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Review Article

Comprehensive Review on Soft Gelatin Capsules: Industrial Manufacturing, Technological Advancements, and Regulatory Perspectives

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Abstract

Soft gelatin capsules (SGCs) are versatile and the most established oral dosage forms in pharmaceutical and nutraceutical product development due to their ability to facilitate the delivery of liquid and semisolid formulations, improve patient acceptability, and enhance the bioavailability of poorly water-soluble drugs. Over the years, SGC technology has evolved from a conventional encapsulation approach into an advanced drug delivery platform capable of supporting complex formulation strategies and therapeutic applications. Current review aims to comprehensively examines the historical development, classification, composition, physicochemical characteristics, advantages, and limitations of soft gelatin capsules, with particular emphasis on the functional roles of gelatin, plasticizers, fill materials, and auxiliary excipients in determining product quality and performance. This review further discusses compatibility assessment, formulation development, and stability considerations, together with critical aspects of industrial manufacturing, including rotary die encapsulation, ribbon formation, encapsulation mechanisms, drying processes, and moisture control. Quality-focused manufacturing approaches, such as Quality by Design (QbD), Process Analytical Technology (PAT), process optimization, and in-process quality control, are highlighted for their contributions to robust and efficient production. Important characterization methods, including mechanical evaluation, in vitro evaluation studies and stability studies, are also summarized. In addition, emerging applications involving lipid-based formulations, self-emulsifying drug delivery systems, controlled-release technologies, and bioavailability enhancement strategies are critically reviewed. Recent advancements in digital manufacturing, non-gelatin shell materials, nanotechnology-based systems, advanced sealing technologies, automation, and three-dimensional (3D) printing are discussed in the context of next-generation capsule development. Regulatory requirements, cGMP compliance, validation practices, sustainability considerations, intellectual property trends, and future industrial opportunities are also addressed, providing a comprehensive perspective on the current status and future direction of soft gelatin capsule technology.

Keywords: Soft gelatin capsules; Rotary die encapsulation; Quality by Design (QbD); Lipid-based drug delivery systems; Regulatory compliance.

1.0 INTRODUCTION

Soft gelatin capsules (SGCs) are a well-established pharmaceutical dosage form widely employed for the delivery of liquid, semisolid, suspension, and lipid-based formulations. They consist of a hermetically sealed, one-piece, flexible gelatin shell enclosing a precisely measured fill material. Unlike conventional hard capsules, soft gelatin capsules are formed, filled, and sealed simultaneously in a continuous manufacturing operation, most commonly using rotary die encapsulation technology. This unique design offers several formulation and manufacturing advantages, making SGCs an important platform for both pharmaceutical and nutraceutical products [1,2].

The growing prevalence of poorly water-soluble drug molecules has increased the significance of soft gelatin capsules in modern drug delivery. A substantial proportion of newly developed drug candidates exhibit low aqueous solubility and variable oral absorption, presenting challenges for formulation scientists[3]. Soft gelatin capsule technology provides an effective solution by enabling incorporation of drugs in solubilized, suspended, or lipid-based systems, thereby improving dissolution characteristics and enhancing oral bioavailability. Consequently, SGCs are particularly suitable for Biopharmaceutics Classification System (BCS) Class II and Class IV compounds, as well as highly lipophilic drugs, high-molecular-weight molecules, low-melting-point substances, and drugs requiring precise dose administration[4]. Beyond bioavailability enhancement, soft gelatin capsules offer several additional benefits, including improved content uniformity, protection of sensitive active

pharmaceutical ingredients (APIs) from environmental factors, reduced gastrointestinal irritation, ease of swallowing, and enhanced patient compliance[5]. The ability to encapsulate solutions, emulsions, and semisolid formulations further enables flexible formulation design and supports modified or targeted drug delivery approaches. These attributes have facilitated the successful development of numerous therapeutic products including anticancer, antimicrobial, antiviral, cardiovascular, hormonal, nutritional, and vaccine-related applications[6,7].

Recent advances in formulation science, manufacturing automation, process analytical technologies, and quality-by-design principles have further expanded the capabilities of soft gelatin capsule systems[8,9]. Moreover, the integration of lipid-based drug delivery systems, novel shell materials, nanotechnology, and personalized medicine approaches has transformed SGCs from conventional dosage forms into sophisticated drug delivery platforms[10,11]. As a result, soft gelatin capsules continue to play a critical role in pharmaceutical innovation, offering opportunities to address complex formulation challenges while meeting evolving regulatory and patient-centered requirements[12].

1.1 Historical Evolution of Soft Gelatin Capsules

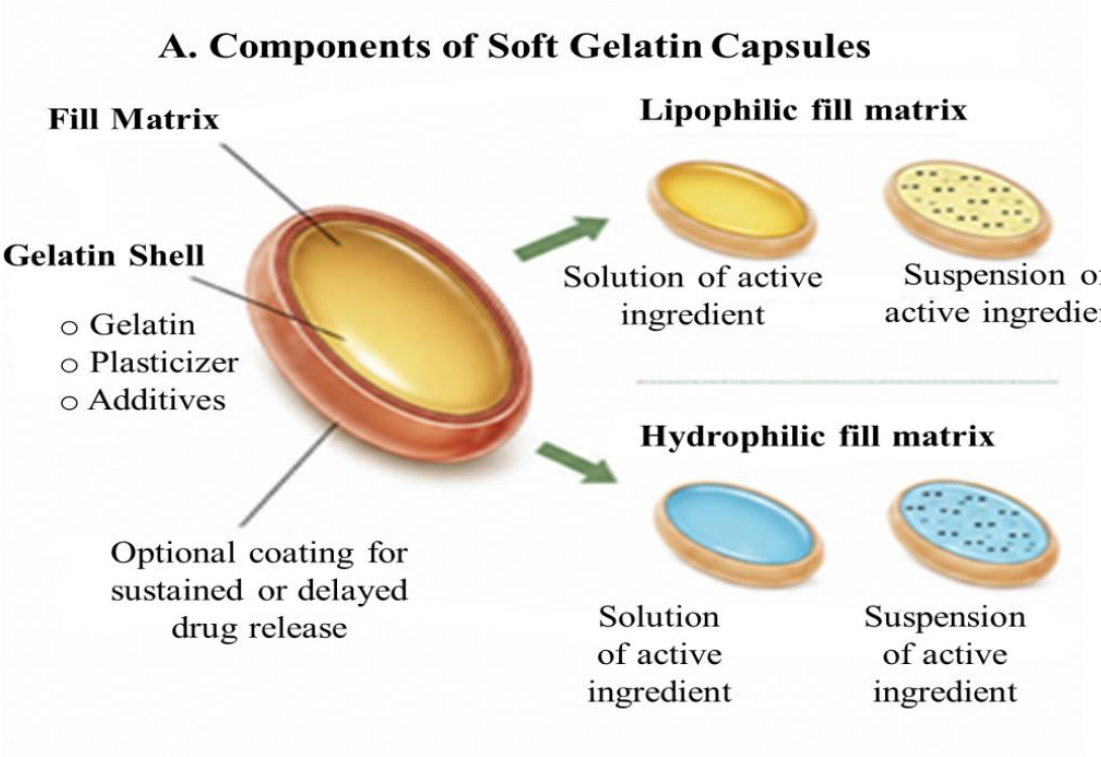
The development of SGCs represents a significant milestone in the evolution of pharmaceutical dosage forms. The concept of encapsulating liquid medicines in gelatin shells dates back to the early nineteenth century, when attempts were made to improve the palatability, stability, and dosing accuracy of medicinal oils and liquid preparations. In 1834, Mothes and Dublanc patented one of the earliest gelatin encapsulation techniques, laying the foundation for modern capsule technology. Subsequent innovations by pharmaceutical pioneers improved manufacturing efficiency and expanded the therapeutic applications of encapsulated dosage forms. A major breakthrough occurred during the twentieth century with the introduction of the rotary die encapsulation process by Robert P. Scherer in the 1930s. This technology enabled the continuous formation, filling, and sealing of soft gelatin capsules in a single operation, significantly enhancing production speed, product uniformity, and scalability. The rotary die process remains the predominant manufacturing method used in commercial soft gelatin capsule production today [2,13].

In early days of SGC development, soft gelatin capsules were primarily utilized for the delivery of vitamins, fish oils, and other lipid-soluble compounds. However, advances in formulation science gradually expanded their application to pharmaceutical products containing active ingredients in solution, suspension, and emulsion forms. The growing number of poorly water-soluble drug candidates further accelerated the adoption of SGC technology due to its ability to enhance drug dissolution and oral bioavailability through lipid-based and solubilized formulations[14,15]. Over the past few decades, soft gelatin capsule technology has evolved from a simple encapsulation system into a sophisticated drug delivery platform. Integration of lipid-based drug delivery systems, self-emulsifying formulations, controlled-release technologies, and advanced excipient systems has broadened their therapeutic utility. More recently, developments in automation, process analytical technology (PAT), Quality by Design (QbD), non-gelatin shell materials, nanotechnology, and personalized medicine have further transformed the manufacturing and performance capabilities of SGCs[16,17]. Consequently, soft gelatin capsules continue to occupy a prominent position in modern pharmaceutical development, offering versatile solutions for improving drug delivery, product stability, and patient compliance.

2.0 COMPOSITION, PHYSICOCHEMICAL PROPERTIES, TYPES AND CLASSIFICATION

SGCs are single-unit dosage forms consisting of a hermetically sealed, flexible shell that encloses a liquid, semisolid, suspension, or self-emulsifying fill formulation. Their unique structural design allows the simultaneous incorporation of APIs and formulation excipients within a one-piece capsule shell, thereby providing protection against environmental factors and facilitating efficient drug delivery. The composition and physicochemical characteristics of both the shell and fill material play critical roles in determining capsule integrity, stability, manufacturability, and in vivo performance[18].

Composition of Soft Gelatin Capsules **-** A typical soft gelatin capsule comprises two major components: the capsule shell and the fill formulation. The capsule shell primarily consists of gelatin, water, and plasticizers **Figure 1**. Gelatin serves as the principal film-forming material and imparts elasticity, strength, and sealing properties to the capsule. Plasticizers such as glycerine, sorbitol, or combinations thereof are incorporated to improve flexibility and reduce brittleness. Water functions as a processing aid and contributes to the mechanical properties of the shell. Additional excipients including opacifiers, colorants, preservatives, flavouring agents, sweeteners, and antioxidants may be incorporated depending on formulation requirements. The fill formulation may contain APIs dissolved or dispersed in suitable vehicles such as vegetable oils, medium-chain triglycerides, polyethylene glycols, surfactants, co-solvents, or lipid-based systems. The choice of fill composition is governed by drug solubility, stability, compatibility with gelatin, and desired release characteristics. Modern formulations frequently utilize lipid-based carriers and self-emulsifying systems to enhance the oral absorption of poorly water-soluble drugs[19,20].



