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# Evaluation of Gel Formulations by Quality by Design Concept

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**ABSTRACT**

*Quality by Design* is "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product & process understanding and process control, based on sound science and quality risk management" *(ICH Q8(R2).* The current research topic was evaluated from the overall concepts of quality by design, through a detailed evaluation was not done but however, critical and required parameters were taken to check the quality by design impact on the current research topic.

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## INTRODUCTION:

To document product development report by *"Quality by Design"* approach for proposed research product of Voriconazole Gel Formulations. The objective of the product development report is to present the quality by design aspect for Gel based formulations, The elements of quality by design are examined and a consistent nomenclature is proposed with the help of quality target product profile, critical quality attribute, critical process parameter, critical material attribute, design space, and control strategy.

*Quality by Design* is "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product & process understanding and process control, based on sound science and quality risk management" *(ICH Q8(R2)).*[1-4]

The following elements are taken into consideration for Gel product & process development

- Quality target product profile (QTPP)
- Critical Quality Attributes (CQAs) of the drug substance, excipients and drug product
- Product design and understanding including identification of critical material attributes (CMAs) of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters (CPPs) and in-process material attributes of a drug product
- Control strategy and justification to ensure the product reliability
- Manage product lifecycle, including continual improvement

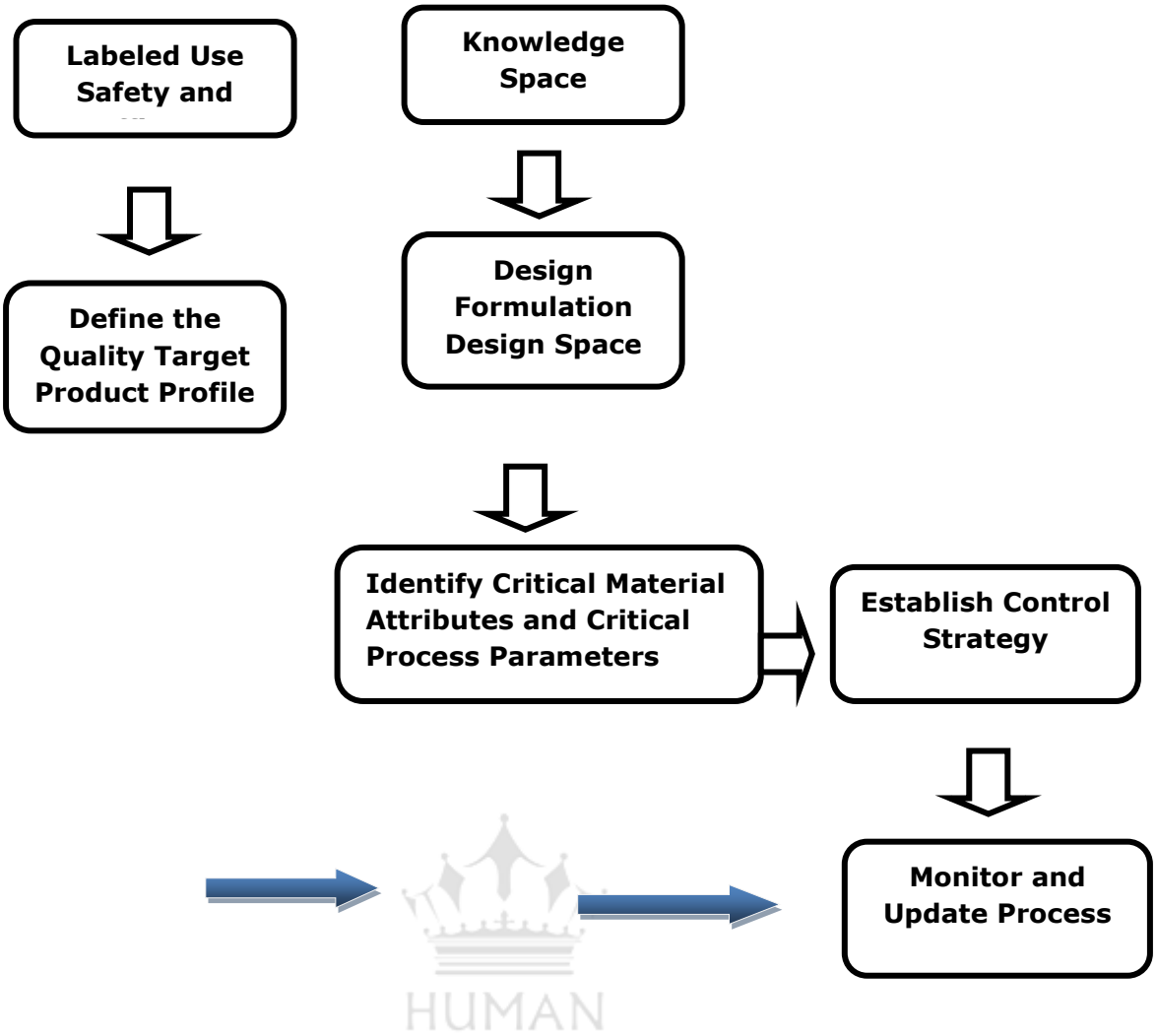


**Figure 1: Overview of Quality by Design**

## TARGET DESIGN IMPLEMENTATION[5-9]

The present product development report is aimed with designing and developingVoriconazole Gel formulation and manufacturing processes to ensure a pre-defined quality product.

The following elements are taken into consideration for Gel product & process development;

1. Begin with a "Quality Target Product Profile" (QTPP) that describes the use, safety, and efficacy of Gel.

2. Defining "Quality Target Product Profile" that will be used by formulation scientist as a quantitative surrogate for aspects of chemical safety and efficacy during Gel product development.

3. To gather relevant prior knowledge about the Voriconazole (Drug Substance), excipients & process operations into knowledge space.

4. Use of risk assessment to prioritize knowledge gaps for further investigations.

5. Designing a formulation & identifying the critical quality material attributes of final formulations [Gel] that must be controlled to meet "Quality Target Product Profile".

