

SOFT GELATIN CAPSULES: APPLICATION OF QUALITY BY DESIGN (QbD) APPROACHES IN FORMULATION DEVELOPMENT AND STABILITY CHALLENGES

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Abstract

Soft gelatin capsules are widely used for delivering drugs, nutraceuticals, and poorly water-soluble active ingredients. However, their quality and stability are influenced by complex interactions among the gelatin shell, fill formulation, manufacturing process, packaging, and storage environment. This review highlights the application of Quality by Design (QbD) principles in softgel development, focusing on the Quality Target Product Profile, Critical Quality Attributes, Critical Material Attributes, Critical Process Parameters, risk assessment, Design of Experiments, and control strategies. Major stability challenges, including gelatin cross-linking, moisture migration, shell brittleness, leakage, fill-shell interactions, oxidation, and dissolution changes, are discussed. The effects of temperature, relative humidity, light, oxygen, formulation, packaging, and transportation are also examined. Emerging approaches such as Process Analytical Technology, predictive stability modelling, advanced packaging, and digital technologies are highlighted for improving softgel robustness and lifecycle management. Overall, QbD provides a systematic approach for developing stable, reproducible, and high-quality formulation of soft gelatin capsule products.

Keywords: *Soft gelatin capsules; Quality by Design; Stability; Formulation; Manufacturing; Gelatin cross-linking; Drug deliver; Packaging*

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1. Introduction

Soft gelatin capsules (SGCs), commonly known as softgels, are widely used pharmaceutical dosage forms in which active pharmaceutical ingredients (APIs) or other active substances are enclosed within a flexible gelatin-based shell. The fill material may contain the drug in dissolved, dispersed, or suspended form and can accommodate a wide range of liquid and semisolid formulations. This formulation flexibility has made softgels particularly attractive for compounds that present challenges in conventional solid dosage forms, including drugs with poor aqueous solubility. Damian et al. (2021) reported that soft gelatin capsules have gained considerable importance for the oral delivery of poorly water-soluble drugs because appropriate fill formulations can address solubility and dissolution-related limitations. Naharros-Molinero et al. (2024) emphasized that shell formulation, manufacturing and storage conditions, and interactions between the fill and shell are among the major factors governing softgel performance throughout its shelf life.

1.1 Soft Gelatin Capsules: Overview and Applications

A typical soft gelatin capsule consists of a gelatin shell containing gelatin, water, and plasticizers, together with optional components such as colorants, opacifiers, preservatives, and other functional excipients. The fill can be formulated as a solution, suspension, emulsion, lipid-based system, or semisolid preparation depending on the physicochemical properties of the API and the intended therapeutic performance. Industrial softgel production is predominantly based on the rotary-die encapsulation process, which enables simultaneous formation, filling, and sealing of the capsules. Garcia-Gallego et al. (2024) highlighted the importance of shell composition and processing conditions in determining the mechanical and thermal properties of softgel capsules.

Softgels have found extensive application in the formulation of poorly water-soluble and lipophilic drugs. Incorporation of APIs into lipidic vehicles, cosolvent systems, or self-emulsifying formulations can improve drug solubilization and facilitate drug release following administration. Commercial examples include softgel formulations of Tocopherol, cyclosporine, isotretinoin, progesterone, dutasteride, calcitriol, and several other therapeutically important compounds. Damian et al. (2021) described softgels as an important formulation platform for overcoming physicochemical limitations associated with poorly soluble drug candidates.

The versatility of softgels also permits modification of capsule size, shape, shell composition, fill characteristics, and release performance according to product requirements. Consequently, softgel technology has evolved from a conventional encapsulation approach

into a platform capable of supporting sophisticated lipid-based and bioavailability-enhancing drug delivery systems. However, increasing formulation complexity also increases the number of variables that must be understood and controlled during pharmaceutical product development.

1.2 Advantages and Development Challenges

One of the major advantages of soft gelatin capsules is their ability to accommodate liquid and semisolid formulations, thereby providing greater formulation flexibility than many conventional solid dosage forms. This characteristic is particularly valuable for poorly water-soluble APIs, which may be incorporated into lipidic or self-emulsifying systems to maintain the drug in a solubilized or readily dispersible state. Such approaches can enhance dissolution and, depending on the drug and formulation, improve oral bioavailability. Pouton (2006) established the importance of lipid-based formulation strategies for improving the oral delivery of poorly water-soluble drugs.

Softgels also offer advantages such as ease of swallowing, accurate unit dosing, protection of the encapsulated formulation, and the possibility of incorporating a wide range of pharmaceutical and nutraceutical ingredients. Nevertheless, their development is more complex than simply optimizing the fill formulation. The gelatin shell is sensitive to changes in moisture, temperature, plasticizer concentration, and interactions with the encapsulated material. Naharros-Molinero et al. (2024) demonstrated that these factors can modify the mechanical and thermal characteristics of the shell and consequently influence capsule integrity and stability.

Other common development concerns include shell brittleness or softening, stickiness, deformation, leakage, variation in fill weight, and changes in dissolution performance. Moisture migration between the fill and shell represents another important mechanism because changes in water distribution can alter the mechanical properties of gelatin. Thus, softgel development requires simultaneous consideration of formulation composition, shell properties, manufacturing parameters, packaging, and storage conditions rather than optimization of individual components in isolation.

1.3 Need for Quality by Design Approaches in Softgel Capsule Development

The complexity of softgel systems creates a strong rationale for implementing a Quality by Design (QbD) approach. Conventional empirical development may involve changing individual formulation or process variables sequentially, which can provide limited understanding of interactions among multiple factors. In contrast, QbD provides a systematic framework that begins with predefined objectives and emphasizes product and process

understanding, risk assessment, experimental design, and control throughout the product lifecycle. Yu et al. (2014) identified the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), control strategy, and continual improvement as fundamental elements of pharmaceutical QbD.

For soft gelatin capsules, QbD can be applied to establish relationships between material attributes, manufacturing parameters, and product quality. Potential CQAs may include assay, content uniformity, fill-weight variation, shell thickness, mechanical strength, disintegration, dissolution, moisture content, leakage, and stability. Similarly, characteristics such as gelatin type, gelatin concentration, plasticizer level, viscosity, moisture content, and fill composition may function as important material attributes, while ribbon thickness, Gel mass temperature, fill temperature, sealing temperature, encapsulation speed, drying temperature, and environmental humidity may influence critical process performance.

Importantly, QbD can extend beyond initial formulation optimization to address the long-term stability of softgel products. Understanding the relationships among shell composition, fill formulation, manufacturing conditions, packaging, and environmental exposure can facilitate development of a robust product capable of maintaining its intended quality throughout its shelf life. Therefore, integrating QbD with stability assessment provides an opportunity to shift softgel development from empirical optimization toward a science- and risk-based approach capable of controlling variability, minimizing defects, and improving product robustness.

2. Fundamentals of Soft Gelatin Capsule Development

Soft gelatin capsule development involves the coordinated selection and optimization of the capsule shell and internal fill formulation (called fill matrix) to achieve the desired drug loading, product performance, stability, and patient acceptability. Unlike conventional tablets, softgels represent an integrated system in which the properties of the shell and fill can influence one another throughout manufacturing and storage. Therefore, understanding the composition, physicochemical characteristics, and compatibility of both components is fundamental to robust product development. Nair et al. (2020) emphasized that successful softgel development requires consideration of formulation composition, encapsulation characteristics, and interactions that may influence drug release and product stability.