B. Shapes and Sizes of Soft gelatin capsules

Shape	Description	Typical Size	Fill volume (Approx.)
	3 Oblong - 22 Oblong	14.2 mm - 33.5 mm	0.142 mL- 1.355 mL
	2 oval - 40 oval	12.3 mm - 24.0 mm	0.092 mL- 2.454 mL
	2 round - 110 round	7.5 mm - 20.0 mm	0.074 mL- 6.160 mL
Fish tail	Teardrop	Twist-off	Rectangular

Figure 1: Illustration of A). Components of Soft gelatin capsules; B). Examples of size and shape parameters of soft gelatin capsules

Physicochemical Properties **-** The performance of soft gelatin capsules is influenced by several physicochemical properties of both the shell and the encapsulated formulation.

- *Mechanical Properties:* Capsule shells must possess adequate tensile strength, elasticity, and flexibility to withstand handling, packaging, transportation, and storage without cracking or deformation.

- *Moisture Content:* Water acts as a plasticizing agent within the gelatin matrix. Optimal moisture content is required in SGC. Excessive moisture may result in capsule deformation and microbial growth, whereas insufficient moisture can lead to shell brittleness and cracking.

- *Permeability Characteristics:* Gelatin shells exhibit selective permeability toward water vapor and gases. Therefore, controlling environmental humidity is essential for maintaining capsule stability throughout its shelf life.

- *Disintegration and Dissolution Behavior:* Upon oral administration, the shell rapidly hydrates and disintegrates by dissolving in gastrointestinal fluids, releasing the encapsulated formulation. The rate of drug release is influenced by shell composition, fill viscosity, and overall formulation characteristics.

- *Chemical Stability:* Interactions between gelatin, plasticizers, active ingredients, and excipients can affect product stability. Factors such as pH, oxidation, cross-linking reactions, and moisture migration shall be carefully controlled during formulation development for stabilized products of SGC.

Types of Soft Gelatin Capsules – Soft gelatin capsules can be classified based on the nature of the fill formulation and intended therapeutic application.

Based on Fill Composition

Liquid-Filled Capsules: Contain drug substances dissolved in oils, co-solvents, or hydrophilic vehicles and represent the most common type of soft gelatin capsule.

Suspension-Filled Capsules: Contain finely dispersed solid particles suspended within a suitable liquid vehicle when complete drug solubilization is not feasible.

Semisolid-Filled Capsules: Utilize semisolid matrices that liquefy during encapsulation and solidify upon cooling, providing improved stability for specific formulations.

Self-Emulsifying and Self-Microemulsifying Capsules: Contain lipid-based systems that spontaneously form emulsions or microemulsions upon contact with gastrointestinal fluids, enhancing drug solubilization and absorption.

Based on Therapeutic Function - Immediate-release, Modified-release, Controlled-release, Targeted drug delivery, Nutraceutical and dietary supplement soft gelatin capsules

Based on Capsule Shape - Commercial soft gelatin capsules are available in a variety of shapes and sizes, including spherical, oval, oblong, tube-shaped, and specialty configurations designed to optimize dose delivery and product differentiation.

Classification of Soft Gelatin Capsules

Soft gelatin capsules can be broadly classified into Conventional Soft Gelatin Capsules – are designed for immediate drug release and absorption; Lipid-Based Soft Gelatin Capsules – incorporating oils, surfactants, and solubilizers to improve bioavailability; Modified-Release Soft Gelatin Capsules – engineered to achieve delayed, sustained, or controlled drug release purpose; Specialty Soft Gelatin Capsules – developed for targeted delivery, combination therapies, and advanced therapeutic applications; Nutraceutical Soft Gelatin Capsules – used for vitamins, minerals, omega fatty acids, herbal extracts, and dietary supplements. The increasing prevalence of poorly soluble drug molecules and the demand for patient-friendly dosage forms have expanded the utilization of soft gelatin capsules across pharmaceutical, nutraceutical, and biotechnology sectors, reinforcing their importance as a versatile drug delivery platform.

2.1 Advantages and Limitations

Soft gelatin capsules offer several formulation, manufacturing, and therapeutic advantages that have contributed to their widespread adoption. However, certain formulation and processing challenges remain associated with this dosage form.

Advantages

- Improved oral bioavailability of poorly water-soluble and lipophilic drug molecules.

- Capability to encapsulate liquids, semisolids, suspensions, and lipid-based formulations.

- Enhanced content uniformity and dose accuracy, particularly for low-dose and potent drugs.

- Rapid shell disintegration leading to faster drug release and onset of action.

- Improved patient compliance due to ease of swallowing and aesthetic appearance.

- Protection of sensitive active ingredients from oxidation, light exposure, and environmental contamination.

- Reduced dust generation and handling issues compared with powder-filled dosage forms.

- Suitability for drugs with narrow therapeutic indices requiring precise dose control.

- Compatibility with self-emulsifying and advanced lipid-based drug delivery systems.

- Improved product differentiation through customization of capsule size, shape, color, and branding.

Limitations

- Sensitivity of gelatin shells to environmental humidity and temperature variations.

- Potential incompatibility between gelatin and certain aldehydes, reactive compounds, or hygroscopic materials.

- Risk of shell cross-linking during storage, potentially affecting dissolution performance.

- Higher manufacturing and equipment costs compared with conventional tablet formulations.

- Limited suitability for highly aqueous, volatile, or chemically reactive fill formulations.
- Requirement for stringent moisture control during production and storage.
- Potential challenges associated with shell leakage, deformation, and migration of formulation components.
- Dependence on animal-derived gelatin, which may raise religious, ethical, or dietary concerns.
- Additional regulatory and formulation considerations for non-gelatin alternatives and novel delivery systems.

Despite these limitations, continuous advancements in formulation science, encapsulation technologies, shell materials, and process control strategies have significantly enhanced the functionality and industrial applicability of soft gelatin capsules, making them one of the most effective platforms for the delivery of complex pharmaceutical and nutraceutical products.

3.0 RAW MATERIALS USED IN SOFT GELATIN CAPSULE FORMULATION

The performance, stability, manufacturability, and therapeutic effectiveness of soft gelatin capsules are largely determined by the quality and functionality of the raw materials used in both the capsule shell and fill formulation. The selection of appropriate materials is critical because each component influences capsule formation, mechanical integrity, compatibility, drug release behavior, and shelf-life. SGC formulations generally comprise shell-forming materials, plasticizers, water, APIs, solvents, lipid vehicles, surfactants, antioxidants, and other functional excipients. A comprehensive understanding of these materials is essential for the successful development of robust and reproducible SGC products.

3.1 Gelatin: Sources, Properties, and Functional Characteristics

Gelatin is the principal structural component of conventional soft gelatin capsule shells and serves as the primary film-forming material. It is a natural protein obtained through the partial hydrolysis of collagen, which is predominantly derived from animal connective tissues such as bovine hides, porcine skin, and bovine bones. Depending on the extraction process, gelatin is classified into Type A gelatin, produced through acid hydrolysis, and Type B gelatin, obtained through alkaline treatment **Table 1**. These gelatin types differ in their isoelectric point, viscosity, and gelling behavior, influencing capsule shell characteristics.

Table 1: Comparative parameters of different gelatin types used in manufacturing of soft gelatin capsule

Property	Type A Gelatin	Type B Gelatin
Raw Material	Porcine skin, bovine hide	Bovine bone, bovine hide
Extraction Method	Acid treatment	Alkaline treatment
Isoelectric Point (pI)	7.0–9.0	4.8–5.2
Typical pH Range	4.5–6.0	5.0–6.5
Gel Formation Rate	Faster	Slower
Clarity	Higher	Moderate
Elasticity	Excellent	Good
Mechanical Strength	High	Moderate to High
Compatibility with Plasticizers	Excellent	Excellent
Typical use in Softgels	Most common	Frequently blended with Type A
Regulatory acceptance	Widely accepted globally	Widely accepted globally

The widespread use of gelatin in capsule manufacturing is attributed to its unique physicochemical properties, including excellent film-forming ability, thermo-reversible gelation, elasticity, transparency, biocompatibility, and biodegradability. When dissolved in water at elevated temperatures and subsequently cooled, gelatin forms a three-dimensional gel network capable of producing strong yet flexible capsule shells. This characteristic enables efficient encapsulation and sealing during industrial processing. Several physicochemical parameters influence gelatin performance, including bloom strength, viscosity, molecular weight distribution, gel strength, moisture content, and isoelectric point **Table 2**.

Table 2: Representative Pharmaceutical Gelatin Grades Used in Soft Gelatin Capsule Manufacturing and Their Functional Properties

Commercial Gelatin Grade	Source	Gelatin Type	Extraction Method	Bloom Strength (g)	Viscosity (mPa·s)	pH	Conductivity (mS/cm)	Isoelectric Point (pI)	Functional Characteristics	Typical Pharmaceutical Applications
Rousselot 160 LB B	Bovine limed bone	Type B	Alkaline	145–175	3.5–5.5	5.3–6.2	<1.0	4.8–5.2	Good film-forming ability, moderate elasticity, excellent shell stability	Soft gelatin capsules, hard capsules
Rousselot 200 AH 8	Bovine hide	Type A	Acid	175–205	4.5–6.5	5.0–6.2	<1.0	7.0–9.0	High clarity, good sealing performance, rapid gel formation	Pharmaceutical softgels
Rousselot 200 BH	Bovine hide	Type B	Alkaline	175–205	4.0–6.0	5.6–6.2	<1.0	4.8–5.2	Improved shell strength and mechanical stability	Soft capsule shells
Rousselot 200 H 6	Bovine hide	Type A	Acid	175–205	4.5–6.5	5.0–6.0	<1.0	7.0–9.0	Excellent processability and ribbon formation	Rotary die encapsulation
Rousselot 250 PS 8	Porcine skin	Type A	Acid	240–250	5.0–7.5	4.5–6.9	<0.4	7.0–9.0	High gel strength, superior elasticity and sealing properties	Premium soft gelatin capsules
Gelita 170 LB Type B NF SRM Free Bone	Bovine limed bone	Type B	Alkaline	155–185	3.5–5.5	5.3–6.0	<1.0	4.8–5.2	Consistent viscosity and excellent shell integrity	Pharmaceutical softgels
Gelita RXL 150	Porcine skin	Type A	Acid	140–160	3.0–5.0	4.8–5.8	<0.5	7.0–9.0	Good flexibility and ribbon quality	Soft capsule production
Gelita RXL 200	Porcine skin	Type A	Acid	190–210	4.0–6.0	4.8–5.8	<0.5	7.0–9.0	High elasticity and sealing efficiency	Pharmaceutical and nutraceutical softgels
Nitta Gelatin Type A 250 Bloom	Porcine skin	Type A	Acid	240–260	5.0–7.0	4.5–6.0	<0.5	7.0–9.0	High mechanical strength and clarity	Soft capsules and specialty formulations
Nitta Gelatin Type B 180 Bloom	Bovine bone	Type B	Alkaline	170–190	4.0–5.5	5.0–6.0	<1.0	4.8–5.2	Enhanced stability and reduced hygroscopicity	Pharmaceutical encapsulation
Weishardt Pharmagel A220	Porcine skin	Type A	Acid	210–230	4.5–6.5	4.8–5.8	<0.5	7.0–9.0	Excellent film strength and elasticity	Soft gelatin capsule shell production
Weishardt Pharmagel B180	Bovine bone	Type B	Alkaline	170–190	3.5–5.5	5.2–6.2	<1.0	4.8–5.2	Good shell robustness and processing stability	Pharmaceutical soft capsules

Bloom strength is particularly important because it reflects the mechanical strength of the gelatin gel and directly affects shell rigidity, elasticity, and processing behavior. Gelatin with appropriate bloom strength ensures adequate capsule integrity while maintaining flexibility during manufacturing and storage[21]. Functionally, gelatin provides structural support, maintains shell elasticity, protects encapsulated ingredients from external environmental factors, and contributes to rapid disintegration upon ingestion. Furthermore, its ability to form a hermetically sealed shell minimizes oxygen exposure and moisture ingress, thereby enhancing product stability. Despite these advantages, concerns related to animal origin, religious restrictions, dietary preferences, and transmissible animal diseases have stimulated research into alternative shell materials, including hydroxypropyl methylcellulose (HPMC), pullulan, starch derivatives, carrageenan, and other plant-based polymers.

