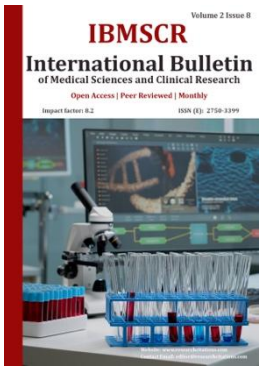

MODERN TECHNOLOGIES FOR THE PRODUCTION OF SOFT PHARMACEUTICAL DOSAGE FORMS

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https://doi.org/10.5281/zenodo.22327811

Abstract: Soft pharmaceutical dosage forms are an important group of medicines used for topical, local, and, in selected cases, systemic drug delivery. Creams, ointments, gels, pastes, and related semisolid systems combine the advantages of direct application with the ability to modify drug release, improve residence time, and influence drug penetration through biological barriers. Modern pharmaceutical technology has moved beyond traditional mixing and fusion methods toward rational formulation design, advanced rheological characterization, nanocarrier incorporation, controlled-release systems, and Quality by Design approaches. This article reviews contemporary technologies used in the production and development of soft pharmaceutical dosage forms, focusing on formulation principles, excipient selection, manufacturing methods, emulsion systems, gels, oleogels, nano-enabled semisolids, process control, quality evaluation, stability, and future perspectives. Particular attention is given to the relationship between microstructure and product performance. Modern analytical methods such as rheology, microscopy, spectroscopy, particle-size analysis, and in vitro release testing can improve understanding and control of semisolid products. The application of Quality by Design and risk-based development can further improve robustness, scalability, and reproducibility. Despite significant progress, challenges remain in physical and chemical stability, scale-up, bioequivalence, patient acceptability, and regulatory evaluation. Continued integration of formulation science, advanced manufacturing, and analytical technology is expected to support the development of safer, more effective, and patient-oriented soft pharmaceutical dosage forms.

Keywords: soft dosage forms; semisolid formulations; creams; ointments; gels; pharmaceutical technology; rheology; nanocarriers; oleogels; topical drug delivery; Quality by Design

Introduction: Soft pharmaceutical dosage forms occupy an important position in pharmaceutical technology because they can deliver active pharmaceutical ingredients directly to the skin or other accessible biological surfaces. Common examples include creams, ointments, gels, pastes, lotions, and related semisolid preparations. Their physical behavior lies between that of liquids and solids: they can maintain their structure at rest but spread under applied force. This characteristic provides practical advantages during administration and can contribute to prolonged residence at the application site. Topical administration may provide localized treatment while limiting systemic exposure for appropriately selected drugs. It can also avoid gastrointestinal degradation and first-pass metabolism. However, drug delivery through the skin is complex because the stratum corneum represents an effective biological barrier. The formulation vehicle, drug physicochemical properties, microstructure, hydration,

and application conditions can all influence drug release and penetration. Modern development therefore emphasizes a scientific understanding of the formulation rather than relying exclusively on empirical trial-and-error procedures. Current approaches include rational excipient selection, controlled microstructure, advanced emulsification, nanotechnology, novel gel systems, and systematic quality management. Recent literature highlights the importance of rheology, chemical stability, skin penetration mechanisms, and early consideration of product quality during development.

Soft pharmaceutical dosage forms can be classified according to their composition, physical structure, route of administration, and therapeutic purpose. Ointments generally contain a semisolid base in which the active ingredient is dissolved or dispersed. Creams are commonly emulsions of oil and water stabilized with suitable emulsifying systems. Gels contain a liquid phase immobilized within a three-dimensional polymeric or colloidal network. Pastes usually contain a relatively high proportion of finely divided solid materials dispersed in a suitable base.The choice of dosage form depends on the desired therapeutic effect, anatomical site, drug properties, required residence time, patient preference, and stability requirements. For example, an occlusive ointment may be useful when protection and moisturization are desired, whereas a gel may provide a lighter sensory profile and easier washing. Creams can combine emollient and aqueous characteristics and are widely used for dermatological therapy.

The development of a modern soft dosage form begins with preformulation studies. Important characteristics include drug solubility, partition coefficient, melting behavior, particle size, polymorphic form, chemical stability, and compatibility with excipients. For topical products, the ability of the drug to partition into and diffuse through the skin is especially important. Excipient selection is equally important. Emulsifiers, co-emulsifiers, humectants, emollients, gelling agents, penetration modifiers, antioxidants, preservatives, and pH-adjusting agents may be used to obtain the required product characteristics. The concentration and combination of excipients can affect viscosity, droplet size, microstructure, drug release, stability, and sensory properties. A rational design strategy considers the intended product profile before selecting the formulation and manufacturing process. The objective is to establish a robust relationship between composition, process parameters, microstructure, and performance. This principle is consistent with Quality by Design concepts described in ICH pharmaceutical development guidance.