2.1 Composition of Softgel Shell

The softgel shell is primarily composed of gelatin, plasticizer, and water, with additional ingredients incorporated to modify appearance, stability, mechanical properties, or

functionality. Gelatin is generally obtained from the partial hydrolysis of collagen and acts as the principal film-forming polymer. Its gel strength, viscosity, molecular-weight distribution, and bloom value can substantially influence shell formation, elasticity, mechanical strength, and dissolution behavior. Jones (2004) described gelatin as a versatile biomaterial whose functional properties depend strongly on its source, processing history, molecular structure, and environmental conditions.

Plasticizers, such as glycerol and sorbitol, are incorporated to provide flexibility and reduce the brittleness of the gelatin film. The concentration and type of plasticizer influence tensile strength, elongation, hardness, and moisture sensitivity. An inappropriate plasticizer-to-gelatin ratio may result in excessive softness, brittleness, or deformation during manufacturing and storage. Among the available plasticizers, Glycerin is the highly preferred plasticizer. Naharros-Molinero et al. (2024) demonstrated that variations in shell composition can significantly affect the mechanical and thermal properties of soft gelatin capsules.

Water acts as an essential component of the gelatin matrix and contributes to gelatin hydration and processing. Quantity of water in the gel mass formulation depends up on the bloom strength of gelatin being used. Higher the bloom strength, quantity of water is to be increased accordingly. However, changes in water content during drying and subsequent storage can alter shell properties. Excessive moisture may increase softness and stickiness, whereas excessive moisture loss can cause brittleness and cracking. Peyre et al. (2019) highlighted the importance of water-gelatin interactions in determining the structural and functional characteristics of gelatin-based materials.

Additional shell components may include colorants, opacifying agents, preservatives, antioxidants, flavors, and other functional excipients. Titanium dioxide has historically been used as an opacifying agent, although regulatory considerations have encouraged investigation of alternative approaches. The selection and concentration of these ingredients must be carefully controlled because they may affect shell appearance, stability, processing behavior, and regulatory acceptability.

Thus, shell development should consider the gelatin source and grade, gelatin-to-plasticizer ratio, moisture content, additives, mechanical properties, and dissolution characteristics as interconnected variables rather than independent formulation factors.

2.2 Types of Fill Formulations

The fill formulation is selected according to the physicochemical properties of the API, dose requirements, solubility, stability, and intended drug-release characteristics. Softgels are

particularly advantageous because they can accommodate liquid and semisolid formulations that may be difficult to manufacture as conventional solid dosage forms.

2.2.1 Lipophilic and Lipid-Based Formulations

Lipid-based fills commonly contain oils, medium-chain or long-chain glycerides, fatty acids, and other lipidic excipients. These systems are particularly useful for poorly water-soluble drugs because they can enhance drug solubilization and facilitate dispersion within the gastrointestinal tract. Pouton (2006) established the importance of lipid-based formulation approaches for improving the oral delivery of poorly water-soluble compounds.

2.2.2 Self-Emulsifying Drug Delivery Systems

Self-emulsifying drug delivery systems (SEDDS), including self-microemulsifying and self-nanoemulsifying systems, contain combinations of oils, surfactants, and cosurfactants that spontaneously form fine emulsions or nanoemulsions following exposure to gastrointestinal fluids. These systems have been extensively investigated for enhancing dissolution and oral bioavailability of poorly soluble APIs. Porter et al. (2008) described lipid-based formulations as an important strategy for overcoming solubility and absorption limitations associated with poorly water-soluble drugs.

2.2.3 Solutions and Suspensions

Drug solutions are among the simplest softgel fills and are appropriate when the API can be adequately solubilized in a pharmaceutically acceptable vehicle. Most of the time solution involves simple mixing of API with solvents like soybean oil. Suspensions may be employed when the drug concentration exceeds its solubility or when a stable dispersed system is required. However, suspension fills require careful control of particle size, sedimentation, viscosity, and dose uniformity.

2.2.4 Semisolid and Specialized Fill Systems

Semisolid fills can be developed using materials that undergo controlled changes in viscosity or physical state during processing or administration. More advanced softgel formulations may incorporate supersaturating systems, amorphous drug systems, lipid formulations, and combination delivery technologies to improve drug loading and bioavailability. Williams et al. (2013) discussed the role of lipid-based formulations in enhancing the oral absorption of challenging drug candidates.

The selection of fill type should therefore be guided by the API's solubility, dose, lipophilicity, melting point, chemical stability, gastrointestinal behavior, and desired bioavailability, together with its compatibility with the gelatin shell.

2.3 Drug-Excipient and Fill Shell Compatibility

Compatibility assessment is a critical stage in softgel development because interactions between the API, fill excipients, and gelatin shell can influence both product quality and stability. Drug-excipient incompatibility may result in degradation, precipitation, changes in drug solubility, oxidation, or alteration of the physical characteristics of the formulation.

Common compatibility investigations include Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (PXRD), chromatographic analysis, and accelerated compatibility studies. These approaches can help identify chemical interactions, physical transformations, or degradation pathways before final formulation development.

Particular attention is required for fill-shell compatibility. Components of the fill may interact with gelatin through chemical reactions, hydrogen bonding, plasticization, extraction, or migration. Water and low-molecular-weight components can migrate between the fill and shell, resulting in changes in shell moisture content and mechanical behavior. Damian et al. (2021) identified fill-shell interactions and gelatin cross-linking as important considerations when evaluating dissolution and performance of soft gelatin capsules.

A major concern is gelatin cross-linking, which may occur through reactions between reactive compounds in the fill and functional groups present in gelatin. Cross-linking can reduce gelatin hydration and consequently delay capsule disintegration and drug release. Cole et al. (2014) reported that interactions between gelatin and reactive substances can produce changes in dissolution behavior and represent an important source of variability during softgel development.

3. QbD Framework for Softgel Development

Quality by Design (QbD) is a systematic approach to pharmaceutical development in which product and process understanding is established from predefined objectives and scientific knowledge. Rather than relying primarily on finished-product testing, QbD seeks to understand how material attributes and manufacturing variables influence product quality and to establish appropriate controls for reducing variability. Yu et al. (2014) described QbD as an integrated framework involving the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), risk assessment, Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), design space, and control strategy. The approach has subsequently become an important component of modern pharmaceutical development and regulatory science.

Soft gelatin capsules are particularly suitable for a QbD-based development strategy because their quality is influenced by multiple interconnected variables. The composition of the gelatin shell, plasticizer level, moisture content, fill formulation, ribbon characteristics, encapsulation conditions, drying environment, and packaging system can collectively affect capsule integrity, drug release, and stability. Naharros-Molinero et al. (2024) demonstrated that changes in shell formulation can significantly influence the mechanical and thermal characteristics of soft gelatin capsules. Therefore, a systematic understanding of the relationships among formulation variables, manufacturing parameters, and CQAs is essential for establishing a robust softgel product.