3.2 Plasticizers and Their Role in Capsule Shell Formation

Plasticizers are indispensable components of SGC shells and are incorporated to modify the mechanical properties of gelatin films. Their primary function is to reduce intermolecular interactions between gelatin chains, thereby increasing flexibility, elasticity, and resistance to brittleness. Without plasticizers, gelatin shells would become rigid, fragile, and susceptible to cracking during manufacturing, handling, and storage. Plasticizers function by inserting themselves between adjacent polymer chains, increasing molecular mobility and lowering the glass transition temperature of the gelatin matrix. This results in enhanced flexibility and improved shell performance under varying environmental conditions.

Glycerin and sorbitol are the most commonly used plasticizers in soft gelatin capsule manufacturing. Glycerin imparts excellent flexibility and softness, making it suitable for capsules requiring enhanced elasticity. Sorbitol, either alone or in combination with glycerin, provides improved dimensional stability and reduced moisture sensitivity. The choice and concentration of plasticizer significantly influence shell hardness, elasticity, moisture content, disintegration characteristics, and long-term stability. The gelatin-to-plasticizer ratio represents a critical formulation parameter. Excessive plasticizer concentrations may lead to soft, sticky, or deformed capsules, whereas insufficient levels can result in brittle shells prone to cracking. Therefore, optimization of plasticizer content is essential to achieve the desired balance between flexibility and mechanical strength. Beyond mechanical modification, plasticizers also influence moisture migration, shell permeability, and compatibility with fill materials. Careful selection of plasticizers is required to ensure consistent product quality and prevent adverse interactions during storage.

3.3 Fill Formulations for Soft Gelatin Capsules

The fill formulation constitutes the therapeutically active portion of the SGC and plays a decisive role in drug release, absorption, stability, and bioavailability. One of the major advantages of SGC technology is its ability to accommodate a wide range of liquid, semisolid, and suspension-based formulations that are difficult to formulate as conventional solid dosage forms. The selection of fill materials depends on the physicochemical properties of the API, including solubility, stability, melting point, dose, and therapeutic requirements. Drugs may be incorporated as true solutions, suspensions, emulsions, semisolid dispersions, or lipid-based systems depending on formulation objectives. Lipid-based formulations have gained significant importance because of their ability to improve the oral absorption of poorly water-soluble drugs. Common lipid vehicles include vegetable oils, medium-chain triglycerides, long-chain triglycerides, fatty acid esters, and phospholipids. These systems facilitate drug solubilization within the gastrointestinal tract and may promote lymphatic transport, thereby reducing first-pass metabolism. Hydrophilic solvents such as polyethylene glycols, propylene glycol, and glycerin are also employed to dissolve or disperse active ingredients. In addition, surfactants and co-solvents may be incorporated to improve drug solubility and maintain formulation stability. Modern SGC products increasingly utilize advanced lipid-based drug delivery systems, including self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), and nanoemulsion-based formulations[22]. These technologies generate fine oil-in-water dispersions upon contact with gastrointestinal fluids, resulting in enhanced dissolution, improved absorption, and reduced variability in drug exposure. An ideal fill formulation should exhibit chemical stability, adequate flow properties, compatibility with the capsule shell, and resistance to leakage, precipitation, or phase separation throughout the product's intended shelf life.

3.4 Excipients Used in Soft Gelatin Capsule Manufacturing

In addition to gelatin and plasticizers, a variety of functional excipients are incorporated into SGC formulations to optimize manufacturing performance, stability, appearance, and therapeutic efficacy. These excipients may be included in either the capsule shell or the fill formulation depending on their intended function. Water serves as a critical processing component in capsule shell manufacture by facilitating gelatin hydration and controlling shell rheology. However, its concentration must be carefully regulated because excessive moisture can compromise capsule stability, while insufficient moisture may result in brittleness. Colorants and pigments are commonly incorporated to enhance product identification, brand differentiation, and patient acceptance. Opacifying agents such as titanium dioxide or alternative inorganic pigments may be employed to protect light-sensitive drugs from photodegradation. Antioxidants, including butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tocopherols, and ascorbyl derivatives, are frequently used to prevent oxidative degradation of susceptible active ingredients and lipid vehicles. Chelating agents such as

ethylenediaminetetraacetic acid (EDTA) may further enhance oxidative stability by sequestering trace metal ions. Surfactants play a vital role in improving wetting, solubilization, emulsification, and dispersion of poorly soluble drugs. Common examples include polysorbates, polyoxylglycerides, and polyethylene glycol derivatives. Co-solvents are frequently added to increase drug solubility and maintain formulation homogeneity. Preservatives may be incorporated when necessary to inhibit microbial growth, particularly in formulations containing higher moisture levels. Flavoring agents and sweeteners are occasionally utilized in chewable or nutraceutical soft gelatin products to improve palatability.

The careful selection and optimization of excipients are essential for achieving desired product performance, ensuring compatibility among formulation components, maintaining capsule integrity, and supporting long-term product stability. As SGC technologies continue to evolve, excipient innovation remains a key driver for improving formulation flexibility, manufacturing efficiency, and therapeutic outcomes.

4.0 FORMULATION DEVELOPMENT STRATEGIES

The successful development of SGCs requires a systematic approach that integrates drug properties, excipient selection, shell-fill compatibility, manufacturing feasibility, and product stability. Formulation development for soft gelatin capsules represents a multidisciplinary process involving pharmaceutical technology, material science, process engineering, and quality assurance principles.

4.1 Compatibility Studies and Stability Considerations

Compatibility assessment is a critical component of SGC development because undesirable interactions between the API, excipients, and capsule shell can adversely affect product quality, efficacy, and shelf life. Comprehensive compatibility studies are therefore conducted during the early stages of formulation development to identify potential physicochemical and chemical incompatibilities **Figure 2A**. Drug-excipient compatibility is commonly evaluated using analytical techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and chromatographic methods. These investigations help identify interactions that may alter drug stability, solubility, crystallinity, or release characteristics. A unique aspect of SGC formulation is shell-fill compatibility. Certain formulation components, particularly volatile solvents, aldehydes, reactive compounds, and highly hygroscopic materials, may interact with gelatin, resulting in shell softening, brittleness, leakage, discoloration, or cross-linking. Cross-linking is of particular concern because it may reduce capsule disintegration and dissolution performance. Stability considerations extend beyond chemical degradation to include physical changes such as phase separation, precipitation, sedimentation, moisture migration, and changes in shell mechanical properties. Environmental factors including temperature, humidity, oxygen exposure, and light can significantly influence product stability[23]. Therefore, accelerated and long-term stability studies are conducted in accordance with regulatory guidelines to establish appropriate storage conditions and shelf-life specifications. A robust stability strategy should ensure the preservation of capsule appearance, shell integrity, drug potency, dissolution behavior, and microbiological quality throughout the product lifecycle.

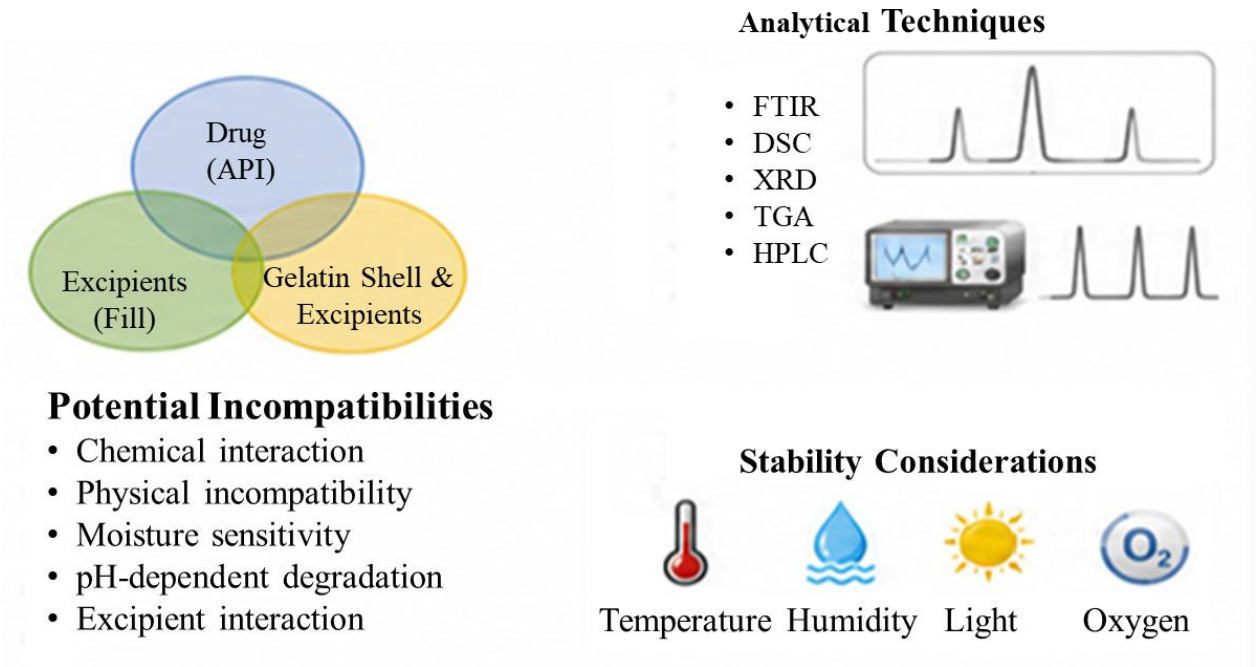


Figure 2A: Illustration of compatibility studies and stability, B). Industrial manufacturing process for soft gelatin capsules

4.2 Industrial Manufacturing Process

The industrial manufacture of SGCs is a highly specialized operation designed to produce capsules with consistent quality, uniform fill weight, and reliable sealing characteristics. Although equipment configurations may vary among manufacturers, the overall process generally consists of gelatin preparation, fill formulation preparation, encapsulation, drying, inspection, and packaging **Figure 2B**. The manufacturing process begins with the preparation of the gelatin mass, where gelatin, plasticizers, purified water, and optional additives are mixed under controlled temperature conditions to produce a homogeneous molten mass. Simultaneously, the fill formulation is prepared by dissolving or dispersing the API in suitable solvents, oils, surfactants, or lipid-based vehicles. Following preparation, both shell and fill materials are transferred to the encapsulation system, where capsule formation, filling, and sealing occur as a continuous operation. The resulting capsules are subsequently subjected to controlled drying processes to achieve the desired moisture content and mechanical properties. After drying, capsules undergo sorting, inspection, polishing, and quality evaluation to ensure compliance with predefined specifications. Final products are then packaged in moisture-protective containers or blister systems designed to preserve stability during storage and distribution. The industrial manufacturing process requires strict control of temperature, humidity, mixing conditions, fill viscosity, and encapsulation parameters to achieve reproducible product quality and regulatory compliance.