6. Designing a manufacturing process to produce a final product having above mentioned critical quality material attributes.

7. Identifying the critical process parameters and input (Raw Materials) material attributes that must be controlled to achieve critical material attributes of the final product.

***QbD* Approach for Formulations [Gel]**

**Product Development Outline:**

- Defining Quality Target Product Profile (QTPP)
- Identification of Critical Quality Attributes (CQAs) for the drug substance, excipients and drug product (DP)
- Identification and prioritization of potential risks for each unit operation (Risk assessment)
- Screening and optimization of the formulation (Design of Experiments (DOE) for high-risk components)
- Development of a robust process (DOE for high-risk parameters)
- Establishment of control strategies
  - Raw material specification
  - Process controls and monitoring, design spaces around individual or multiple unit operations
  - Finished product specifications

**Pharmaceutical Development**

**a. Overview**

Voriconazole is an active substance.

The section summarizes the product development activity of Voriconazole Gel Formulations. Preliminary information on product formulation, critical manufacturing parameters; packaging components; specifications and testing profiles that will be further verified during manufacturing and stability testing of samples from submission batch are included.

**b. Development Summary**

The following product development report summarizes the development of Voriconazole Gel Formulations.

The development of any drug product is always guided by the goal of designing a product which complies with defined specifications at release and that is able to maintain its physic-chemical properties and stability within acceptable limits during its shelf-life. Therefore, compliance with the principles of Quality, Safety, and Efficacy depends on meticulous and planned pharmaceutical development work.

The present work focused on the formulation of a stable semisolid dosage form, through a Drug Substance, the excipients, and selection of an optimized manufacturing process.

Critical factors affecting stability were discussed and evaluated under a risk management strategy considering their importance to the stability of the drug product.

Selection of excipients was done through a DS/excipients compatibility studies and known, unknown and total impurities were quantified by HPLC analytical technique, to select those who showed better chemical stability.

Development of the formulation aimed to produce a quickly extrude, stable Gel by conventional gel formulation technique.

Finished product pharmaceutical performance and chemical stability after three months short term stability study, in ICH conditions, was evaluated.

Statistical evaluation of the multiple parameters suggests that, in this period, there are no significant differences between test and reference, either in pharmaceutical performance or chemical stability.