3.1 Quality Target Product Profile (QTPP)

The Quality Target Product Profile (QTPP) represents the prospective description of the desired characteristics of a pharmaceutical product and provides the foundation for subsequent development activities. It translates clinical requirements, route of administration, dosage considerations, and product-performance expectations into predefined quality objectives. Yu et al. (2014) identified QTPP as the starting point of QbD because it establishes the intended quality characteristics against which formulation and manufacturing decisions can be evaluated.

In softgel development, the QTPP should incorporate both conventional pharmaceutical requirements and characteristics specific to the capsule system. These may include dosage form, route of administration, API strength, capsule size and appearance, fill weight, assay, content uniformity, disintegration, dissolution, mechanical integrity, moisture characteristics, microbiological quality, stability, packaging, and intended shelf life. The relative importance of these attributes depends on the physicochemical properties of the API and the intended therapeutic application. For example, dissolution and drug-release characteristics may receive greater emphasis for poorly soluble APIs, whereas mechanical strength and moisture control may become particularly important for maintaining capsule integrity during storage. Naharros-Molinero et al. (2024) reported that shell composition and processing conditions substantially influence softgel mechanical properties, supporting the inclusion of shell performance within the overall product-quality profile.

The QTPP should also be sufficiently flexible to accommodate formulation and process understanding generated during development. As experimental studies identify relationships between material properties, manufacturing variables, and product performance, the initial QTPP can provide a reference framework for determining which characteristics require tighter control. Thus, QTPP establishment ensures that softgel formulation development

remains focused on patient needs, therapeutic performance, manufacturability, and long-term product quality.

3.2 Critical Quality Attributes (CQAs)

Critical Quality Attributes (CQAs) are physical, chemical, biological, or microbiological characteristics that must remain within an appropriate limit, range, or distribution to ensure the desired product quality. Identification of CQAs establishes a direct relationship between the QTPP and the variables that must be investigated and controlled during development. ICH Q8(R2) identifies CQA assessment as an important element of enhanced pharmaceutical development, while Yu et al. (2014) emphasized that CQAs should be established using scientific knowledge, prior experience, and risk-based assessment.

For soft gelatin capsules, potential CQAs include assay, content uniformity, fill-weight variation, dissolution, disintegration, shell thickness, moisture content, mechanical strength, appearance, leakage, and stability. Among these, dissolution can be particularly sensitive to changes in shell properties and formulation composition. Damian et al. (2021) reported that gelatin cross-linking and other formulation-related factors can complicate dissolution testing of soft gelatin capsules and may result in altered drug-release behavior. Similarly, mechanical properties are important because insufficient shell strength may result in cracking or leakage, whereas excessive strength or altered hydration may interfere with capsule disintegration.

The criticality of an attribute should not be assigned solely because it is measurable. Instead, its relationship with product performance and patient safety should be considered. A risk-based approach can classify attributes according to their potential impact and enable development scientists to prioritize experimental investigations. Consequently, CQA identification forms the bridge between the desired product profile and the formulation/process variables requiring scientific evaluation.

3.3 Critical Material Attributes (CMAs)

Critical Material Attributes (CMAs) are physical, chemical, or microbiological properties of raw materials and formulation components that can influence one or more CQAs. In softgel development, CMAs originate from both the gelatin shell and the internal fill formulation, making systematic material characterization particularly important. Lionberger et al. (2008) emphasized that identification and control of material attributes can improve process understanding and support the development of robust pharmaceutical products.

For the gelatin shell, important CMAs may include gelatin source, grade, Bloom strength, viscosity, molecular-weight distribution, gelatin concentration, plasticizer type and concentration, moisture content, and characteristics of colorants or opacifiers. These

properties influence gelatin hydration, film formation, elasticity, mechanical strength, and dissolution. Naharros-Molinero et al. (2024) demonstrated that changes in gelatin and plasticizer composition can produce significant differences in the mechanical and thermal behavior of softgel shells.

Fill-related CMAs may include API particle size, polymorphic form, solubility, concentration, water content, viscosity, density, lipid composition, surfactant concentration, and antioxidant level. Special attention is to be paid for oxygen and light sensitive APIs such as Isotretinoin. These attributes can affect drug solubilization, dose uniformity, fill behavior, and chemical stability. In addition, certain fill components may interact with gelatin or promote migration of water and low-molecular-weight substances across the shell-fill interface. Damian et al. (2021) highlighted the importance of understanding such interactions when evaluating softgel dissolution and performance.

3.4 Critical Process Parameters (CPPs)

Critical Process Parameters (CPPs) are process variables whose variability can influence one or more CQAs and therefore require monitoring or control. ICH Q8(R2) recommends establishing relationships between process parameters and product quality through scientific understanding and risk assessment. In softgel production, CPPs may occur during gelatin preparation, ribbon formation, filling, encapsulation, sealing, drying, and conditioning.

During gelatin preparation, temperature, hydration time, vacuum intensity and viscosity can influence the consistency and film-forming characteristics of the gelatin mass. During ribbon formation, ribbon temperature, ribbon thickness, and moisture can affect capsule dimensions and sealing behavior. During encapsulation, fill temperature, fill viscosity, fill volume, die-roll speed, sealing temperature and machine settings can influence fill-weight uniformity and capsule geometry. Subsequent drying and conditioning require careful control of temperature, relative humidity, and duration because these factors directly affect shell moisture and mechanical properties.

The interdependence of CPPs is particularly important in softgel manufacturing. For example, excessive drying may reduce shell moisture and produce brittle capsules, whereas inadequate drying can produce excessive softness or stickiness. Similarly, inappropriate ribbon thickness or sealing conditions can increase the risk of leakage. Naharros-Molinero et al. (2024) demonstrated the importance of processing and environmental conditions in determining the final characteristics of softgel shells.

Table 1: Major CPPs and Their Potential Effects on Softgel CQAs

Manufacturing Stage	Critical Process Parameter (CPP)	Potentially Affected CQA	Reference
Gelatin preparation	Temperature	Shell uniformity	Polyak et al. (2024)
Gelatin preparation	Water quantity & Hydration time	Shell strength	Gullapalli & Mazzitelli (2017)
Ribbon formation	Ribbon thickness	Shell integrity	Kolcák et al. (2003)
Ribbon formation	Ribbon moisture	Mechanical properties	Molokhova et al. (2018)
Filling	Fill temperature	Fill uniformity	Marques et al. (2009)
Filling	Fill viscosity	Dose uniformity	Martins et al. (2021)
Encapsulation	Die-roll speed	Capsule dimensions	Gullapalli (2010)
Encapsulation	Fill volume	Fill-weight variation	Marques et al. (2009)
Sealing	Sealing temperature/Die roll pressure	Leakage and seam integrity	Gullapalli & Mazzitelli (2017)
Drying	Temperature	Moisture and brittleness	Kolcák et al. (2003)
Drying	Relative humidity	Shell flexibility	Naharros-Molinero et al. (2024)
Conditioning	Time and RH	Final mechanical properties	Molokhova et al. (2018)

3.5 Design Space and Control Strategy

The design space represents the multidimensional combination and interaction of material attributes and process parameters that has been demonstrated to provide assurance of product quality. It differs from a simple collection of individual operating ranges because it considers the interactions between multiple variables. According to ICH Q8 (R2), movement within an approved design space is not considered a change in the design of the product, provided the established quality requirements continue to be satisfied.