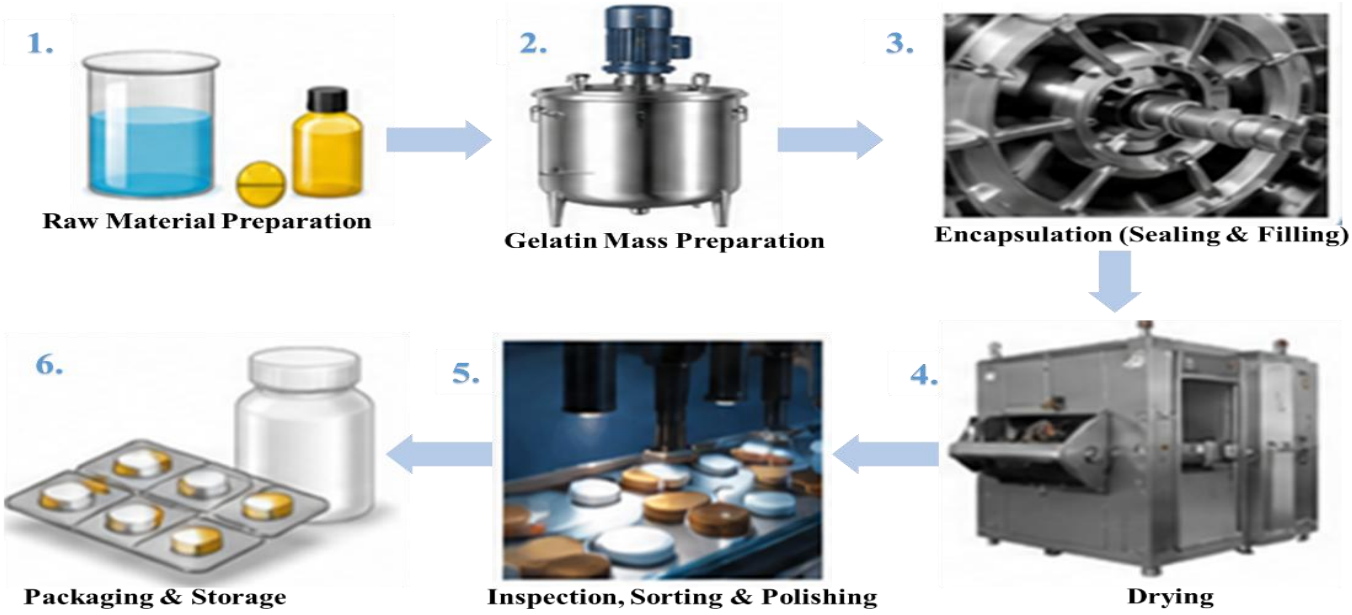


Figure 2B: Illustration of industrial manufacturing process for soft gelatin capsules

4.3 Rotary Die Encapsulation Technology

Rotary die encapsulation is the most widely employed manufacturing technology for commercial SGC production. Originally developed by Robert P. Scherer, this process revolutionized capsule manufacturing by enabling the simultaneous formation, filling, and sealing of soft gelatin capsules in a continuous and highly efficient operation **Figure 3**. In the rotary die process, two gelatin ribbons are continuously fed from opposite sides of the encapsulation machine. As the ribbons converge between rotating die rolls, the fill formulation is injected through a precisely controlled wedge assembly positioned between the ribbons. Simultaneous application of pressure and heat causes the gelatin ribbons to fuse and form sealed capsules containing the desired fill volume. The rotary dies determine capsule shape, size, and dimensions, allowing manufacturers to produce a wide variety of capsule configurations, including oval, oblong, round, tube-shaped, and customized designs. The technology provides excellent fill weight accuracy, high production throughput, minimal product wastage, and superior sealing efficiency. Modern rotary die systems incorporate automated controls, precision metering pumps, real-time process monitoring, and computerized operating platforms to enhance process consistency and reduce manufacturing variability[24]. These advancements have significantly improved productivity while supporting contemporary quality-by-design and process analytical technology initiatives.

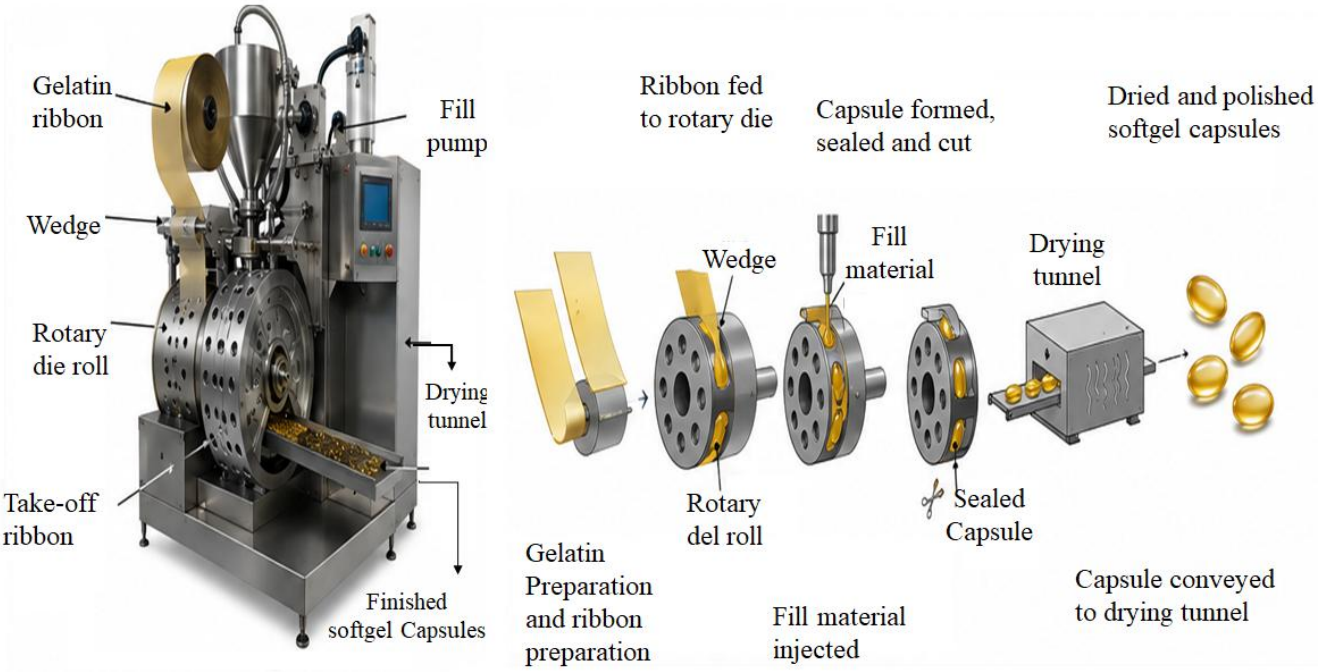


Figure 3: Schematic representation of Rotary die encapsulation technology and its working principle

4.4 Ribbon Formation and Encapsulation Mechanism

Ribbon formation represents a critical stage in SGC manufacturing because the physical properties of the gelatin ribbons directly influence capsule quality and process performance. Uniform ribbon thickness, elasticity, temperature, and moisture content are essential for successful encapsulation and sealing **Figure 4**. The gelatin mass is continuously pumped into heated spreader boxes where it is distributed onto rotating cooling drums. As the gelatin film contacts the cooled drum surface, it solidifies into thin, flexible ribbons of controlled thickness. These ribbons are subsequently transported to the encapsulation zone while maintaining carefully controlled temperature and moisture conditions. During encapsulation, the gelatin ribbons converge at the rotary die assembly. Simultaneously, the fill formulation is introduced through a metered injection system. Mechanical pressure generated by the rotating dies shapes the capsule, while localized heat and compression create a hermetic seal around the fill material. The efficiency of the encapsulation mechanism depends on several process variables, including ribbon thickness, gelatin viscosity, ribbon temperature, fill viscosity, injection pressure, and die-roll alignment. Inadequate control of these parameters may result in defects such as leakage, incomplete sealing, malformed capsules, air entrapment, or fill weight variability. A thorough understanding of ribbon dynamics and encapsulation behavior is therefore essential for achieving robust manufacturing performance and consistent product quality.

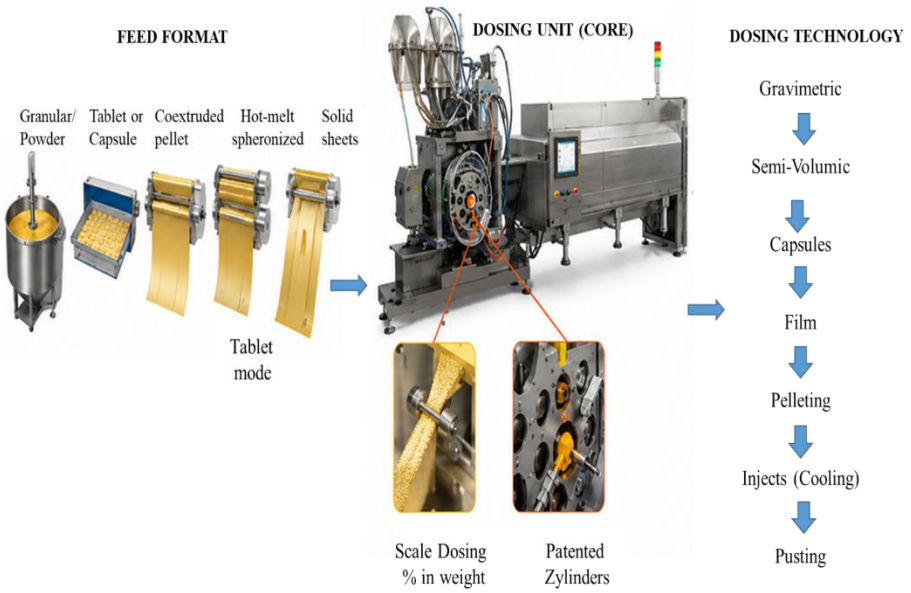


Figure 4: Process flow and machine illustration of Ribbon formation and encapsulation mechanism

4.5 Drying Techniques and Moisture Control

Drying is a critical post-encapsulation operation that removes excess water from the capsule shell and establishes the final mechanical properties required for product stability. Freshly manufactured soft gelatin capsules typically contain relatively high moisture levels and therefore require controlled drying to achieve equilibrium moisture content. Drying generally occurs in two stages. The first stage involves tumble drying, where capsules are placed in rotating drying drums supplied with conditioned air. This step rapidly removes surface moisture and prevents capsule adhesion or deformation. Following tumble drying, capsules undergo secondary drying in controlled drying tunnels or drying rooms where temperature and relative humidity are carefully regulated. The objective of drying is to achieve a balance between shell flexibility and mechanical strength. Excessive moisture removal may produce brittle capsules susceptible to cracking, whereas inadequate drying can result in soft capsules, deformation, microbial growth, and reduced shelf stability. Moisture migration between the shell and fill formulation represents an additional challenge during storage. The direction and extent of moisture transfer depend on the hygroscopicity and water activity of the fill material. Moisture control strategies must be incorporated throughout formulation development and manufacturing to maintain product quality. Modern drying systems employ automated environmental controls, humidity sensors, airflow management systems, and process monitoring technologies to ensure reproducible drying performance. Effective moisture management not only preserves capsule integrity but also minimizes stability issues such as shell hardening, softening, leakage, and dissolution variability, thereby contributing to long-term product reliability and regulatory compliance.