**d. Quality target product profile**

The quality target product profile (QTPP) is “a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.” The QTPP is an essential element of a QbD approach and forms the basis of the design of the generic product. The target should be defined early in development based on the properties of the drug substance (DS) and characterization of the reference product. The QTPP includes all product attributes that are needed to ensure equivalent safety and efficacy of the formulation. By beginning with the end in mind, the result of development is a robust formulation and manufacturing process with a control strategy that ensures the performance of the drug product.

A critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." The identification of a CQA from the QTPP is based on the severity of the adverse effect on a patient should the product fall outside the acceptable range for that attribute. All quality attributes are target elements of the drug product and should be achieved through a good quality management system as well as appropriate formulation and process design and development. From the perspective of pharmaceutical development, we only investigate the subset of CQAs of the drug product that also has a high potential to be impacted by the formulation and/or process variables. Our investigation culminates in an appropriate control strategy.

A quality target product profile (QTPP) was defined below.

**Table 1: Quality Target Product Profile (QTPP) for Proposed Generic Product**

| Parameter | QTPP Elements | Justification | Is it a CQA? |
|---|---|---|---|
| Dosage form and route of administration | Gel | The proposed dosage form is new. The proposed dosage form is for topical application. | No |
| Dosage design | Immediate Release | Equivalent type of immediate release. | No |
| Dosage strength | 1 gm | Taken as generally applied | No |
| Assay | 100%w/w label claim<br><br>Total impurities on the drug | Assay affects safety and efficacy. Formulation and process variables can affect assay, therefore, this is considered a CQA of the drug product. | Yes |
| Impurity level | Product to be quantified after 3 months stability study and at least comparable to the RP in the same conditions<br>Known impurities: NMT0.2%<br>Unknown impurities: NMT 0.20 % | Degradation products affect safety and efficacy Formulation and process variables can affect the formation of degradation products; therefore this is considered CQA of the drug product. Limits defined are based on international guidelines and consider the maximum daily dose intake of | Yes |
| Dissolution | Immediate release that can meet NLT 80% (Q) in 90 Minutes | Dissolution is critical to ensure the therapeutic effect. Formulation and process variables can affect dissolution performance; therefore considering the Immediate release target profile this is considered a CQA of the drug product. | Yes |
| Drug Permeation | Flux | Important for the therapeutic point of view | Yes |
| pH | Between 5 and 8 | pH to compatible with skin | No |
| Colour and appearance | White to off while | Colour and appearance are not critical attributes although they are a long term stability indicator of physical incompatibilities and should be evaluated. | No |
| Viscosity | Medium | The viscosity has an impact on the rate of drug release, hence should be medium | Yes |
| Extrudability | Medium | Extruding from the tube during application | No |
| Spreadability | Medium | Spreading uniformity on the skin | No |
| Gel Strength | Medium | Polymer concentration that determines gel strength | No |

**Component of the Drug Product**

**a) Drug Substance:**

Voriconazole is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.

Voriconazole, a broad-spectrum, triazole antifungal agent, is available as film-coated tablets for oral administration, powder for oral suspension and as a lyophilized powder for solution for intravenous infusion.

Voriconazole is designated chemically as (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H* -1,2,4-triazole-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3. Voriconazole drug substance is a white to the off white powder. Its aqueous solubility is very low at 0.7 mg/mL at 25ºC.

Voriconazole is a triazole antifungal agent. Voriconazole‟s primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14α-lanosterol demethylation, an essential step in ergosterol biosynthesis. Voriconazole is more selective than some other azole drugs for fungal as opposed to various mammalian cytochrome P-450 enzyme systems. The subsequent loss of normal sterols correlates with the accumulation of 14α-methyl sterols in fungi and may be responsible for its fungistatic/fungicidal activity.

Attributes of the drug substance that can affect the drug product performance or manufacturability are Solubility and Chemical Stability. These have been identified to impact on the Critical Quality Attributes (CQA) of the Drug product, and consequently impact to patient safety or product efficacy. Critical attributes of the drug substance used in the drug product that can affect the product performances are controlled by the drug substance manufacturer. Other attributes of the drug substance are not likely to affect product performance or manufacturability.

