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REVIEW ARTICLE

Qbd Approach for the Development of Soft gelatin Capsule

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ABSTRACT
Quality by design (QbD) is an crucial component of current drug development which could increase efficiencies, provide regulatory relief, flexibility, and offer important business benefits throughout the product's life cycle. The FDA permitted the QbD approach in order to maintain the quality of drug by understanding the process knowledge before they are launched onto the market. QbD is in accordance with ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. The proposed review scrutinises the processes involved in engendering a soft gelatin capsule in light of the industry's current shift toward QbD-based submissions. A soft gelatin capsule is being developed by employing a plasticizer such as glycerin or polyhydric alcohol and are hermetically sealed. The significance of QbD lies in its comprehensive framework, which includes desired product quality profile, critical quality attributes, risk assessments, design space, control strategy, product lifecycle management, and continual improvement. The adoption of QbD has transformed the pharmaceutical landscape by reducing out-of-specification results, facilitating easier transfer to manufacturing sites, and eventually ensuring a higher level of product quality.
Keywords: *QbD, Softgel, ICH guidelines, Risk management, Quality.*

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INTRODUCTION

A systematic method of developing pharmaceuticals called "Quality by Design" places a focus on the comprehension and control of both the product and the process [1]. It entails creating objectives and requirements based on a reference listed drug, such as dose form, administration route, and therapeutic indication [2,3]. The QbD technique is ideal for all stages of pharmaceutical development, including formulation development. Soft gels with extended-release times can be created using the QbD approach. The technique entails selecting the suitable material and quality qualities, such as lubrication, elasticity, cohesion, and weight variation, in order to shorten the time required to develop tablets [4]. The purpose of QbD is to guarantee that the finished product meets set quality standards and is appropriate for its intended use [5].

Steps involved in applying QbD principles to soft gelatin capsules:

1. Target product profile (TPP) and quality TPP (QTPP) will be selected based on the referenced pharmaceutical.
2. Critical quality attributes (CQAs) of the soft gelatin capsule, such as dissolve rate, content homogeneity, and disintegration time will be identified.
3. Critical process parameters (CPP) such as temperature, humidity, and mixing speed which affect the CQA will be selected
4. A risk assessment approach will be conducted to identify the potential sources of variability and their effects on the CQA.
5. Influence of CPP on CQA were assessed and the process conditions were optimized.
6. Control strategy will be performed to ensure that the CQA are consistently met and the CPP are within the acceptable range.

7. Process analytical technology technologies that monitor process and product performance include real-time release testing.
8. To constantly improve the process and product performance, QbD principles will be applied throughout the product lifecycle.
Overall, the QbD technique can help ensure that the finished soft gelatin capsule product meets the defined quality standards and is suitable for the intended purpose. Figure 1 explains the overall process of QbD involved in the development of soft gelatin capsule.