4.6 Quality by Design (QbD) Approach in Manufacturing

The increasing complexity of pharmaceutical products and regulatory emphasis on product quality have accelerated the adoption of the Quality by Design paradigm in SGC manufacturing. QbD is a systematic, science-based, and risk-oriented approach that emphasizes designing quality into a product rather than relying solely on end-product testing. In SGC manufacturing, QbD facilitates a comprehensive understanding of the relationships among raw material attributes, process parameters, and critical quality attributes (CQAs). Key CQAs for SGCs include capsule appearance, shell thickness, moisture content, fill weight uniformity, seal integrity, disintegration, dissolution performance, and stability. Through systematic risk assessment tools such as Failure Mode and Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP), and Ishikawa diagrams, manufacturers can identify critical material attributes (CMAs) and critical process parameters (CPPs) that significantly influence product quality. The implementation of QbD offers several advantages, including improved process robustness, enhanced manufacturing efficiency, reduced batch failures, greater regulatory flexibility, and accelerated product lifecycle management[25]. Furthermore, the integration of advanced analytical technologies and real-time monitoring systems supports continuous process verification and facilitates the transition toward modern pharmaceutical manufacturing practices.

4.6.1 Process Optimization and Process Analytical Technology (PAT)

Process optimization is a fundamental element of QbD and aims to establish a robust manufacturing process capable of consistently delivering products that meet predefined quality specifications. In SGC manufacturing, optimization involves systematic evaluation of formulation variables and process conditions affecting capsule formation, encapsulation efficiency, drying behavior, and product stability. Design of Experiments (DoE) is widely employed to investigate the influence of formulation and process variables on critical quality attributes. Parameters commonly optimized include gelatin concentration, plasticizer ratio, ribbon thickness, fill viscosity, encapsulation temperature, wedge temperature, drying conditions, and residual moisture content. Statistical modeling and multivariate analysis enable the establishment of a design space within which acceptable product quality can be consistently achieved. Process Analytical Technology, introduced by the US FDA, further strengthens process understanding by enabling real-time monitoring and control of manufacturing operations[8,26]. PAT utilizes analytical tools and process sensors to measure critical process parameters and quality attributes during production rather than relying solely on end-product testing. In contemporary SGC manufacturing, PAT applications include Real-time monitoring of gelatin viscosity and temperature, measurement of ribbon thickness and uniformity, online assessment of fill weight and dosing accuracy, Near-infrared spectroscopy for moisture analysis, Automated inspection of capsule dimensions and defects and Continuous monitoring of drying conditions and environmental parameters. The integration of PAT with advanced automation, machine learning algorithms, and digital manufacturing platforms has enhanced process predictability and facilitated the emergence of smart manufacturing environments. These technologies enable proactive process adjustments, reduce variability, and improve overall manufacturing performance.

4.6.2 In-Process Quality Control Parameters

In-process quality control (IPQC) serves as a critical component of manufacturing operations by ensuring that product quality is maintained throughout the production cycle. Unlike final product testing, IPQC focuses on continuous monitoring of critical parameters during manufacturing to identify and correct deviations before they affect product quality. For SGCs, IPQC activities begin with the evaluation of gelatin mass characteristics, including viscosity, bloom strength, temperature, and homogeneity. During encapsulation, parameters such as ribbon thickness, ribbon temperature, fill formulation viscosity, fill weight

variation, capsule dimensions, seam quality, and seal integrity are continuously monitored **Table 3**. Automated vision systems have become increasingly important in modern manufacturing facilities. These systems utilize high-speed cameras and AI-based image analysis to detect defects such as air bubbles, dents, leaks, incomplete seals, surface irregularities, and colour inconsistencies. Such technologies improve inspection accuracy while minimizing operator-dependent variability. A comprehensive IPQC strategy not only ensures regulatory compliance but also contributes to process capability, product consistency, and reduced manufacturing waste.

Table 3: Presented critical in-process parameters and their significance in soft gelatin capsule manufacturing

Process Stage	Parameter	Significance
Gel Mass Preparation	Gelatin viscosity	Influences ribbon formation, shell uniformity, and encapsulation efficiency
	Gel mass temperature	Controls gelatin flow characteristics and processability
	Gelatin bloom strength	Determines shell elasticity, mechanical strength, and sealing performance
	pH of gel mass	Affects gelatin stability and shell quality
	Plasticizer-to-gelatin ratio	Influences shell flexibility, brittleness, and drying behavior
	Deaeration efficiency	Prevents air bubble formation and shell defects
Ribbon Formation	Ribbon thickness	Affects capsule strength, fill capacity, and drying characteristics
	Ribbon temperature	Ensures proper ribbon elasticity and die performance
	Ribbon moisture content	Influences sealing efficiency and shell integrity
	Ribbon uniformity	Maintains capsule dimensional consistency
Fill Material Preparation	Fill viscosity	Impacts fill pump performance and dose reproducibility
	Drug content uniformity	Ensures dosage accuracy and therapeutic consistency
	Suspension homogeneity	Prevents sedimentation and fill variability
	Fill temperature	Maintains flowability and formulation stability
	Particle size distribution	Influences content uniformity and dissolution behavior
Encapsulation Process	Fill weight variation	Ensures dose accuracy and content uniformity
	Fill pump calibration	Maintains precise fill volume delivery
	Die roll alignment	Critical for capsule shape consistency and seal formation
	Wedge temperature	Controls ribbon sealing and capsule formation
	Encapsulation speed	Affects production efficiency and capsule quality
	Injection timing	Ensures accurate fill placement within capsule shells
Sealing Process	Seam thickness	Indicates seal robustness and capsule integrity
	Seal strength	Prevents leakage during handling and storage
	Seam alignment	Ensures hermetic sealing and product appearance
Drying Process	Tumble drying time	Removes surface moisture and stabilizes capsule shape
	Drying air temperature	Influences moisture removal rate and shell properties
	Relative humidity	Prevents over-drying or under-drying of capsules
	Final moisture content	Critical for capsule flexibility and shelf-life stability
Finished Capsule Evaluation	Capsule dimensions	Maintains product consistency and packaging compatibility
	Capsule weight variation	Confirms process uniformity
	Shell thickness	Influences mechanical strength and dissolution performance
	Visual appearance	Detects malformed, leaking, dented, or damaged capsules
	Color uniformity	Indicates process consistency and product acceptability
	Surface defects	Identifies cracks, dimples, bubbles, or deformation
Packaging and Storage	Leak testing	Ensures package and capsule integrity
	Packaging seal integrity	Prevents moisture ingress and product degradation
	Storage temperature	Maintains long-term product stability
	Storage humidity	Prevents shell hardening, softening, or brittleness

4.6.3 Packaging and Storage Requirements

Packaging plays a crucial role in preserving the physical integrity, chemical stability, and therapeutic performance of SGCs throughout their shelf life. Because gelatin shells are sensitive to environmental conditions, particularly moisture and temperature fluctuations, the selection of appropriate packaging systems is essential for maintaining product quality. SGCs are typically packaged in blister packs or high-density polyethylene (HDPE) containers equipped with moisture-resistant closures. Packaging materials must provide adequate protection against humidity, oxygen, light exposure, and mechanical damage. For moisture-sensitive formulations, desiccants may be incorporated to maintain optimal storage conditions. The selection of packaging systems is guided by stability data, product characteristics, climatic zone requirements, and regulatory expectations. Key packaging considerations include moisture barrier properties, oxygen transmission rate, light protection capability, mechanical strength and durability, compatibility with capsule shell and formulation and tamper-evident and child-resistant features where required.

Storage conditions are equally important for maintaining capsule performance. Excessive humidity can lead to shell softening, stickiness, microbial growth, and deformation, whereas low humidity may result in brittleness, cracking, and compromised seal integrity. Elevated temperatures may accelerate gelatin cross-linking, oxidation, and drug degradation, ultimately affecting dissolution behavior and product efficacy. Current industry practices recommend storing soft gelatin capsules under controlled temperature and humidity conditions, typically in a cool and dry environment away from direct sunlight. Continuous environmental monitoring during warehousing and distribution has become increasingly important as manufacturers adopt risk-based stability management strategies. Recent advances in packaging technology include intelligent packaging systems, humidity-indicating labels, RFID-enabled traceability solutions, and digital monitoring platforms that support real-time tracking of storage conditions across the supply chain. These innovations align with contemporary pharmaceutical quality systems and contribute to improved product protection, regulatory compliance, and patient safety. Overall, the integration of QbD principles, PAT-enabled process monitoring, robust in-process controls, and scientifically designed packaging strategies provides a comprehensive framework for ensuring the consistent quality, safety, efficacy, and lifecycle performance of SGC products.

4.7 Lipid-Based Drug Delivery Systems in Soft Gelatin Capsules

Lipid-based drug delivery systems have emerged as one of the most important applications of SGC technology, particularly for drugs exhibiting poor aqueous solubility and limited oral bioavailability. These systems utilize oils, surfactants, co-surfactants, and lipid excipients to maintain the drug in a solubilized state within the gastrointestinal tract, thereby enhancing dissolution and absorption. SGCs provide an ideal dosage form for lipid-based formulations due to their ability to encapsulate liquid and semisolid systems while protecting sensitive drug substances from environmental degradation. In addition to improving bioavailability, lipid-based formulations may reduce food effects, enhance dose reproducibility, and facilitate lymphatic drug transport, thereby minimizing first-pass metabolism for selected compounds[27].

4.7.1 Self-Emulsifying and Self-Microemulsifying Drug Delivery Systems

Self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) are advanced lipid-based formulations widely incorporated into SGCs to improve the oral delivery of poorly soluble drugs. These systems consist of oils, surfactants, and co-solvents that spontaneously form fine emulsions or microemulsions upon contact with gastrointestinal fluids under gentle agitation. The resulting droplets provide a large interfacial surface area that promotes rapid drug dissolution and absorption. SMEDDS generally produce smaller droplet sizes than conventional SEDDS, leading to enhanced drug solubilization and more efficient absorption. These technologies have been successfully applied to various therapeutic agents, including anticancer, antiviral, immunosuppressive, and cardiovascular drugs, where improved bioavailability is critical for therapeutic effectiveness.