**b) Risk Assessment of Drug Substance**

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further

investigation whereas the low-risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk.

**Table 2: Overview of Relative Risk Ranking System**

| | |
|---|---|
| Low | Broadly acceptable risk. No further investigation is needed. |
| Medium | A risk is acceptable. Further investigation may be needed in order to reduce the risk. |
| High | A risk is unacceptable. Further investigation is needed to reduce the risk. |

Based upon the physicochemical and biological properties of the drug substance, the risk assessment of drug substance attributes on drug product CQAs is shown in below table.

**Table 3: Risk Assessment of the drug substance attributes on drug product CQA**

| Drug product CQA's | Particle Size distribution | Solubility | Chemical stability |
|---|---|---|---|
| Assay | Medium | Low | High |
| Degradation products | Medium | Low | High |
| Dissolution | Medium | Low | High |
| Viscosity | Low | Low | High |

**6.2.3 Justification for the initial risk assessment of the drug substance attributes**

The justification for the assigned level of risk is provided in **Table.**

The classification is presented on Table. This rationale is based on a correlation between DS attributes and their potential effect on the drug product's CQA's.

**Table 4: Justification for the Risk Assessment of the Drug Substance Attributes**

| | | | |
|---|---|---|---|
| Particle size distribution | Assay | Small particle size may result in segregation of DS particles with consequences on powder homogeneity and hence assay failure on the dosage form of Nicorandil DS forms lumps and microscopic aggregates that are difficult to scatter. Proper mechanical action upon DS while preparing a blend can bypass homogeneity issue | The risk is medium. |
| | Degradation products | PSD alone is not expected to have any impact on the degradation products of the DS, although during manufacturing it might be necessary to use mechanical sieving or milling process to promote powder blend homogeneity which can introduce mechanical stress degradation reaction. Milling and particle reduction should be evaluated to assess its influence on DS and drug product stability. | The risk is medium. |
| | Dissolution | Solubility testing done on indicates that it is soluble in the pH range of the GIT. Sink conditions are also observed. Voriconazole is soluble. | The risk is medium. |
| Solubility | Assay | Solubility in water has been established as sparingly soluble though solubility in buffer solutions on the H range from1.0 to 7.0 comply with sink conditions and is highly soluble according to BCS standards, therefore assay determination should not be compromised by solubility. | The risk is low. |
| | Degradation Products | Solubility is not directly related to the degradation rate. | The risk is low. |
| | Viscosity | This test parameter is not directly related to solubility. | The risk is low. |
| | Dissolution | Solubility in water has been established as sparingly soluble though solubility in buffer solutions on the H range from1.0 to 7.0 comply with sink conditions and is highly soluble according to BCS standards, therefore dissolution profile should not be compromised by DS solubility. | The risk is low. |
| | Gel Strength | This parameter is not expected to have an impact on the formulation strength. | The risk is low. |
| Chemical stability | Assay Degradation products | Based on available bibliography and supplier information, voriconazoleissensitive to higher levels of humidity, heat and mechanical stress, there fore chemical | The risk is high |

| | | | |
|---|---|---|---|
| | | stability can seriously affect assay and degradation products levels on the finished drug product. These CQA's must be carefully studied and monitored | |
| | Dissolution | Dissolution is affected by DS particle size distribution, formulation composition and DS solubility. As mentioned assay CQA, chemical stability can ultimately lower content and therefore will the percentage of total DS dissolved. | The risk is high. |
| | Viscidity | Viscosity is a major factor in drug product instability. This CQA must be carefully studied and monitored. | The risk is high. |
| | Gel Strength | Higher strength is a factor that promotes propose flow of gel from the tube. This CQA must be carefully studied and monitored | The risk is high. |

**DS / Excipients compatibility**

Excipients should not be regarded as inert materials. In fact, the choice of the excipients to include in a formulation must be justified.

An excipient is any substance other than active drug substance which has been appropriately evaluated for safety and is included in a drug delivery system to protect, support or enhance stability or enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use. In the last decades, excipient manufacturers became increasingly aware of the demands of pharmaceutical industry to ensure that the patients are provided with a drug product compliant with the intended dosage consistent and safely which is intimately related to eh choice of excipients.