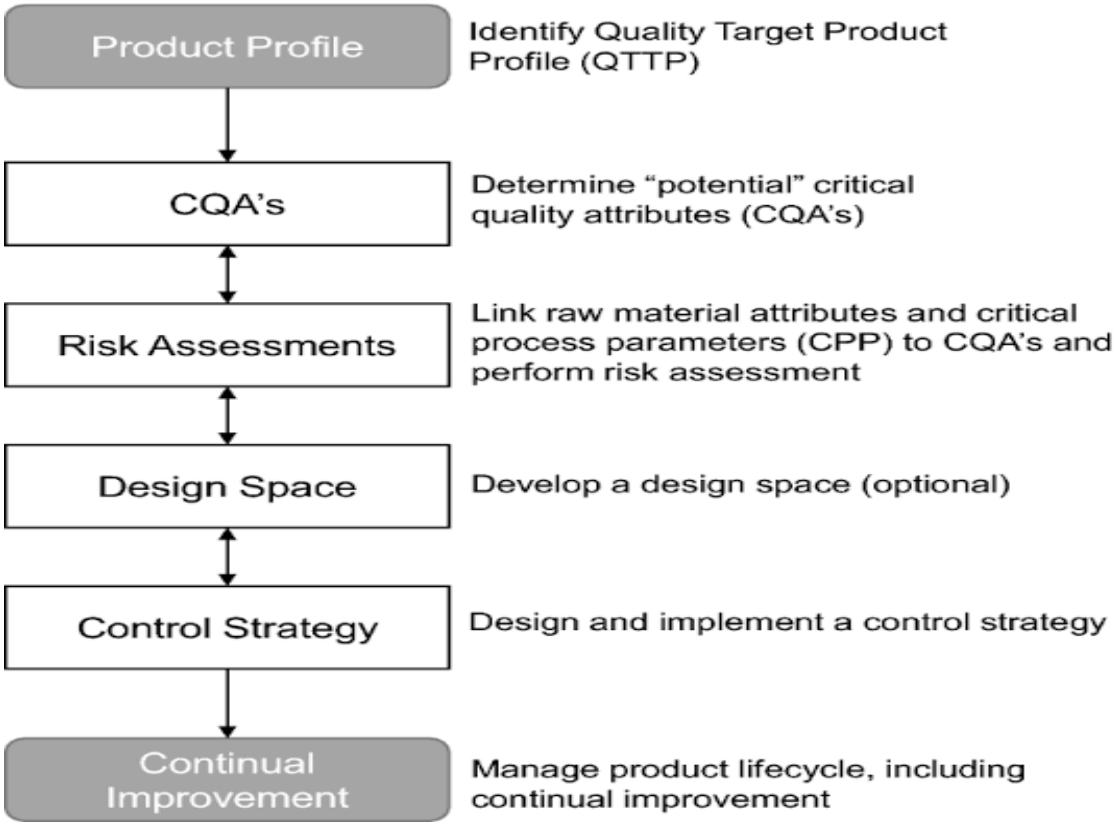

Figure 1 Flowchart of the QBD process

SOFTGEL CAPSULES

Soft gelatin capsules are comprised of soft shells that are hermetically sealed. Gelatin is made more elastic by the addition of a plasticizer, such as glycerin or polyhydric alcohol (such as sorbitol), to create soft gelatin capsules (Shape - spherical, elliptical, oblong, and unique tubes with and without twists). They may include suspensions, pasty substances, or nonaqueous liquids. This kind of pharmacological form provides a number of benefits, including: swallowing comfort; accurate liquid filling unit amount provides higher precision and batch-to-batch consistency of capsules; requirements for consistent manufacturing: More precise liquid filling composition, mixing, and distribution; homogenous liquid mixtures; and higher bioavailability make manufacturing easier. To promote absorption and bioavailability, As needed, substances in solution can be produced using solubilizers and absorption enhancers. Drugs that are not soluble in water can be made into soft capsules; enhanced stability and safety: cross-contamination and air are prevented by the airtight seal; It is possible to create a gelatin shell that blocks UV radiation; For administration via oral, topical, chewable, and suppository, flexibility enables for bespoke shapes and sizes; transport: encapsulated liquid dose formulations become incredibly adaptable for patients and consumers. Table 1 describes about the product characterization of the capsule it includes the API solid state, compositional Testing Manufacturing process and product performance

TABLE 1: Product Characterization For Capsule

API Solid state	Polymorphism Particle size distribution
Compositional testing	Number of excipients in the original formulation. Number of excipients after equilibrium Thermal analysis for the shell Gelatin: MWD, ISOELECTRIC POINT, PH
Manufacturing process	Printing, solvents, lubrication Shell thickness Effect of water uptake for a weight variation
Product performance	Dissolution profiles Effect of stability on cross linking Effect of stability on migrations

There are numerous benefits to employing the Quality by Design (QbD) approach for producing soft gelatin capsules. Here are a couple such examples:

Ease of swallowing: soft gelatin capsules are a popular dosage form among patients because they are simple to chew and digest.

Precise liquid filling for precise dosing, soft gelatin capsules give higher precision in liquid filling unit volume.

Versatility For consumers and patients, encapsulated liquid dose formulations are incredibly flexible.

Manufacturing simplification: soft gelatin capsule manufacture is a straightforward approach with fewer steps than other solid oral technologies, making it ideal for QbD applications.

Approach based on risk: Starting with the project and iterating throughout the project life cycle, soft capsule product designs are easily adaptable to QbD concepts. Projects can be accepted at any stage of development and growth when using a risk-based strategy [6,7].

