topical semi-solid goods. It takes well-thought-out designs in development and procedure to ensure the consistency and efficiency of these goods. In short, it is possible to facilitate the achievement of the optimal consistency of the finished product by using the QbD method to produce topical semi-solid products. Not only the QAs but also the CMAs and CPPs should be taken into account to define a QTPP for a topical semi-solid product. As a guide to the development and manufacture of the products, potential product CQAs derived from QTPP and prior knowledge must be used.

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