The technological evolution of today's excipients, allow pharmaceutical companies many options to choose from when developing a drug product of high quality, effective and safe helping to place on the market. The choice of excipients is of utmost importance to formulation scientists and this choice will dictate the future quality attributes of the drug product.

Excipients and their concentration in a formulation are selected based not only on their functionality, on the compatibility between the drug substance and excipients. The choice of excipients for the compatibility study should be done considering factors such as the DS

nature and its impurities, their impurities, degradation mechanisms and process conditions of the drug product.

The rationale behind excipients choice and concentration should be based on compatibility studies which are conducted to predict the potential incompatibility of the drug and the excipients in the final dosage form. When developing a drug product with low stability DS strategies to mitigate such instability can be adopted.

A typical drug product development starts with some early pre-formulation studies to characterize the candidate drug and to determine which properties will be relevant during the development of the drug product.

Pre-formulation data from solubility, stressed stability, excipient compatibility [by DSC/IR], and other pre-formulation studies may influence the selection of the formulation dosage form and excipients. The results may also influence the choice of manufacturing process. The pre-formulation data should also help to identify the critical material attributes and critical process parameters for each process step.

Thus, methodical, carefully planned and executed compatibility studies can lead to savings in terms of resources and time delays associated with stability issues arising during late-stage product development. The results from these studies can also be useful in determining the causes of stability issues if they happen at later stages in development.

Design of compatibility studies involves the use of mixtures of DS with one or more excipients.

These were incubated at the form of physical mixtures *per se* or after compaction. Often water is added in these systems to evaluate its role in accelerating drug-excipient interactions.

One of the important goals of pre-formulation compatibility testing is to determine the feasibility of processing conditions, such as conventional gel preparation and the moisture resistance need for packages.

Prior to the start of the work a general literature review of voriconazole was done. Topics searched were related to chemistry, degradation, and impurities, pharmacological information, analytical information, and formulation.

**Excipient grade used in the formulation**

The selection of excipient grade and supplier was based on knowledge about excipient that has been used successfully in approved products manufactured.

**Table 5: Excipient Type and grade**

| Excipient | Grade |
|---|---|
| Carbopol 940 | USP/Ph.Eur |
| Glycerol | USP/Ph.Eur |
| Benzyl Alcohol | USP/Ph.Eur |
| Triethanolamine | USP/Ph.Eur |
| Oleic acid | USP/Ph.Eur |

**The rationale for Excipient Selection:**

Excipients used in the proposed research topic are based on some reference product of different geography and other literature searches.

**a) Drug Product**

**b) Formulation development**

The development studies were aimed at developing a gel. The drug would be developed to comply with general Requirements for semi-solid dosage form products.

**Initial risk assessment of Formulation Variables:**

In this initial risk assessment for formulation development, the detailed manufacturing process has not been established. Thus, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established. For these studies, polymer level in the formulation, as well as talc and Stearic acid levels, is considered as formulation variables while hardness is considered as a process variable and risk assessment had been discussed.

**Table 6: Initial Risk Assessment of Formulation Variables**

| Drug product Critical Quality Attributes | Formulation Variables | | |
|---|---|---|---|
| | Polymer concentration | Permeation Enhancer | Gel Neutraliser |
| Assay | Medium | Low | Low |
| Dissolution | High | Low | Low |
| Viscosity | High | Low | Low |

**Table 7: Justification for the Initial Risk Assessment of Formulation Variables**

| Formulation Variables | Drug product Critical Quality Attributes | Justification |
|---|---|---|
| Polymer concentration* | Viscosity | Polymer concentration can impact the viscosity and also dissolution. This, in turn, can impact gel viscosity. The risk is high. |
| | Dissolution | The release of drug from gel depends on the amount of polymer in the formulation, hence the risk is high |
| Permeation Enhancer | Assay | Permeation enhancer is added to get drug permeated from the membrane. Hence the addition of enhancer won't impact the assay, dissolution, and viscosity. Hence the risk is low |
| | Viscosity | |
| | Dissolution | |
| Gel Neutralizer | Assay | Neutralizer is added to a polymer which was added. This won't have an impact on assay, viscosity& dissolution. The risk is low |
| | Viscosity | |
| | Dissolution | |

*Polymers are compatible with the drug substance and will not impact drug product degradation, the risk is low, hence not captured in the above table.