1) QUALITY TARGET PRODUCT PROFILE

QTPP can be optimized by designing a formulation and manufacturing process which is a quantitative alternative for determining the characteristics with scientific safety and efficacy [8, 9]. Optimisation of QTPP (dosage form, strength, route of administration, pharmaceutical elegance, release/delivery of the drug) supports in creating formulation strategies and keeping formulation efforts efficient and well-targeted [10, 11]. QTTP is widely used in regulatory interactions, clinical and business decisions, risk management, and product development planning [12]. Table 2 explains the Quality attribute for the drug product that ideally ensure the quality of the drug product. In the QbD paradigm, this novel concept of TPP serves as the foundation for product design.

TABLE-2 QTPP for the Drug Product

Quality attributes of the drug product		Target	CQA	Justification
Identification		Positive	Yes	It has an impact on safety and efficacy, but is generally controlled by proper quality practices
Assay		100% of label	Yes	Influences both safety and efficacy
Content uniformity		Compendial requirement	Yes	Influences both safety and efficacy
Dissolution		Product requirement	Yes	Can have an effect on bioavailability
Another attributed	Color	Acceptable to patients	No	It has no effect on safety or efficacy.
	Size and shape	Patients /RLD	No	There are new regulations for generic products.
	odor	No unpleasant	No	Typical gelatin odor
	pH	Specific range	Yes /No	API and gelatin stability may be affected.
	Clumping	Not significant	Yes /No	If severe enough, leakers can form.
	Water content	Product specific	Yes /No	Possible crystallization problem
	Weight variation	No significant changes	Yes /No	If severe can produce leakers

2) CRITICAL QUALITY ATTRIBUTE

CQA is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution"[13]. Determining the CQA is the next step after identifying the QTPP. CQA are QTPP subgroups that could be influenced by formulation or process changes [14]. CQA

can be identified using literature reviews, manufacturing experience, technology transfer, stability reports, raw material testing data, adverse event reports, and recalls. CQA is used to determine a product's performance by monitoring mechanistic characteristics such as particle size and hardness. As a result, QTPP could be utilized to explain both product performance and product performance factors [15]. The Critical Quality Parameter (CQP) & CPP of Soft gelatin Capsules are explained in Table 3.

TABLE -3 Critical Quality Parameter & Critical process parameter

CQP	CPP
Content uniformity	Temperature
Dissolution rate	Humidity
Stability	Drying time
Appearance	Drying temperature
Purity	Gelatin viscosity
Identity	Gelatin concentration
Potency	Fill weight
Microbial limits	Mixing time, mixing speed

3) CRITICAL PROCESS PARAMETER

CPP are "parameters whose variability has an impact on a CQA and should be monitored or controlled to ensure the process produces the desired quality" [16]. As part of product design and understanding, the QbD process includes the identification of Critical method Attributes (CMA), which differ from CQA. CMA are used for input materials like drug substances, excipients, and in-process materials, whereas CQA are used for output materials like finished goods. A downstream manufacturing process may convert a CQA of an intermediate into a CMA of the same intermediate [17]. Scientific reasoning and quality risk management procedures are used to determine the criticality of quality attributes and process parameters. The primary factor in assessing the importance of quality traits is the degree of harm, and this factor is unaffected by risk management [18].

4) QUALITY RISK ASSESSMENT

For the development of soft gel capsules, QbD is essential, it assists in identifying and reducing any hazards that could affect the final product's quality, safety, and effectiveness. In QbD for the development of soft gel capsules, risk assessment plays the following role:

Quality Risk Assessment tools

1. Based on scientific knowledge, the study of the risk to quality should offer the patient safety.
2. Outlines the methods that are used to assess, manage, communicate, and review quality risks in a systematic way.
3. This applies throughout the entire product lifetime, including development, manufacture, and distribution.
4. Risk assessment using tools mentioned in ICH Q9 guideline

Risk Identification: The purpose of risk assessment is to identify potential risks connected to formulation, manufacturing, and other elements that may have an impact on softgel capsule quality. Excipient compatibility, medication stability, production equipment, and environmental conditions are all aspects to consider [19].

Risk Prioritization: After dangers have been discovered, they are graded based on their seriousness and likelihood of occurring. This makes it easier to identify threats that require prompt attention. Prioritization allows for efficient resource allocation to the most significant concerns [20].