In softgel development, design-space establishment may involve simultaneous evaluation of gelatin concentration, plasticizer level, shell moisture, fill viscosity, fill temperature, ribbon thickness, encapsulation speed, sealing conditions, and drying parameters. Yu et al. (2014)

emphasized that DoE and multivariate approaches can provide greater understanding of interactions among formulation and process variables. Such approaches are particularly valuable for softgels because a combination of individually acceptable parameters may nevertheless produce an undesirable quality outcome when their interaction is unfavorable.

Following establishment of the design space, a control strategy should be developed to maintain the process in a state capable of consistently producing capsules that meet the predefined CQAs. The control strategy may include raw-material specifications, supplier qualification, in-process controls, environmental monitoring, CPP monitoring, finished-product specifications, packaging controls, and stability testing. ICH Q10 (2008) further places these controls within the broader pharmaceutical quality system and emphasizes monitoring, corrective action, and continual improvement throughout the product lifecycle.

4. Risk Assessment and Formulation Optimization

Risk assessment is a fundamental component of Quality by Design (QbD) because it provides a structured approach for identifying, evaluating, and controlling variables that may affect the quality of soft gelatin capsules. Unlike conventional development approaches that may rely heavily on empirical experimentation, QbD-based risk assessment uses scientific knowledge and prior experience to identify variables with the greatest potential impact on Critical Quality Attributes (CQAs). According to ICH Q9 (R1) (2023), quality risk management should be based on scientific knowledge and should be appropriately proportionate to the level of risk associated with the pharmaceutical product.

Soft gelatin capsules present a complex risk profile because quality can be influenced by raw-material properties, formulation composition, encapsulation parameters, drying conditions, environmental factors, and packaging. Variations in gelatin concentration, plasticizer level, shell moisture, fill viscosity, ribbon thickness, sealing conditions, and drying temperature may influence capsule integrity, fill uniformity, dissolution, and stability. Naharros-Molinero et al. (2024) demonstrated that changes in shell formulation and processing conditions can significantly modify the mechanical and thermal properties of soft gelatin capsules. Therefore, systematic risk assessment is essential for prioritizing variables that require detailed experimental investigation.

4.1 Risk Identification and Assessment

Risk identification involves determining potential sources of variability and establishing their possible effects on product quality. In softgel development, risk assessment can begin with a systematic evaluation of the complete product lifecycle, including raw-material selection, formulation preparation, gelatin-shell manufacture, encapsulation, sealing, drying,

conditioning, packaging, and storage. Potential risks can subsequently be linked to relevant CQAs to determine which variables require enhanced control.

Important sources of risk include API solubility and stability, gelatin grade, plasticizer concentration, shell moisture, fill viscosity, fill temperature, ribbon thickness, encapsulation speed, sealing conditions, drying temperature, relative humidity, and packaging permeability. The significance of each factor depends on its potential severity, probability of occurrence, and detectability. ICH Q9(R1) (2023) recommends that risk assessment should be continuously refined as additional product and process knowledge becomes available.

Risk assessment should not be regarded as a purely theoretical exercise. Initial risk ranking should be followed by experimental verification to determine whether a suspected high-risk variable actually affects a CQA. This combination of risk-based prioritization and experimental confirmation prevents unnecessary experimentation while ensuring that potentially critical variables are adequately investigated.

4.2 Role of FMEA and Fishbone Analysis in Formulation Development of Soft Gels

Failure Mode and Effects Analysis (FMEA) and Fishbone or Ishikawa analysis are useful tools for systematically identifying and evaluating risks during softgel development. Fishbone analysis provides a structured method for identifying potential causes of a quality problem, whereas FMEA evaluates individual failure modes according to their potential consequences and likelihood.

For softgel manufacturing, a Fishbone diagram can categorize potential causes under materials, methods, machines, measurement, environment, and personnel. For example, capsule leakage may be associated with inappropriate gelatin properties, inadequate sealing temperature, incorrect ribbon thickness, excessive fill volume, machine misalignment, or environmental conditions. Such analysis provides a broad overview of possible causes before detailed experimental studies are initiated.

FMEA can subsequently be used to rank these failure modes according to parameters such as severity, occurrence, and detectability. The resulting risk ranking can help prioritize development studies and determine where additional controls are required. Sangshetti et al. (2017) highlighted the importance of systematic risk-management tools in QbD-based pharmaceutical development. However, numerical risk scores should be interpreted together with scientific knowledge and experimental evidence rather than being treated as absolute measures of risk.

4.3 Design of Experiments (DoE)

Design of Experiments (DoE) is an important statistical tool for investigating the effects of multiple formulation and process variables simultaneously. Unlike one-factor-at-a-time experimentation, DoE can identify both individual effects and interactions between variables while reducing the number of experimental runs required for systematic investigation. Yu et al. (2014) identified DoE as an important tool for establishing product and process understanding within a QbD framework.

In softgel development, DoE can be applied to both the shell and fill formulation. Shell-related factors may include gelatin concentration, plasticizer concentration, and moisture content, whereas fill-related factors may include API concentration, lipid concentration, surfactant level, solvent composition, and viscosity. Process variables such as ribbon thickness, fill temperature, die-roll speed, sealing conditions, and drying parameters can subsequently be investigated.

The responses selected for DoE should correspond to relevant CQAs. These may include shell thickness, tensile strength, elasticity, moisture content, fill-weight variation, dissolution, disintegration, leakage, and drug-release characteristics. Screening designs can initially identify significant variables, followed by response-surface designs such as Central Composite Design (CCD) or Box-Behnken Design (BBD) for optimization. Myers et al. (2016) described response-surface methodology as an effective approach for evaluating nonlinear relationships and interactions between formulation or process variables.

DoE is particularly useful for softgels because formulation and process parameters frequently interact. For example, the influence of plasticizer concentration on shell flexibility may depend on gelatin concentration and moisture content. Similarly, fill viscosity may interact with fill temperature to influence dosing and encapsulation performance. Understanding these interactions is essential for developing a robust formulation rather than simply identifying an isolated optimum.

4.4 Optimization of Formulation and Process Variables

Optimization involves using experimentally established relationships between formulation variables, process parameters, and CQAs to identify conditions that consistently produce acceptable softgel quality. The objective should be to establish a robust operating region rather than merely obtaining a single optimum formulation. Such an approach is consistent with the QbD concept of establishing a design space within which acceptable product quality can be maintained.

For shell optimization, gelatin concentration, plasticizer concentration, water content, and other functional additives can be evaluated against responses such as mechanical strength, elasticity, shell thickness, moisture content, and dissolution. Naharros-Molinero et al. (2024) demonstrated that shell composition has a substantial influence on the mechanical and thermal behavior of soft gelatin capsules.

Optimization of the fill formulation may involve API concentration, solvent selection, lipid composition, surfactant concentration, and viscosity. For poorly water-soluble drugs, lipid-based and self-emulsifying systems can be optimized to improve drug solubilization and oral absorption. Pouton (2006) and Porter et al. (2008) established the importance of systematic lipid-formulation development for improving the delivery of poorly water-soluble drugs.