**Formulation Development**

***Effect of polymer concentration:***

In an initial risk assessment of the formulation variables, risks were rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established. The goal of formulation development was to select the polymer level so as to get the desired gel strength and also desired to extrude from the tube that spreads smoothly on the applied skin. Different concentration of polymer was taken for the study during developmental trials. Finally, polymer concentration was proposed to meet the desired

strength, good credibility, desired viscosity and proper release of drug from the formulation as stated in QTPP. Various materials selected for formation of a proper gel that includes gel former, preservative, permeation enhancer. Conventional Gel formulation technique was employed used for gel preparation.

**Updated Risk Assessment of the Formulation Variables**

Acceptable ranges for the high-risk formulation variables have been established and are included in the control strategy. Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated as given in below Table with the justifications provided in the next Table.

**Table 8: Updated Risk Assessment of Formulation Variables**

| Drug product Critical Quality Attributes | Formulation Variables | | |
|---|---|---|---|
| | Polymer concentration | Permeation Enhancer | Gel Neutraliser |
| Assay | Low* | Low | Low |
| Dissolution | Low* | Low | Low |
| Viscosity | Low* | Low | Low |

*The level of risk was not reduced from the initial risk assessment.

**Manufacturing Process Development (Design of experiments)**

The history of the drug product manufacturing process, including the development of critical parameters and their control is discussed below. The differences between the manufacturing process used to produce the registration stability batches and the proposed commercial manufacturing process are described and justified in this section.

**a) Description of the Manufacturing Process**

Manufacturing process parameters were determined through feasibility studies. Critical attributes investigated included Dispensing, sifting, granulation, drying, granulation, compression, and packing.

**b) Design of Experiments**

A cornerstone of the Quality by Design paradigm is the concept of a design space, where the design space is a multidimensional combination of input variables and process parameters that have been demonstrated to provide the assurance of product quality. If a design space can be established for a pharmaceutical process or product, then operate within the design space confirms that the product or process output possesses the required quality attributes. This concept of design space can be applied to the manufacturing process ofVoriconazole gel formulation. Critical process attributes in such a design space would include those affect the interaction of the voriconazole formulation and its manufacturing process development, including

(a) Dispensing, (b) Soaking & Neutralization (c) Drug Mixing (d) Packaging

The multidimensional interaction of input variables and closely binds the establishment of design space to conduct of Design of Experiment studies that includes interactions among the input variables. All these Designs of Experiment studies were performed to identify and optimize critical process parameters and their ranges, laboratory scale screening DOE study was conducted to assess the effect of process parameters on the assay and degradation to identify the CPPs and scale up, DOE study was conducted to confirm the knowledge gained from manufacturing process development studies.

As part of the manufacturing process development, compatibility of excipients and drug substance

**Table 9: List of Experiments with their Objective**

| Experiment | Objective |
|---|---|
| Dispensing | To freeze dispensing conditions to weigh ingredients which are hygroscopic. |
| Soaking & Neutralization | To soak the polymer for the desired time to get suitable gel consistency followed by neutralization with gel former. |
| Drug Addiction | Dispersing the drug in the soaked gel polymer |
| Packing | To select suitable packing material for better quality control of the DP till shelf life. |

**Initial Risk Assessment of the Drug Product Manufacturing Process**

A risk assessment of the overall drug product manufacturing process was performed to identify the high-risk steps that may affect the CQAs of the final drug product.

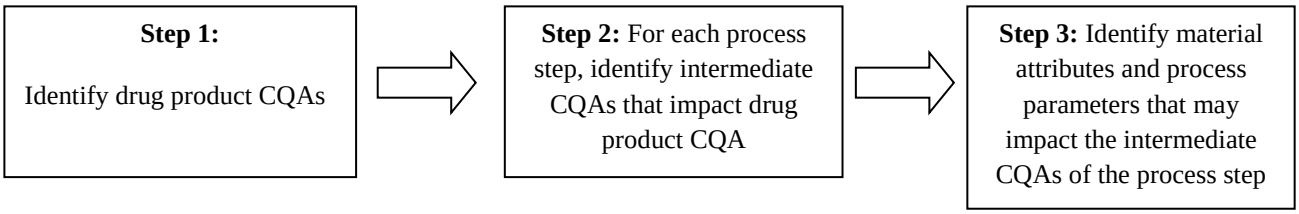


**Figure 2: Details of Initial Risk Assessment**

The initial risk assessment of the overall manufacturing process is shown in previous Table and justifications are provided in Table 93 are based on previous experience with these process steps was used to determine the degree of risk associated with each process step and its potential to impact the CQAs of the finished drug product.