Risk Control Strategies: Risk assessment guides the development of risk control techniques to reduce recognized risks. These solutions may involve modifying the formulation, changing the procedure, or implementing specific control measures to decrease or eliminate the detected dangers.

Risk Monitoring and Verification Risk assessment is still necessary for monitoring and confirming the effectiveness of risk control strategies after they have been implemented. CPP and CQA must be continuously monitored to ensure that the desired quality requirements are satisfied on a consistent basis [21]. By incorporating risk assessment into the QbD approach, pharmaceutical companies can proactively identify and resolve possible risks, enhancing product quality, patient outcomes, and patient safety. It permits the production of tougher and more durable soft gel capsules.

The quality risk assessment process is given in Figure 2.

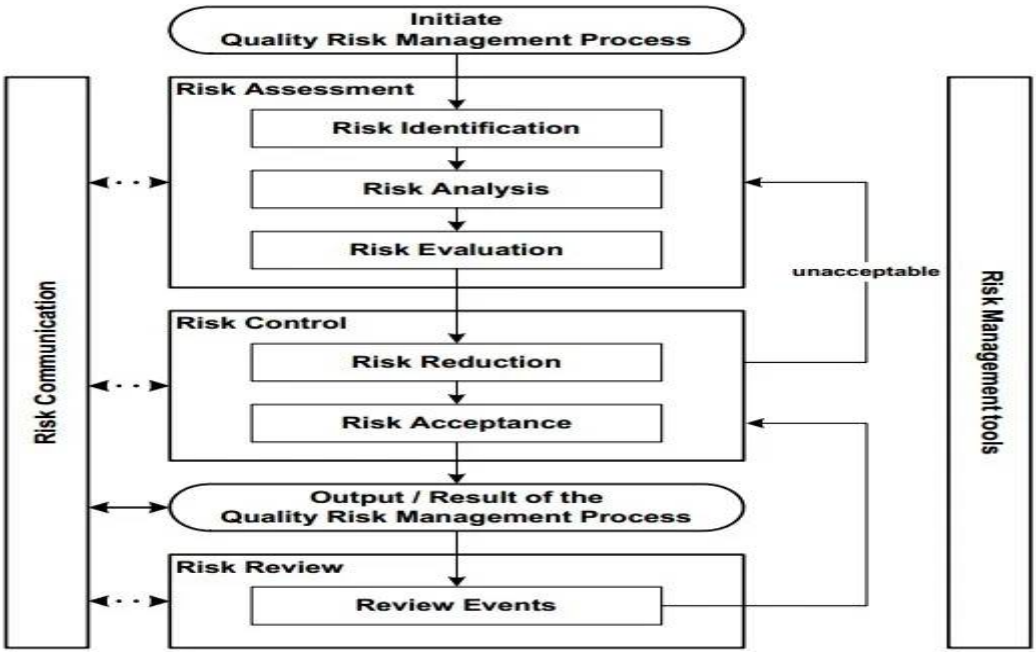

Figure 2 Overview of Quality Risk Management process

CONTROL STRATEGY

ICH Q8 (R1) defines a control strategy as "a planned set of controls developed from current product and process information that ensures process performance and product quality" [22]. Currently, a control strategy exists for every process. Furthermore, the manufacturers are often obliged to conduct extensive in-process quality control tests, such as those for tablet hardness or blend consistency. The completed pharmaceutical items are checked for quality by determining whether they adhere to standards [22, 23].

DESIGN SPACE

Design space acts as a link between manufacturing design and development which provides assurance of quality. It allows manufacturers to explore combinations of multiple variables (CMA and CPP) using appropriate statistical tools. Design space refers to the multidimensional combination and interplay of input variables (material attributes) and process parameters that have been proved to provide quality assurance. The applicant submits the design space, which is evaluated and approved by regulatory authorities [24]. A design space can be created for a single unit operation, a collection of unit operations, or the full process. The ability to operate within a design space without seeking further regulatory permission can be obtained by submitting the design space to the FDA. [25].

CONCLUSION

QbD is a suitable technique for the creation of soft gel capsules in the pharmaceutical industry which involves well-defined goals, reliable science, and effective risk management. Optimization of soft gels by adopting QbD encourages a methodical, science-based approach that results in reliable formulations, high rates of regulatory approval success, and constant product quality.

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