Process optimization should subsequently address variables such as ribbon thickness, fill temperature, encapsulation speed, sealing conditions, drying temperature, drying duration, and relative humidity. The optimized conditions should provide consistent fill weight, adequate capsule integrity, acceptable mechanical properties, and reproducible drug-release performance. The resulting formulation and process knowledge can then be integrated into the design space and control strategy established under the QbD framework.

4.4.1 Formulation Optimization of Soft Gelatin Capsules

4.4.1.1 Fill Formulation Optimization

The optimization of the fill formulation is a critical step in softgel development because it directly influences drug solubility, bioavailability, stability, and manufacturability. For poorly water-soluble APIs, lipid-based delivery systems, polyethylene glycol (PEG), propylene glycol, medium-chain triglycerides (MCT), and self-emulsifying drug delivery systems (SEDDS) are commonly employed to maintain the drug in a dissolved state. Such systems eliminate dissolution-limited absorption and improve oral bioavailability. In addition to solubility enhancement, the fill formulation must possess suitable viscosity and physical stability to facilitate efficient encapsulation. Low-viscosity fills may result in leakage and poor content uniformity, whereas excessively viscous fills can create pumping difficulties and inconsistent fill weights. Therefore, optimization efforts focus on achieving an appropriate balance between drug loading, solvent composition, rheological properties, and stability while ensuring compatibility with the gelatin shell.

4.4.1.2 Suspension Formulation Considerations

Many APIs are formulated as suspensions within softgel capsules. In such cases, particle size distribution, sedimentation rate, and suspension uniformity become critical formulation parameters. Fine particle size and adequate suspending agents are required to prevent settling

during manufacturing and storage. The suspension system must maintain physical stability while remaining compatible with encapsulation equipment and capsule shell materials. Optimization studies often evaluate viscosity modifiers, suspending agents, and wetting agents to achieve uniform drug distribution and reproducible content uniformity.

4.4.1.3 Optimization of Softgel Shell Composition

The gelatin shell serves as both a protective barrier and a functional component of the dosage form. A typical softgel shell consists of gelatin, water, plasticizers such as glycerin and sorbitol, and optional additives including colorants, opacifiers, preservatives, flavoring agents, and sweeteners. The ratio of gelatin to plasticizer significantly influences shell elasticity, tensile strength, flexibility, and sealing characteristics. An insufficient level of plasticizer may produce brittle capsules, whereas excessive plasticizer may lead to soft or sticky shells. Therefore, optimization of shell composition aims to achieve the desired mechanical strength while ensuring appropriate disintegration and dissolution characteristics. Recent industry developments have highlighted the benefits of partially replacing glycerin with sorbitol-based plasticizers to reduce moisture uptake and minimize plasticizer migration. Such modifications can enhance drying efficiency and improve long-term capsule stability. Consequently, shell optimization requires careful consideration of gelatin type, bloom strength, plasticizer concentration, water content, and shell additives to ensure consistent product performance.

4.4.1.4 Fill-Shell Compatibility Optimization

One of the most challenging aspects of softgel development is the interaction between the fill formulation and the gelatin shell. Unlike conventional solid dosage forms, softgel capsules represent an integrated system in which fill and shell components continuously interact during manufacturing and storage. These interactions may result in physical or chemical instability if not properly controlled.

Physical incompatibilities commonly include moisture migration, shell softening, shell brittleness, leakage, and plasticizer extraction. Chemical incompatibilities may involve oxidation, hydrolysis, gelatin cross-linking, and API degradation. Moisture transfer between the shell and fill can significantly alter shell mechanical properties, while certain solvents and excipients may weaken the gelatin network. Therefore, comprehensive compatibility studies are essential during formulation development to identify and minimize these interaction mechanisms. The optimization process should include evaluation of shell integrity, dissolution performance, moisture balance, and API stability under different storage conditions.

4.4.1.5 Manufacturing Process Optimization

Manufacturing parameters have a profound impact on softgel quality and product consistency. Optimization of the manufacturing process typically begins with preparation of the gelatin mass, where factors such as gelatin bloom strength, gel mass temperature, mixing conditions, and vacuum deaeration must be carefully controlled. Improper gelatin preparation can adversely affect ribbon formation, sealing performance, and capsule uniformity.

During encapsulation, critical parameters include ribbon thickness, wedge temperature, fill temperature, die-roll speed, and pump speed. Variations in these parameters can influence capsule shape, fill weight variation, leakage incidence, and sealing efficiency. Drying conditions are equally important because excessive drying may produce brittle shells, while insufficient drying results in soft and sticky capsules. Achieving the appropriate residual moisture content is therefore essential for maintaining shell flexibility and mechanical integrity. Process optimization studies are generally designed to identify the operating conditions that consistently produce capsules meeting predefined quality specifications.

4.4.1.6 Stability Optimization

Long-term stability remains one of the most important considerations in soft gelatin capsule development. Softgels are sensitive to environmental factors such as temperature, humidity, oxygen, and light exposure. Common stability issues include shell brittleness, shell softening, leakage, fill precipitation, oxidation of lipid components, dissolution changes, and gelatin cross-linking. The optimization process therefore extends beyond formulation development and includes the selection of appropriate packaging materials and storage conditions.

Strategies to enhance stability include the incorporation of antioxidants, moisture-control measures, oxygen barriers, nitrogen flushing, and protective packaging systems such as aluminum-aluminum blister packs. Accelerated and long-term stability studies are essential for understanding degradation pathways and establishing suitable shelf-life specifications. By integrating stability considerations into the formulation development process, manufacturers can improve product robustness and ensure consistent therapeutic performance throughout the product's shelf life.

5. Manufacturing Process and Quality Control

Manufacturing of soft gelatin capsules is a multistage process in which the gelatin shell and fill formulation are prepared separately and subsequently combined through encapsulation, sealing, drying, and conditioning operations. The quality of the finished capsule depends on the controlled interaction of material characteristics and processing conditions throughout these stages. Variability in gelatin viscosity, ribbon thickness, fill viscosity, encapsulation

temperature, sealing conditions, and drying environment can influence capsule dimensions, mechanical integrity, fill-weight uniformity, dissolution, and stability. Therefore, manufacturing should be considered as an integrated process within the QbD framework rather than as a sequence of independent operations. Naharros-Molinero et al. (2024) demonstrated that shell composition and processing conditions have a significant influence on the mechanical and thermal properties of soft gelatin capsules.

5.1 Softgel Manufacturing Process

The manufacture of soft gelatin capsules generally begins with preparation of the gelatin mass. Gelatin is hydrated in water and subsequently heated under controlled conditions to obtain a homogeneous mass. Plasticizers such as glycerol or sorbitol are incorporated to provide the flexibility required for capsule formation, while colorants, opacifiers, and other functional excipients may be added according to the product requirements. The gelatin mass must possess suitable viscosity, temperature, and homogeneity to produce ribbons with consistent physical characteristics. Variations in these properties can subsequently affect ribbon formation and capsule integrity. Nair et al. (2020) emphasized the importance of controlling shell composition and processing conditions in the development of soft gelatin capsule systems.

In parallel, the fill formulation is prepared according to the physicochemical properties of the API. The drug may be incorporated as a solution, suspension, emulsion, lipid-based formulation, or self-emulsifying system. Homogeneity, viscosity, density, drug concentration, and chemical stability of the fill are important considerations because they directly influence dosing accuracy and encapsulation performance. For poorly water-soluble drugs, lipid-based systems can be particularly advantageous because they provide opportunities for improving drug solubilization and oral absorption. Porter et al. (2008) highlighted the importance of lipid-based formulations for enhancing the delivery of lipophilic and poorly water-soluble drugs.