4.7.2 Controlled and Targeted Drug Delivery Applications

Recent advances in SGC technology have expanded their utility beyond immediate-release formulations to include controlled and targeted drug delivery systems. Controlled-release SGCs are designed to modulate drug release rates through specialized fill formulations, polymeric matrices, or modified shell technologies, thereby maintaining therapeutic drug concentrations for extended periods and reducing dosing frequency. Targeted delivery approaches incorporate lipid carriers, functional excipients, and nanotechnology-based systems to enhance site-specific drug distribution and therapeutic efficacy. Such strategies have shown considerable potential for improving the delivery of anticancer agents, peptide therapeutics, and other complex drug molecules. The integration of lipid-based systems with controlled and targeted delivery technologies continues to broaden the therapeutic applications of soft gelatin capsules and supports the development of next-generation oral drug delivery platforms[27,28].

5.0 CHARACTERIZATION AND EVALUATION OF SOFT GELATIN CAPSULES

Comprehensive characterization and evaluation of SGCs are essential to ensure product quality, safety, efficacy, and regulatory compliance. The performance of SGC is influenced by the physicochemical properties of both the capsule shell and fill formulation. Therefore, a combination of mechanical, physicochemical, biopharmaceutical, and stability assessments is

required to establish product consistency throughout its lifecycle. These evaluations provide critical information regarding capsule integrity, drug release behavior, storage stability, and therapeutic performance.

5.1 Mechanical and Physicochemical Evaluation Tests

Mechanical and physicochemical characterization serves as the primary assessment of capsule quality and functionality. These tests evaluate the structural integrity of the capsule shell, uniformity of the encapsulated formulation, and overall product consistency. Visual inspection is performed to assess capsule appearance, color uniformity, transparency, surface smoothness, and the absence of defects such as leakage, deformation, or seam imperfections. Dimensional measurements including capsule length, width, thickness, and shell uniformity are evaluated to ensure manufacturing consistency. Mechanical properties such as tensile strength, elasticity, hardness, and rupture resistance are critical indicators of shell quality[29]. These parameters influence capsule handling, packaging, transportation, and storage performance. Moisture content determination is particularly important because it directly affects shell flexibility and stability. Additional physicochemical evaluations include fill weight variation, content uniformity, viscosity of fill formulations, and assessment of shell-fill compatibility. Collectively, these tests establish the physical robustness and quality attributes of the finished product.

5.2 Dissolution and Disintegration Studies

Dissolution and disintegration testing are fundamental quality attributes that predict the in vivo performance of SGCs. These studies evaluate the ability of the capsule shell to release the encapsulated formulation and the subsequent availability of the API for absorption. Disintegration testing determines the time required for capsule rupture and release of the fill material under simulated physiological conditions. Rapid and reproducible disintegration is particularly important for immediate-release formulations, whereas modified-release systems may require specialized evaluation protocols. Dissolution testing assesses the rate and extent of drug release from the capsule. The results are influenced by shell composition, fill formulation characteristics, drug solubility, and dissolution medium conditions. For lipid-based formulations, dissolution studies provide valuable information regarding formulation performance and potential bioavailability enhancement. Dissolution profiles are also widely used for formulation optimization, quality control, batch-to-batch consistency assessment, and regulatory submissions.

5.3 Stability Testing and Shelf-Life Determination

Stability testing is performed to evaluate the ability of SGCs to maintain their quality, safety, and efficacy throughout the intended storage period. Because SGCs contain both a gelatin shell and a liquid or semisolid fill, they are particularly susceptible to environmental factors such as temperature, humidity, oxygen, and light[30, 31]. Stability studies typically include physical, chemical, microbiological, and performance-related evaluations conducted under long-term, intermediate, and accelerated storage conditions. Parameters commonly monitored include capsule appearance, shell integrity, moisture content, assay, degradation products, dissolution characteristics, and microbial quality. Particular attention is given to phenomena such as gelatin cross-linking, shell hardening or softening, moisture migration, leakage, oxidation, and drug precipitation, as these changes can adversely affect product performance. Stability data generated according to ICH guidelines are used to establish storage conditions, packaging requirements, and product shelf life. Reliable stability programs are therefore essential for ensuring consistent product quality throughout commercial distribution and use.

5.4 Bioavailability Enhancement Using Soft Gelatin Capsules

One of the most significant advantages of SGC technology is its ability to improve the oral bioavailability of poorly water-soluble drugs. Many contemporary drug candidates exhibit limited aqueous solubility, which can restrict dissolution and absorption following oral administration. SGCs address this challenge by enabling incorporation of drugs into solubilized, suspended, or lipid-based delivery systems. The encapsulation of drugs in solution eliminates the dissolution step often required for conventional solid dosage forms, resulting in faster and more predictable absorption. Furthermore, lipid-based formulations incorporated within SGCs can enhance drug solubilization within gastrointestinal fluids and facilitate absorption through intestinal membranes. Advanced delivery systems such as SEDDS, SMEDDS, nano-emulsions, and lipid-based carriers have demonstrated substantial improvements in the bioavailability of poorly soluble compounds. In certain cases, lipid-mediated lymphatic transport may reduce first-pass metabolism and further enhance systemic drug exposure. As a result, SGCs have become an important platform for the development of bioavailability-enhanced formulations, particularly for BCS Class II and Class IV drugs. Their ability to improve dissolution characteristics, reduce pharmacokinetic variability, and enhance therapeutic outcomes continues to drive their widespread use in modern pharmaceutical product development.

6.0 NEXT GENERATION CAPSULE DEVELOPMENT

The pharmaceutical industry is undergoing a major transformation driven by automation, digitalization, advanced materials, nanotechnology, and personalized medicine. These technological developments have significantly expanded the capabilities of SGC systems beyond conventional oral drug delivery. Modern manufacturing platforms are increasingly focused on improving process efficiency, product quality, patient-centric design, and regulatory compliance while addressing the challenges associated with poorly soluble and complex therapeutic molecules.

Technological innovation has become a key driver in the evolution of SGCs as advanced drug delivery systems.

6.1 Automation and Digitalization in Capsule Production

Automation has revolutionized SGC manufacturing by improving process consistency, reducing human intervention, and minimizing production variability. Modern encapsulation lines integrate automated material handling systems, computerized process controls, robotic inspection units, and real-time monitoring technologies to ensure reproducible manufacturing performance. The adoption of New Industry principles has further accelerated digital transformation within pharmaceutical manufacturing. Advanced process monitoring systems utilize sensors, machine vision technologies, artificial intelligence, and machine learning algorithms to collect and analyse manufacturing data in real time. These technologies facilitate predictive maintenance, process optimization, deviation detection, and continuous process verification. Digital manufacturing platforms also support electronic batch records, automated documentation, data integrity compliance, and regulatory traceability. As a result, automation and digitalization contribute to enhanced product quality, increased operational efficiency, and reduced manufacturing costs while supporting modern QbD initiatives[32].

6.2 Novel Shell Materials and Non-Gelatin Alternatives

Although gelatin remains the most widely used shell-forming material, increasing demand for vegetarian, vegan, religiously acceptable, and animal-free products have stimulated the development of alternative capsule shell materials. Several non-gelatin polymers have demonstrated potential as shell-forming agents, including hydroxypropyl methylcellulose (HPMC), pullulan, modified starches, carrageenan, pectin, alginate, and other polysaccharide-based materials. These alternatives offer advantages such as reduced sensitivity to humidity, improved chemical stability, lower risk of cross-linking, and broader consumer acceptance. Recent research has focused on hybrid polymer systems and multifunctional shell compositions capable of providing enhanced mechanical strength, controlled-release properties, and improved compatibility with complex fill formulations. Such innovations are expanding the applicability of soft capsule technology in pharmaceuticals, nutraceuticals, and biologics.

6.3 Advances in Capsule Sealing and Leak Detection Technologies

Seal integrity is one of the most critical quality attributes of SGCs because defective seals may result in leakage, contamination, moisture loss, and reduced product stability. Consequently, significant advancements have been made in sealing and inspection technologies. Modern encapsulation systems employ precision-controlled temperature, pressure, and die alignment mechanisms to achieve highly reproducible hermetic seals. Improved process controls have substantially reduced manufacturing defects and enhanced capsule uniformity. Leak detection has evolved from traditional visual inspection methods to sophisticated automated systems utilizing machine vision, laser-based inspection, vacuum decay testing, high-voltage leak detection, and non-destructive imaging technologies. These systems enable rapid identification of defective capsules during production and significantly improve quality assurance efficiency. The integration of artificial intelligence-based image analysis has further enhanced defect detection accuracy, allowing real-time identification of micro-leaks, seam imperfections, surface defects, and dimensional irregularities that may not be detectable through conventional inspection techniques.

6.4 Nanotechnology and Soft Gelatin Capsule Systems

Nanotechnology has emerged as a promising strategy for enhancing the delivery of poorly soluble, poorly permeable, and biologically complex therapeutic agents[33]. SGCs provide an effective platform for encapsulating nanocarriers because they offer protection from environmental degradation and facilitate convenient oral administration. Various nanotechnology-based systems have been successfully incorporated into SGCs, including nano-emulsions, nanosuspensions, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and lipid-polymer hybrid systems. These nanocarriers increase the effective surface area available for absorption, improve drug solubilization, and enhance membrane permeability. In addition to improving oral bioavailability, nanoparticle-based formulations may facilitate targeted drug delivery, prolonged systemic circulation, controlled release, and reduced toxicity. Nanotechnology-enabled SGCs are currently being investigated for the delivery of antiviral, anticancer agents, peptides, proteins, and other challenging therapeutic molecules. The convergence of lipid-based systems and nanotechnology is expected to play a major role in the future development of advanced soft capsule formulations.

6.5 3D Printing and Personalized Medicine Approaches

3D printing has emerged as a transformative technology capable of redefining pharmaceutical manufacturing and personalized medicine. Unlike conventional mass-production methods, 3D printing enables the fabrication of dosage forms tailored to individual patient requirements, including dose strength, release profile, and combination therapy needs **Figure 5**. Although the application of 3D printing in SGC manufacturing remains in the early stages of development, recent advances have demonstrated the feasibility of producing customized capsule shells, multi-compartment dosage forms, and patient-specific drug delivery systems[34]. These technologies offer the potential to accommodate individualized dosing regimens and improve therapeutic outcomes. The integration of digital health technologies,

pharmacogenomic information, and on-demand manufacturing may further support the development of personalized soft capsule products designed according to patient-specific clinical requirements. Future advancements are expected to combine 3D printing, AI, smart manufacturing systems, and advanced materials science to create highly customized pharmaceutical products. As healthcare increasingly shifts toward precision medicine, 3D-printed soft capsule technologies may become an important platform for individualized drug therapy and next-generation pharmaceutical manufacturing.