**Table 10: Initial Risk Assessment of the Manufacturing Process for Voriconazole Gel Formulations**

| Drug Product CQA's↓ | Batch size | Dispensing | Soaking & Neutralization | Drug Mixing | Packing |
|---|---|---|---|---|---|
| Description | Low | Low | Low | Medium | Medium |
| Assay | Low | Medium | Low | High | Medium |
| Related substances | Low | Medium | Low | High | Medium |
| Dissolution | Low | Medium | High | High | Medium |
| Viscosity | Low | Medium | High | Low | Medium |

**Table 11: Justification for the Initial Risk Assessment of the Drug Product Manufacturing Process**

| Process variables | Drug Products CQAs | Justification |
|---|---|---|
| Batch size | Description | Batch size variation would not affect any of these CQA's. Based on the experience of development, the required process parameters are optimized and hence the batch size would not affect the drug product CQAs. Hence the risk is low. |
| | Assay | |
| | Related substances | |
| | Dissolution | |
| | Viscosity | |
| Dispensing | Description | Dispensing not have any impact on the description |
| | Assay | Lower humidity should be maintained since the DS is less hygroscopic in nature but higher humidity may impact assay parameter if API absorbs moisture during weighing which in turn affects the batch quantity weighed which will have direct impact on assay of and also it may have impact on related substances and % drug release during dissolution testing, hence the risk is medium. |
| | Related substances | |
| | Dissolution | |
| | Viscosity | The lower quantity of dispensing polymer would have an impact on the desired viscosity. Hence the risk is medium. |
| Soaking & Neutralization | Description | Improper soaking and neutralization won't have an impact on description, assay & related substances. Hence the risk is low. |
| | Assay | |
| | Related substances | |
| | Dissolution | Improper soaking and neutralization gives undesired gel consistency and would have an impact on dissolution as the gel strength/consistency gives either erratic release. Hence the risk is high |
| | Viscosity | Improper soaking and neutralization gives undesired gel consistency and would have an impact on viscosity. Hence the risk is high. |
| Drug Mixing | Description | If the drug is not properly mixed, undissolved particles may affect description and hence the risk is medium. |
| | Assay | If the drug is not properly mixed, the content of assay would be highly varying and hence impact on the related substances and dissolution. Hence the risk is high. |
| | Related Substances | |
| | Dissolution | |
| | Viscosity | Since the viscosity is a polymer concentration dependent and hence improper drug mixing won't have an impact on viscosity. Hence the risk is low. |
| Packing | Description | DP being not hygroscopic in nature but however, improper packaging may impact water evaporation and may lead to variation in the assay and other critical parameters. Hence the risk is medium. |
| | Assay | |
| | Related substances | |
| | Dissolution | |
| | Viscosity | |

Further risk assessment was performed subsequently on each high-risk process step to identify which process variables may potentially impact the intermediate CQAs. Evaluation

of all possible process variables that could potentially impact the quality attributes of the output material of any given process step is not feasible; therefore, some of the variables were set constant based on current understanding.

**Updated risk assessment of the manufacturing process**

During process development, the identified high risks for each process step were addressed. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment was updated in line with the current process of understanding. The table presents the risk reduction for a manufacturing process for Gel formulation. The table provides the justification for the reduced risk following process development.