During encapsulation, the prepared gelatin mass is converted into two continuous gelatin ribbons. The ribbons pass through the encapsulation zone, where the fill formulation is accurately dosed between them. Rotary dies simultaneously shape, fill, and seal the capsules. The resulting capsules are then separated from the gelatin web and subjected to controlled drying and conditioning. The drying stage is particularly important because removal of water modifies the mechanical properties of the gelatin shell and determines its final flexibility and strength. Damian et al. (2021) noted that changes in gelatin hydration and shell characteristics can subsequently influence the dissolution behavior of soft gelatin capsules.

After drying and conditioning, capsules undergo inspection and quality control, during which defective units such as leaking, misshapen, excessively soft, brittle, or improperly sealed capsules are removed. The acceptable capsules are subsequently packaged under conditions designed to protect them from moisture, oxygen, light, and other environmental stresses.

5.2 Critical Manufacturing Parameters

The identification and control of critical manufacturing parameters are essential for maintaining reproducible softgel quality. Within a QbD framework, a process parameter becomes critical when its variability has a demonstrated or scientifically justified effect on one or more CQAs. ICH Q8(R2) (2009) recommends establishing relationships between process parameters and product quality through scientific understanding, risk assessment, and appropriate experimental studies.

During gelatin mass preparation, temperature, hydration time, mixing conditions, and gelatin viscosity can influence the uniformity and film-forming behavior of the shell. Insufficient hydration may produce an inhomogeneous gelatin mass, whereas excessive heating can modify gelatin properties. During ribbon formation, ribbon thickness, temperature, and moisture content are particularly important because they influence capsule dimensions, mechanical strength, and sealing performance.

During the filling operation, fill temperature, viscosity, density, and fill volume can influence dosing accuracy and encapsulation efficiency. Excessively viscous fills may result in inconsistent dosing or incomplete filling, whereas low-viscosity formulations may increase leakage or migration problems. Encapsulation parameters such as die-roll speed and synchronization between ribbon formation and fill delivery can also influence capsule dimensions and fill-weight variation.

The sealing stage requires appropriate control of temperature, pressure, and contact time to ensure adequate fusion of the gelatin ribbons. Insufficient sealing may result in leakage, whereas excessive thermal or mechanical stress can produce undesirable deformation. Following encapsulation, drying and conditioning conditions become critical because they determine the final moisture content and mechanical properties of the shell. Naharro-Molinero et al. (2024) showed that processing and environmental conditions can significantly affect softgel shell characteristics.

5.3 Process Monitoring and Validation

Process monitoring is essential for detecting variability during manufacturing and ensuring that the process remains within its established operating conditions. Traditional monitoring may involve measurement of gelatin temperature and viscosity, ribbon thickness, fill weight,

capsule dimensions, shell moisture, environmental temperature, and relative humidity. Such in-process controls allow deviations to be identified before they result in large-scale batch failures.

The QbD approach further encourages the use of Process Analytical Technology (PAT) and real-time monitoring tools where appropriate. Near-infrared spectroscopy, Raman spectroscopy, moisture sensors, machine-vision systems, and automated weight measurements can provide information about material and process behavior during manufacturing. Rathore and Winkle (2009) emphasized that process understanding and real-time monitoring can contribute to improved control of pharmaceutical manufacturing processes.

Process validation provides documented evidence that a manufacturing process is capable of consistently producing a product that meets predetermined quality requirements. For softgels, validation should encompass critical stages including gelatin preparation, ribbon formation, filling, encapsulation, sealing, drying, and conditioning. Validation should demonstrate consistency in relevant CQAs such as fill-weight uniformity, shell thickness, moisture content, mechanical integrity, dissolution, and assay.

Modern pharmaceutical validation is increasingly viewed as a lifecycle activity rather than a one-time exercise. Initial process qualification establishes the capability of the manufacturing process, while continued process verification evaluates process performance during routine commercial production. ICH Q10 (2008) emphasizes continued monitoring and improvement within the pharmaceutical quality system, supporting the integration of process validation with ongoing product and process knowledge.

For softgel manufacturing, continued monitoring is particularly important because small changes in raw-material properties or environmental conditions can influence capsule performance. Trending of process data can therefore help identify gradual shifts before they result in specification failures or stability problems.

5.4 Evaluation of Softgel Quality

Quality evaluation of soft gelatin capsules involves a combination of physical, chemical, mechanical, performance, and stability-related tests. These evaluations are designed to confirm that the finished product conforms to established specifications and maintains its intended performance throughout its shelf life.

Physical evaluation generally includes examination of capsule appearance, shape, dimensions, color, surface characteristics, and absence of visible defects. Weight variation and fill-weight uniformity provide important information about dosing consistency,

particularly for liquid and semisolid fills. Shell thickness and dimensional uniformity may also be assessed to ensure reproducible manufacturing.

Chemical quality testing includes identification, assay, content uniformity, degradation-product analysis, and impurity profiling. Appropriate chromatographic and spectroscopic methods are selected according to the API and formulation. For formulations containing oxidation-sensitive or hydrolysis-sensitive drugs, stability-indicating analytical methods are particularly important.

Performance testing generally includes disintegration and dissolution. Dissolution testing is especially important for softgels containing poorly soluble drugs because formulation composition, shell characteristics, and gelatin cross-linking can affect drug release. Damian et al. (2021) reported that dissolution testing of soft gelatin capsules can present unique challenges because changes in the gelatin shell may influence capsule rupture and subsequent drug release.

Mechanical evaluation may include hardness, tensile strength, elasticity, rupture resistance, and deformation characteristics. These parameters are useful for determining whether capsules can withstand manufacturing, packaging, transportation, and handling without cracking or leaking. Moisture content and water activity may also be evaluated because they strongly influence gelatin flexibility and stability.

Microbiological quality should be controlled according to the nature of the product and applicable pharmacopoeial requirements. Finally, stability studies should monitor relevant physical and chemical attributes under long-term and accelerated conditions to establish whether the softgel maintains its intended quality throughout the proposed shelf life.

6. Stability Challenges in Soft Gelatin Capsules

Stability is a critical quality consideration in soft gelatin capsule development because the capsule is a dynamic system in which the gelatin shell and internal fill can undergo physical and chemical changes during processing and storage. Unlike rigid solid dosage forms, shells of softgels contain substantial amounts of water and plasticizers, and their flexible gelatin matrix is sensitive to temperature, relative humidity, moisture migration, oxygen, and interactions with fill components. Consequently, changes occurring during storage may affect shell integrity, drug release, appearance, and chemical stability. Damian et al. (2021) emphasized that changes in gelatin properties, particularly cross-linking, can substantially influence the dissolution behavior of soft gelatin capsules. More recently, Naharros-Molinero et al. (2024) demonstrated that shell composition and environmental conditions can modify the mechanical and thermal properties of softgel systems.