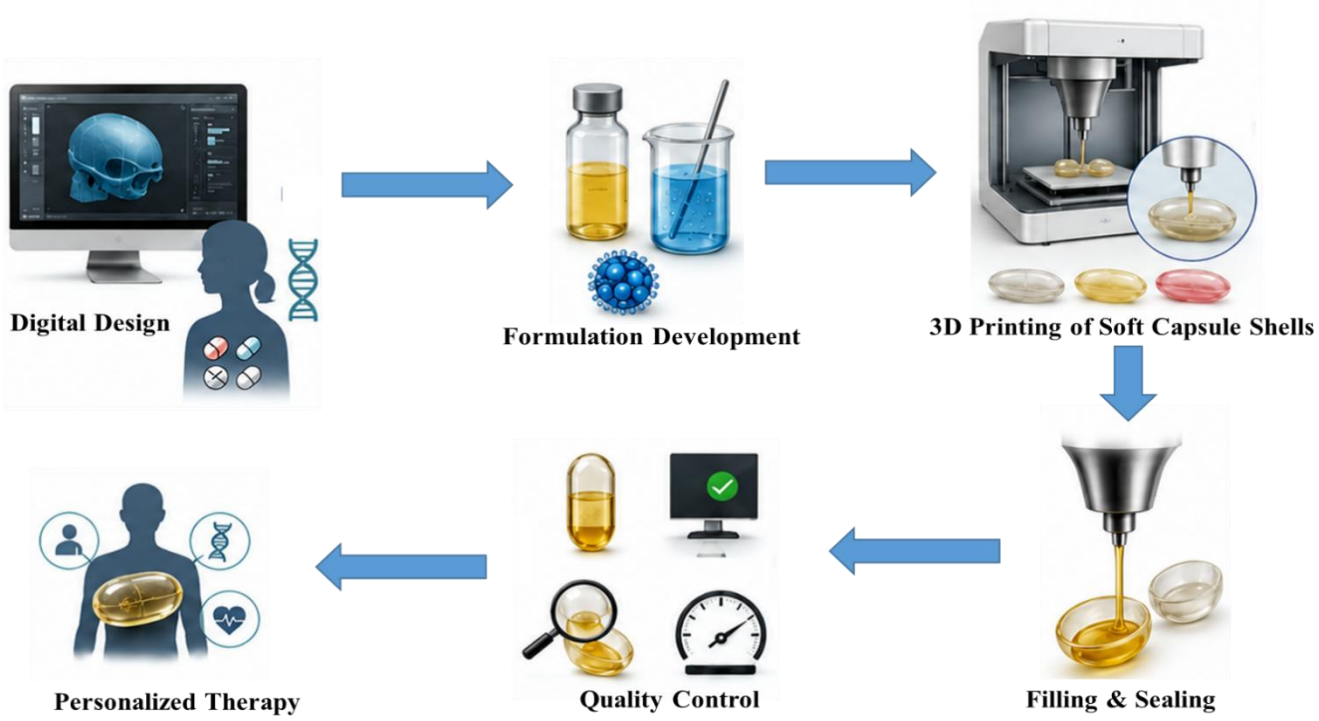


Figure 5: Illustration of 3D Printing and Personalized Medicine Approaches for SGCs

7.0 REGULATORY PERSPECTIVES AND GLOBAL GUIDELINES

Regulatory oversight plays a pivotal role in ensuring the quality, safety, efficacy, and consistency of SGC products throughout their lifecycle. Due to the unique characteristics of SGCs, including the presence of a gelatin shell and liquid or semisolid fill formulation, manufacturers must address additional considerations related to shell-fill compatibility, moisture control, encapsulation processes, stability, and packaging. Global regulatory agencies increasingly emphasize science-based development, risk management, process understanding, and lifecycle quality assurance through harmonized regulatory frameworks. Consequently, compliance with current Good Manufacturing Practices (cGMP), ICH guidelines, and regional regulatory requirements has become essential for successful product development and commercialization.

7.1 GMP Requirements for Soft Gelatin Capsule Manufacturing

Good Manufacturing Practices (GMP) provide the foundation for the consistent production and control of pharmaceutical products. For SGC manufacturing, GMP requirements encompass all stages of production, including raw material qualification, gelatin preparation, fill formulation development, encapsulation, drying, packaging, storage, and distribution. Manufacturers must establish robust quality management systems that ensure process consistency, contamination control, traceability, and product integrity. Particular emphasis is placed on environmental monitoring, equipment qualification, cleaning validation, moisture control, personnel training, and prevention of cross-contamination. Critical manufacturing operations such as ribbon formation, encapsulation, and drying require well-defined procedures and continuous monitoring to maintain product quality. Modern GMP expectations also encourage the implementation of risk-based approaches, quality risk management, data integrity practices, and continuous process improvement programs. These principles support the development of reliable manufacturing systems capable of consistently producing high-quality SGC products.

7.2 Regulatory Requirements by USFDA, EMA, and ICH

Soft gelatin capsule products intended for global markets must comply with the regulatory requirements established by major health authorities, including the USFDA, the European Medicines Agency, and the International Council for Harmonisation **Figure 6**. The USFDA emphasizes QbD, PAT, pharmaceutical quality systems, and lifecycle process verification to ensure product quality and manufacturing robustness.

Similarly, the EMA promotes science-based product development, risk management strategies, and continuous quality improvement throughout the product lifecycle. ICH guidelines provide a harmonized regulatory framework that facilitates global pharmaceutical development and registration. Several ICH guidelines are particularly relevant to SGC products, including ICH Q8(R2) - Pharmaceutical Development; ICH Q9 - Quality Risk Management; ICH Q10 - Pharmaceutical Quality System; ICH Q11 - Development and Manufacture of Drug Substances; ICH Q12 - Product Lifecycle Management; ICH Q1 Series - Stability Testing Requirements. These guidelines collectively support a systematic approach to product development, process control, risk assessment, stability evaluation, and regulatory compliance. Adoption of harmonized standards enables manufacturers to streamline global submissions while maintaining consistent product quality across different markets.

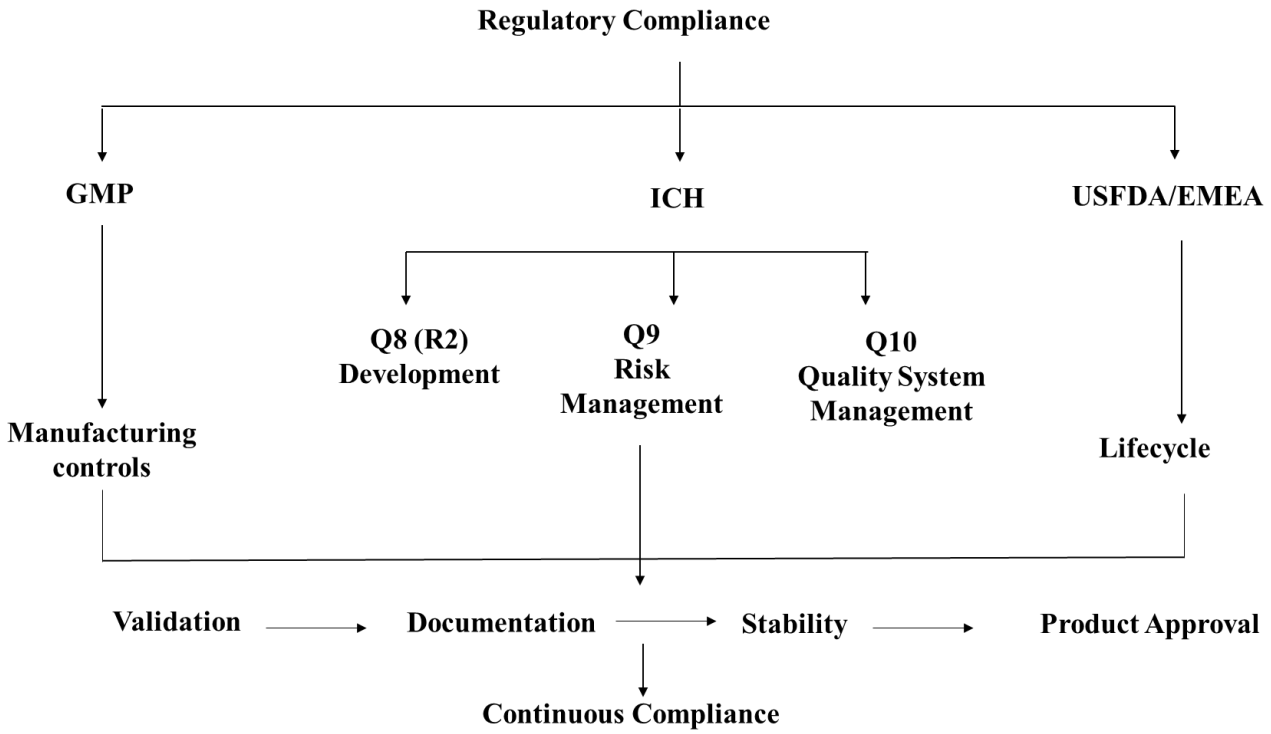


Figure 6: Regulatory Framework Governing Soft Gelatin Capsule Development and Manufacturing

7.3 Validation and Documentation Practices involved in SGCs

Validation is a critical regulatory requirement that provides documented evidence that manufacturing processes, analytical methods, equipment, and supporting systems consistently perform as intended. In SGC manufacturing, validation activities are essential for demonstrating process reliability and ensuring reproducible product quality. Key validation activities include process validation, equipment qualification, cleaning validation, analytical method validation, computerized system validation, and packaging validation. Particular attention is given to critical manufacturing operations such as gelatin preparation, encapsulation, drying, and moisture control because these processes significantly influence capsule quality attributes. Comprehensive documentation forms the backbone of regulatory compliance. Manufacturers are required to maintain accurate records covering raw materials, manufacturing operations, in-process controls, deviations, investigations, validation studies, stability data, and product release activities. Documentation practices must adhere to principles of data integrity, ensuring that records are attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available throughout the product lifecycle. The increasing adoption of electronic quality management systems and digital documentation platforms has further enhanced regulatory compliance, traceability, and inspection readiness.

7.4 Challenges in Regulatory Compliance

Despite significant advances in manufacturing technologies and regulatory harmonization, compliance challenges remain an important consideration in SGC production. The complexity of capsule shell-fill interactions, variability in raw materials, and sensitivity to environmental conditions can complicate product development and regulatory evaluation. One of the major challenges involves maintaining consistent product quality throughout the shelf life, particularly with respect to moisture migration, gelatin cross-linking, dissolution performance, and stability of lipid-based formulations. Regulatory agencies increasingly expect manufacturers to demonstrate comprehensive process understanding and robust control strategies to mitigate these risks. Global manufacturers also face challenges associated with differing regional regulatory

expectations, evolving data integrity requirements, implementation of advanced technologies, and management of increasingly complex supply chains. Furthermore, the introduction of novel shell materials, nanotechnology-based formulations, and personalized medicine approaches creates additional regulatory considerations due to the limited availability of established regulatory precedents. Future regulatory strategies are expected to focus on greater international harmonization, digital transformation, real-time quality monitoring, continuous manufacturing concepts, and lifecycle-based quality management. Organizations that successfully integrate scientific innovation with proactive regulatory compliance will be better positioned to meet evolving global expectations and ensure the sustained quality and reliability of SGC products.

8.0 INDUSTRIAL CHALLENGES AND TROUBLESHOOTING IN MANUFACTURING

SGC manufacturing is a highly specialized process requiring precise control of formulation, processing conditions, and environmental parameters. Despite significant technological advancements, several manufacturing challenges continue to affect product quality, process efficiency, and regulatory compliance. One of the most common challenges is maintaining shell-fill compatibility. Interactions between gelatin and formulation components such as aldehydes, hygroscopic excipients, or reactive drugs may result in shell softening, brittleness, leakage, discoloration, or gelatin cross-linking. Moisture migration between the shell and fill formulation can further compromise capsule integrity and dissolution performance. Process-related issues include variations in gelatin viscosity, ribbon thickness fluctuations, improper sealing, fill-weight variability, air entrapment, capsule deformation, and leakage defects. Environmental factors such as temperature and relative humidity significantly influence shell properties and drying efficiency. Inadequate drying may lead to capsule sticking, microbial growth, or reduced shelf stability, whereas excessive drying can cause brittleness and cracking.