**Table 12: Updated Risk Assessment of the Manufacturing Process for Voriconazole Gel Formulations**

| Drug Product CQA's↓ | Process parameters | | | | |
|---|---|---|---|---|---|
| | Batch size | Dispensing | Soaking & Neutralization | Drug Mixing | Packing |
| Description | Low | Low | Low | Low* | Low* |
| Assay | Low | Low* | Low | Low* | Low* |
| Related substances | Low | Low* | Low* | Low* | Low* |
| Dissolution | Low | Low* | Low* | Low* | Low* |
| Viscosity | Low | Low | Low | Low | Low |

*The level of risk was reduced from the initial risk assessment.

**Table 13: Justification for the Updated Risk Assessment of the Manufacturing Process of Voriconazole Gel Formulations**

| Process Variables | Drug Products CQAs | Justification |
|---|---|---|
| Dispensing | Assay | Lower humidity of NMT 40 % and temperature of NMT 25°C maintained during dispensing which avoided chances of moisture uptake which might have occurred during dispensing, hence the risk is reduced from medium to low. |
| | Related substances | |
| | Dissolution | |
| | Viscosity | |
| Soaking and Neutralization | Dissolution | Proper soaking time definition [overnight soaking] period and proper usage of neutralizing agents would help to reduce the risks associated with soaking and neutralization. Hence the risk is reduced from high to low. |
| | Viscosity | |
| Drug Mixing | Description | Proper and defined mixing time ensure the obtaining of proper gel. Hence the risk is reduced from medium to low. |
| | Assay | Defined mixing times would eliminate risks associated with the improper assay, related substances, and Dissolution. Hence the risk is reduced from high to low. |
| | Related substances | |
| | Dissolution | |
| Packing | Description | Packing materials selected provided a moisture barrier property and hence the risk is reduced from medium to low. |
| | Assay | |
| | Related substances | |
| | Dissolution | |
| | Viscosity | |

**Defining Design Space**

CQAs were identified by the risk assessment and their relationship to critical material attributes/unit operations was established by multivariate experimental design. This relationship is known as "design space" is the space within which the quality of the product can be built. The wider the design space, the more robust and flexible the process is to accommodate variations. Risk assessment, multivariate experimental design, literature, and prior experience/knowledge contribute to defining the design space. Below Table shows design space.

**Table 14: Design Space Applications**

| Formulation Attributes | Design Space | Response |
|---|---|---|
| Drug | White to an off white gel having good gel strength with required consistency.<br>Assay – 97 -102 %<br>Related Substances: Total Imp: Less than 0.1% | CU |
| Polymer level | 1:1, 1750 to 2250 Cps. | Required viscosity and release |
| Permeation Level | 1:1 w/v | Permeation across barrier |
| Gel Former | For 1gm of Polymer, 3 mL of Neutralizer | Physical Characteristics |
| Mixing | Mixing time and speed so that assay must be 98-102% w/w | CU |

**Control Strategy for Drug product**

The control strategy is "a planned set of controls, derived from the development process, which assures process performance and product quality.

For gel dosage form, the control strategy was developed after the estimation of residual risk and an assessment for its acceptability. The control strategy is to detect and mitigate the risk. Thus, the success of the overall product and process performance would depend on the execution of an operating plan, including an appropriate control strategy and appropriate process monitoring, a model for control strategy which links QTPP to the manufacturing controls needed to deliver the objectives.

**Table 15: Control Strategies for Gel**

| Attributes | Control strategy |
|---|---|
| Drug | Assay 98-102%<br>Should be denser |
| Polymer | Carbopol 940 @ 1:1 [Drug:Polymer] |
| Soaking & Neutralization | Overnight soaking and 3 parts of TEA as a neutralizer |
| Drug Mixing | Throughout mixing of ingredients<br>Assay 97-100% of drug |
| Dissolution | The *in-vitro* drug release from gel formulations was studied cellophane |

| | |
|---|---|
| | membranes using modified KesheryChien diffusion cell[15]. The receptor compartment was filled with the mixture of phosphate buffer of pH 5.6 maintained at 37 ± 0.5°C with constant magnetic stirring. Samples were withdrawn at predetermined time intervals and replaced with fresh medium |

Note: The control strategy and risk assessment are being made with the limited knowledge that gained during this dissertation research work. The current research topic was evaluated from the overall concepts of quality by design, through a detailed evaluation was not done but however, critical and required parameters were taken to check the quality by design impact on the current research topic.

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