6.1 Physical and Chemical Instability

Physical instability of soft gelatin capsules may manifest as changes in capsule hardness, elasticity, dimensions, surface appearance, moisture content, or shell integrity. The gelatin matrix can become excessively soft and sticky under conditions of high moisture or elevated temperature, whereas excessive moisture loss may produce a brittle shell that is susceptible to cracking during handling. Changes in the physical state of the fill can also affect capsule performance through precipitation, phase separation, crystallization, or changes in viscosity. Naharros-Molinero et al. (2024) reported that variations in gelatin composition and environmental exposure can significantly influence the mechanical behavior of softgel shells. Chemical instability involves degradation of the API, excipients, or shell components through pathways such as oxidation, hydrolysis, photodegradation, and chemical interaction. APIs incorporated into lipidic fills may be particularly susceptible to oxidative degradation when unsaturated lipid components are present. Similarly, reactive degradation products may interact with gelatin and contribute to changes in shell performance. Rowe et al. (2009) emphasized that excipient selection should consider potential chemical interactions and degradation pathways because excipients may influence the stability of the finished pharmaceutical product.

Temperature and humidity are among the most important external factors affecting both physical and chemical stability. Increased temperature can accelerate chemical degradation and alter gelatin mobility, while changes in relative humidity can modify shell moisture and mechanical properties. Therefore, stability assessment should simultaneously monitor API potency, degradation products, dissolution, shell moisture, mechanical integrity, appearance, and fill-shell interactions rather than relying solely on chemical assay.

6.2 Gelatin Cross-Linking

Gelatin cross-linking represents one of the most important stability-related challenges associated with soft gelatin capsules. Gelatin contains various functional groups that can participate in chemical reactions with reactive substances originating from the API, excipients, impurities, or degradation products. Cross-linking produces additional intermolecular bonds within the gelatin matrix, reducing its ability to hydrate and dissolve normally.

Cross-linking can occur through several mechanisms, including reactions involving aldehydes and other reactive carbonyl compounds. Oxidative degradation of certain formulation components may generate reactive species that subsequently interact with gelatin. Environmental conditions such as elevated temperature and humidity can further

influence these reactions. Ofner and Bubnis (1996) demonstrated that aldehyde-mediated cross-linking of gelatin can significantly modify gelatin dissolution behavior, providing an important mechanistic basis for understanding dissolution failures in gelatin-based dosage forms.

The pharmaceutical significance of cross-linking is particularly evident during dissolution testing. A cross-linked gelatin shell may resist hydration and remain partially intact after exposure to dissolution media, potentially delaying release of the encapsulated drug. Damian et al. (2021) reported that gelatin cross-linking is an important consideration in softgel dissolution testing because it may produce delayed or incomplete capsule rupture and consequently alter the observed drug-release profile.

Detection of cross-linking may involve visual examination, dissolution studies, spectroscopic analysis, thermal analysis, mechanical testing, and chemical characterization of reactive species. Preventive strategies include careful excipient selection, control of impurities and reactive degradation products, incorporation of suitable antioxidants where appropriate, optimized manufacturing conditions, and protective packaging. Thus, cross-linking should be considered during both initial compatibility studies and long-term stability investigations.

6.3 Moisture Migration and Shell Brittleness

Moisture plays a fundamental role in determining the physical properties of gelatin shells. The softgel shell contains water as a structural and processing component, and its equilibrium moisture content depends on gelatin composition, plasticizer concentration, fill formulation, packaging, temperature, and relative humidity. Because the shell and fill may have different water activities, water can migrate across the shell-fill interface until equilibrium is approached.

Moisture loss from the shell can reduce gelatin-chain mobility and increase intermolecular interactions, resulting in increased hardness and brittleness. Excessive moisture uptake, in contrast, can increase molecular mobility and produce a softer, more elastic, or sticky shell. Podczek et al. (2013) demonstrated that moisture and plasticizer-related changes can significantly influence the mechanical properties of capsule shells.

Moisture migration may also occur between the shell and fill when the formulation contains hygroscopic or water-rich components. Hydrophilic fill materials can draw water from the gelatin shell, whereas certain aqueous or moisture-containing fills may increase shell hydration. Such redistribution can cause changes in shell thickness, mechanical strength, dissolution, and capsule dimensions during storage.

The problem is particularly important because moisture-related changes may initially remain within acceptable physical limits while gradually affecting drug-release performance. Therefore, monitoring of water content, water activity, mechanical properties, dissolution, and capsule appearance should be incorporated into stability programs. Appropriate control of manufacturing humidity, drying conditions, packaging permeability, and storage environment can minimize moisture-related variability.

6.4 Leakage, Stickiness, and Shell Deformation

Leakage is a major physical failure mode in soft gelatin capsules and can result from inadequate sealing, inappropriate shell composition, excessive internal pressure, mechanical damage, or incompatibility between the fill and shell. Leakage not only results in loss of drug-containing material but can also cause cross-contamination, changes in dose, and deterioration of capsule appearance. Naharro-Molinero et al. (2024) identified shell formulation and processing conditions as important determinants of the mechanical characteristics and integrity of soft gelatin capsules.

Stickiness is another common stability and manufacturing problem. It may occur when the shell retains excessive moisture, when plasticizer concentration is too high, or when capsules are exposed to elevated temperature and humidity. Sticky capsules can adhere to one another or to packaging surfaces, complicating handling and potentially causing deformation or rupture. Conversely, excessive drying can produce brittle shells that crack or fracture during transportation.

Shell deformation can result from inadequate drying, nonuniform moisture distribution, mechanical stress, inappropriate storage temperature, or migration of components between the fill and shell. Changes in the physical state or volume of the fill may also generate internal stresses within the capsule. Cole et al. (2004) discussed the importance of controlling formulation and manufacturing variables to maintain the physical integrity of soft gelatin capsule systems.

6.5 Fill-Shell Interactions

Fill-shell interaction is one of the most complex stability challenges associated with soft gelatin capsules because the internal formulation remains in prolonged contact with the gelatin matrix throughout storage. Components of the fill may diffuse into the shell, while water, plasticizers, or other low-molecular-weight components may migrate in the opposite direction. Such interactions can modify both the physical properties of the shell and the chemical stability of the fill.

Hydrophilic solvents, surfactants, alcohols, polyols, oils, and other formulation components can influence gelatin hydration and plasticization. Certain reactive substances may also interact chemically with gelatin proteins. These interactions can alter shell elasticity, moisture content, dissolution, and mechanical strength. Damian et al. (2021) identified formulation-shell interactions as an important consideration when interpreting softgel dissolution behavior.

Migration of plasticizers is another potential mechanism of instability. Redistribution of glycerol, sorbitol, or related components can modify shell flexibility and may contribute to changes in capsule hardness during storage. Similarly, migration of API or fill components into the shell can affect dose distribution and may produce localized changes in shell properties.

The likelihood and extent of fill-shell interaction depend on the chemical nature of the fill, water activity, pH, solvent composition, molecular size, temperature, shell composition, and storage duration. Consequently, compatibility should be evaluated using both initial studies and accelerated/long-term stability investigations. Analytical techniques such as FTIR, DSC, thermogravimetric analysis, microscopy, chromatographic analysis, and dissolution testing can provide complementary information regarding these interactions.

An effective QbD strategy should therefore incorporate fill-shell compatibility into the initial risk assessment and identify potentially reactive or migration-prone formulation components as high-priority variables. This approach can reduce the likelihood of delayed stability failures and facilitate development of softgel products with predictable performance throughout their intended shelf life.