Troubleshooting strategies involve systematic root-cause analysis, implementation of QbD principles, optimization of critical process parameters, and utilization of PAT tools. Advanced automation, real-time monitoring systems, and predictive maintenance technologies are increasingly employed to minimize manufacturing variability and improve process robustness. Effective troubleshooting not only reduces production losses but also enhances product quality, regulatory compliance, and operational efficiency.

9.0 CURRENT MARKET TRENDS AND COMMERCIAL OUTLOOK

The global SGC market has experienced steady growth due to increasing demand for patient-friendly dosage forms, bioavailability-enhanced formulations, and nutraceutical products **Figure 7**. SGCs are widely utilized across pharmaceutical, dietary supplement, cosmetic, and veterinary sectors owing to their versatility and superior consumer acceptance. A major market driver is the growing prevalence of poorly water-soluble drug candidates, which has increased the adoption of lipid-based formulations and self-emulsifying drug delivery systems.

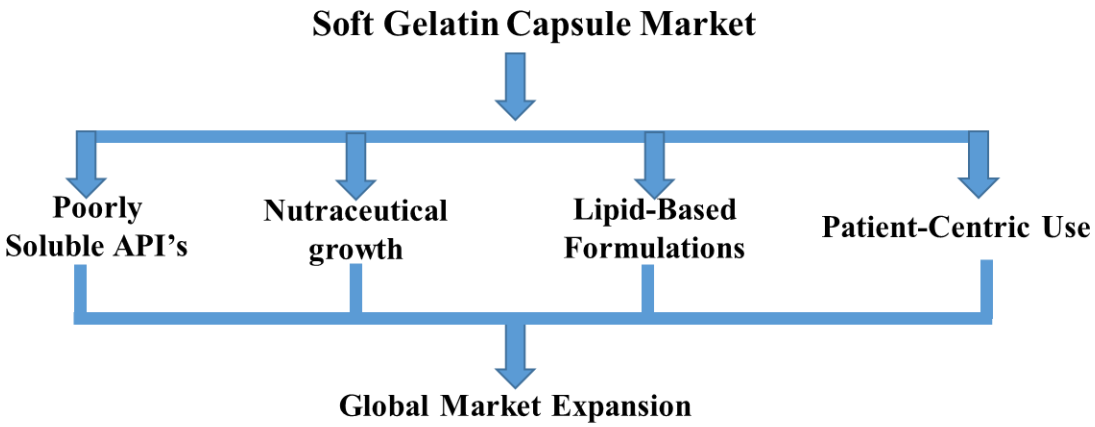


Figure 7: Current Market Drivers for Soft Gelatin Capsules

The expanding nutraceutical industry has also contributed significantly to market growth, particularly for products containing omega-3 fatty acids, vitamins, herbal extracts, probiotics, and functional ingredients. Current commercial trends include:

- Increased utilization of lipid-based and bioavailability-enhancing formulations.
- Growing demand for vegetarian and vegan capsule alternatives.
- Expansion of contract development and manufacturing organizations (CDMOs).
- Adoption of automation and digital manufacturing technologies.
- Rising interest in personalized healthcare and precision medicine.
- Increased focus on sustainable manufacturing and environmentally responsible packaging.

The pharmaceutical industry's shift toward complex drug molecules, biologics, and patient-centric dosage forms is expected to further strengthen the commercial importance of SGC technologies. Emerging markets in Asia-Pacific, Latin America, and the Middle East are anticipated to contribute substantially to future market expansion due to increasing healthcare expenditure and pharmaceutical manufacturing capacity.

Table 4: Representative Commercial Soft Gelatin Capsule Products and Their Therapeutic Applications

Product (Brand Name)	Active Ingredient(s)	Therapeutic Category	Dosage Strength(s)	Manufacturer /Marketing Company
Roaccutane® / Accutane®	Isotretinoin	Dermatology (Acne)	10, 20, 40 mg	Roche / Various Generics
Neoral®	Cyclosporine	Immunosuppressant	25, 50, 100 mg	Novartis
Sandimmune®	Cyclosporine	Immunosuppressant	25, 50, 100 mg	Novartis
Rocaltrol®	Calcitriol	Vitamin D Analog	0.25, 0.5 µg	Roche
Avodart®	Dutasteride	Benign Prostatic Hyperplasia (BPH)	0.5 mg	GSK
Vascepa®	Icosapent Ethyl	Hypertriglyceridemia	0.5 g, 1 g	Amarin
Lovaza®	Omega-3-Acid Ethyl Esters	Hypertriglyceridemia	1 g	GSK
Vitamin E Capsules	Tocopherol	Nutritional Supplement	200 -1000 IU	Multiple Manufacturers
Evion®	Vitamin E	Antioxidant Supplement	200, 400 mg	Merck India
Becosules®	Multivitamins	Nutritional Supplement	Various strengths	Pfizer
Uprise-D3®	Cholecalciferol	Vitamin D Deficiency	60,000 IU	Alkem Laboratories
Oscal D® Softgels	Calcium + Vitamin D	Bone Health	Various strengths	Multiple Manufacturers
Prograf®	Tacrolimus	Immunosuppressant	0.5, 1, 5 mg	Astellas Pharma
Fortovase®	Saquinavir	Antiretroviral	200mg	Roche
Aptivus®	Tipranavir	Antiretroviral	250 mg	Boehringer Ingelheim
Prometrium®	Progesterone	Hormone Replacement Therapy	100, 200 mg	AbbVie
Utrogestan®	Micronized Progesterone	Hormonal Therapy	100, 200 mg	Besins Healthcare
Andriol® Testocaps	Testosterone Undecanoate	Androgen Replacement Therapy	40 mg	Organon
Celebrex®	Celecoxib	Anti-inflammatory (Some markets)	50, 100, 200, 400mg	Pfizer
Advil Liqui-Gels®	Ibuprofen	Analgesic / Anti-inflammatory	200 mg	Haleon
Tamiflu®	Oseltamivir	Antiviral	30, 45, 75mg	Roche

10.0 FUTURE PROSPECTS AND EMERGING INNOVATIONS

The future of SGC technology is expected to be shaped by advances in material science, digital manufacturing, nanotechnology, and personalized medicine. Continuous innovation is transforming SGCs from conventional dosage forms into sophisticated drug delivery platforms capable of addressing increasingly complex therapeutic challenges. One of the most promising areas of development involves the integration of nanotechnology-based systems, including nano-emulsions, nanostructured lipid carriers, and lipid-polymer hybrid formulations **Figure 8**. These technologies offer enhanced solubility, targeted delivery, and improved therapeutic outcomes for poorly soluble and biologically challenging drugs.

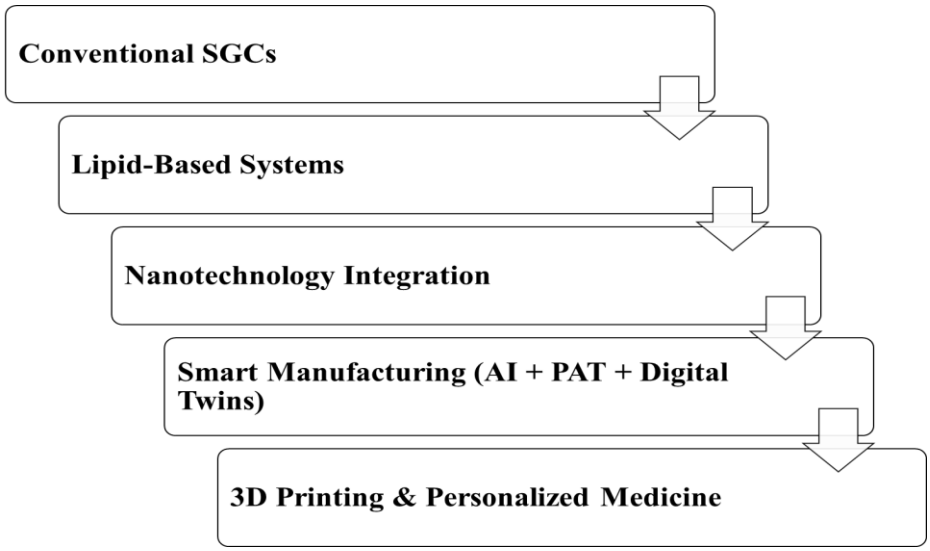


Figure 8: Future Innovation Roadmap for Soft Gelatin Capsules

Advancements in non-gelatin shell materials are expected to broaden the applicability of soft capsules by addressing dietary, religious, and sustainability concerns. Novel polymeric shell systems with improved mechanical properties and controlled-release capabilities may further expand formulation flexibility. AI, machine learning, digital twins, and smart manufacturing platforms are anticipated to revolutionize process optimization, predictive quality control, and real-time decision-making. The convergence of these technologies with PAT and continuous manufacturing concepts will support highly efficient and data-driven production environments.

Furthermore, the emergence of 3D printing and precision medicine offers opportunities for the development of customized soft capsule products tailored to individual patient needs. Future innovations may enable personalized dosing, combination therapies, and on-demand manufacturing of patient-specific formulations. Collectively, these advances are expected to enhance product performance, manufacturing efficiency, regulatory compliance, and patient outcomes, reinforcing the role of SGCs as a key platform in next-generation pharmaceutical development.

11.0 CONCLUSION

Soft gelatin capsules have evolved from conventional encapsulated dosage forms into highly versatile and sophisticated drug delivery systems that play a pivotal role in modern pharmaceutical and nutraceutical development. Their unique ability to encapsulate liquid, semisolid, and lipid-based formulations, coupled with advantages such as enhanced patient compliance, improved content uniformity, and increased bioavailability of poorly water-soluble drugs, has established them as an important platform for oral drug delivery. This review highlights the critical influence of raw material selection, formulation design, shell-fill compatibility, and manufacturing parameters on product quality and performance. Advances in rotary die encapsulation technology, Quality by Design, Process Analytical Technology, automation, and digital manufacturing have significantly improved process robustness, product consistency, and regulatory compliance. Furthermore, the integration of lipid-based drug delivery systems, self-emulsifying formulations, nanotechnology, and novel shell materials has expanded the therapeutic potential of SGCs beyond traditional applications. Despite ongoing challenges related to stability, moisture management, shell-fill interactions, and regulatory requirements, continuous innovation in materials science, process engineering, and quality systems is driving the development of next-generation soft capsule technologies. Emerging trends such as AI-enabled manufacturing, sustainable materials, advanced analytical tools, and personalized medicine approaches are expected to further transform this dosage form. Overall, SGCs remain a dynamic and evolving pharmaceutical platform that effectively combines formulation flexibility, manufacturing efficiency, and patient-centric design. Their continued advancement will play an increasingly important role in addressing future drug delivery challenges and supporting the development of innovative therapeutic products.

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