6.6 API Precipitation or Crystallization

API precipitation or crystallization is a significant stability concern in soft gelatin capsules, particularly for lipid-based formulations, self-emulsifying drug delivery systems (SEDDS), and supersaturated solutions. During storage, changes in temperature, moisture content, solvent composition, or interactions between the fill and shell may reduce the solubility of the active pharmaceutical ingredient (API). As a result, the dissolved drug may precipitate or crystallize out of the formulation. Once crystallization occurs, the drug is no longer present in its intended solubilized state, which can lead to reduced dissolution rate, decreased bioavailability, dose non-uniformity, and visible changes in capsule appearance such as turbidity, sedimentation, or crystal formation. This problem is particularly critical for poorly water-soluble drugs because their enhanced absorption often depends on maintaining the drug in a dissolved form throughout shelf life. Therefore, stability studies must evaluate the

formulation under accelerated and long-term storage conditions to ensure that the API remains physically stable and does not crystallize during the product's intended shelf life.

6.7 Photostability Problems

Photostability refers to the ability of a soft gelatin capsule formulation to resist degradation when exposed to light. Both the gelatin shell and the encapsulated fill material may be susceptible to damage from ultraviolet (UV) and visible light. Exposure to light can cause degradation of light-sensitive APIs, oxidation of lipid-based excipients, discoloration of the capsule shell, changes in odor, and reduction in product potency. In some cases, UV radiation may also induce gelatin cross-linking or alter the physical properties of the shell, leading to brittleness, leakage, or dissolution changes. Softgel formulations containing compounds such as isotretinoin, calcitriol, vitamin A, carotenoids, omega-3 fatty acids, and other oxidation-prone ingredients are especially vulnerable to photodegradation. To minimize these risks, manufacturers often use opaque capsule shells, incorporate antioxidants into the formulation, and package the product in light-resistant blister packs or amber-colored containers. Photostability studies conducted according to ICH Q1B guidelines are essential to demonstrate that the product maintains its quality, safety, and efficacy throughout its shelf life under anticipated storage conditions.

Table: Major Stability Challenges in Soft Gelatin Capsules

Stability challenge	Principal mechanism	Potential quality impact	Key monitoring parameter	Reference
Shell softening	Moisture uptake/plasticization	Loss of mechanical integrity	Moisture, hardness	Naharros-Molinero et al. (2024)
Shell brittleness	Moisture loss	Cracking and rupture	Moisture, elasticity	Podczeczek et al. (2013)
Gelatin cross-linking	Chemical reaction with reactive species	Delayed dissolution	Dissolution, shell integrity	Ofner & Bubnis (1996); Damian et al. (2021)
API degradation	Oxidation/hydrolysis	Reduced potency	Assay, impurities	Rowe et al. (2009)

Fill migration	Diffusion between fill and shell	Composition changes	Chemical/physical analysis	Damian et al. (2021)
Plasticizer migration	Redistribution of plasticizer	Changes in flexibility	Mechanical properties	Naharros-Molinero et al. (2024)
Leakage	Seal failure/mechanical stress	Fill loss	Integrity testing	Cole et al. (2004)
Stickiness	Excess moisture/temperature	Capsule agglomeration	Surface examination	Naharros-Molinero et al. (2024)
Deformation	Moisture/thermal/mechanical stress	Dimensional instability	Dimensions/appearance	Cole et al. (2004)
Dissolution failure	Cross-linking or shell-fill interaction	Altered drug release	Dissolution profile	Damian et al. (2021)
API Precipitation	Change in composition (Solvent ratio) of formulation	Reduces Dissolution	Forced degradation studies are required	Agrasen et al. (2018)
Photostability Problem	Exposure to light causes photochemical reactions	API degradation	Photodegradation studies required	Rowe et al. (2009)

7. Future Perspectives and Conclusion

7.1 Future Perspectives

Future softgel development is expected to increasingly adopt Quality by Design (QbD), Process Analytical Technology (PAT), Design of Experiments (DoE), and predictive modelling to improve formulation and process understanding. Real-time monitoring of moisture, gelatin ribbon properties, fill characteristics, and capsule dimensions may enhance process control and reduce manufacturing variability (Yu et al., 2014; ICH Q10, 2008).

Predictive stability modelling represents another promising area, particularly for understanding the effects of temperature and relative humidity on moisture migration, mechanical properties, leakage, and shelf life. Recent studies demonstrate the potential of combining moisture-sorption data with mechanical analysis for predicting softgel stability

(Pan et al., 2026). Advanced shell formulations and improved moisture-, oxygen-, and light-barrier packaging may further enhance product stability (Naharros-Molinero et al., 2024; Damian et al., 2021).

The integration of artificial intelligence, machine learning, advanced analytical technologies, and digital manufacturing may further accelerate formulation optimization and lifecycle management. These technologies can support prediction of fill-shell compatibility, identification of critical variables, stability assessment, and continuous process improvement. Overall, combining these emerging technologies with established QbD principles can enable more predictive, robust, efficient, and sustainable softgel development.

Overall, the integration of QbD with PAT, advanced DoE, predictive modelling, intelligent packaging, advanced analytical characterization, and digital technologies represents a promising direction for the next generation of softgel development. These approaches have the potential to transform softgel development from an empirical activity into a more predictive, efficient, and scientifically controlled process.

7.2 Conclusion

Soft gelatin capsules represent a versatile and patient-friendly dosage form capable of accommodating solutions, suspensions, emulsions, lipid-based formulations, and semisolid fills. Their ability to enhance the delivery of poorly water-soluble drugs and provide convenient unit-dose administration has contributed substantially to their pharmaceutical importance. However, the simultaneous presence of a moisture-sensitive gelatin shell and a chemically diverse fill formulation creates a complex system that is susceptible to environmental, formulation, manufacturing, packaging, and storage-related variability.

The application of Quality by Design provides a systematic strategy for addressing these challenges. By defining the QTPP, identifying CQAs, evaluating CMAs and CPPs, applying structured risk assessment and DoE, establishing a suitable design space, and implementing an appropriate control strategy, softgel development can be transformed from a largely empirical process into a science- and risk-based development program.

Stability must be considered throughout the product lifecycle rather than only during final shelf-life testing. Temperature, relative humidity, light, oxygen, formulation composition, shell characteristics, packaging, transportation, and storage conditions may interact and influence shell integrity, drug stability, dissolution, and overall product performance. Consequently, robust formulation design, appropriate manufacturing controls, protective packaging, and scientifically justified stability programs are essential for maintaining softgel quality throughout the intended shelf life.

In conclusion, the future of soft gelatin capsule development lies in the integration of QbD, risk-based development, DoE, PAT, predictive stability modelling, advanced analytical technologies, innovative shell materials, optimized packaging, and digital manufacturing tools. Such integration can improve formulation robustness, reduce manufacturing variability, strengthen stability prediction, and support continuous improvement throughout the product lifecycle. Ultimately, a QbD-based approach can enable the development of softgel products that are stable, reproducible, scalable, patient-centered, and capable of consistently delivering the intended therapeutic performance throughout their shelf life.

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9. Conflict of Interest

The author declare that there is no conflict of interest related to the publication of this article.

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