Creams are generally emulsion-based semisolid systems and may be oil-in-water or water-in-oil depending on the desired properties. Modern manufacturing commonly involves controlled heating of appropriate phases, emulsification under defined shear conditions, cooling, and incorporation of heat-sensitive ingredients. The process must achieve suitable droplet size distribution and physical stability. High-shear mixing and homogenization can reduce droplet size and improve emulsion uniformity. However, excessive shear or inappropriate temperature profiles may alter the structure of the formulation. Modern process development therefore evaluates mixing intensity, homogenization time, temperature, phase addition sequence, cooling rate, and holding conditions. Advanced development also considers the internal microstructure of creams. Droplet size, interfacial properties, continuous-phase viscosity, and distribution of the active ingredient may influence release and performance. Thus, microscopic and rheological characterization can provide valuable information beyond conventional appearance testing.

Ointments are traditionally prepared by incorporation of drug substances into a suitable base or by fusion of selected ingredients. Modern technology improves this process through controlled particle-size reduction, temperature management, vacuum processing, homogenization, and improved mixing systems. For poorly soluble drugs, micronization can increase surface area and improve distribution within the base. In other cases, the drug may be dissolved in a suitable vehicle before incorporation. The selected strategy must minimize aggregation and maintain chemical and physical stability during storage. Modern ointment development also focuses on patient acceptability. Excessive greasiness, poor spreadability, staining, or unpleasant sensory properties may reduce adherence. Consequently, formulation scientists increasingly balance occlusive and therapeutic properties with cosmetic elegance and ease of application.

Gels are semisolid systems in which a liquid phase is immobilized by a three-dimensional network. Depending on the gelling agent and formulation environment, gels may be aqueous, hydroalcoholic, organogels, or other specialized systems. Common polymeric materials include carbomers, cellulose derivatives, and natural polymers. Modern gel technology can provide improved drug solubilization, spreading, cooling sensation, and controlled release. Polymer concentration, molecular weight, neutralization, ionic strength, pH, and solvent composition can substantially influence gel strength and drug release. Therefore, systematic optimization is necessary to achieve the desired balance between viscosity and application performance. Advanced gel systems may incorporate liposomes, nanoparticles, microemulsions, or other carriers. These combinations can modify drug solubility, stability, release, and interaction with the skin. However, the addition of complex carriers also increases formulation and analytical requirements.

Nanotechnology has expanded the possibilities of topical drug delivery. Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polymeric nanoparticles may be incorporated into semisolid vehicles. These systems can improve the apparent solubility of poorly water-soluble drugs, protect sensitive active ingredients, and influence drug release and skin interaction.

The incorporation of nanocarriers requires careful control of particle size, polydispersity, surface characteristics, drug loading, physical stability, and interaction with the semisolid matrix. A formulation that is physically stable as a nanoparticle dispersion may behave differently after incorporation into a cream or gel. Therefore, both the carrier and the final dosage form must be characterized. Although nano-enabled semisolids are promising, their industrial application requires robust manufacturing processes, reproducibility, appropriate safety evaluation, and reliable analytical methods. The complexity of these products makes rational formulation development particularly important.

Oleogels are emerging semisolid systems in which a liquid oil phase is structured by a suitable gelator. They can combine the properties of oily vehicles with improved structural stability and controlled release characteristics. Recent research describes oleogels as versatile systems with potential pharmaceutical applications. [7]

Other novel systems include bigels, emulgels, microemulsion gels, and structured lipid systems. Emulgels can combine an emulsion with a gel network, potentially improving the delivery of drugs with different solubility characteristics. Such systems may provide favorable spreadability and controlled release while maintaining acceptable sensory properties. The

development of novel semisolids requires attention to gelator concentration, phase composition, temperature, mixing, cooling behavior, and storage conditions. Changes in internal structure can influence viscosity, drug distribution, release, and stability.

Manufacturing of soft dosage forms may involve weighing, phase preparation, heating, melting, emulsification, homogenization, cooling, deaeration, active incorporation, filling, and packaging. Each stage can influence final product quality. For example, temperature affects viscosity and phase behavior, while mixing conditions influence dispersion and emulsion structure. Process analytical technology and in-process measurements can support control of critical parameters. Temperature, mixing speed, torque, viscosity, particle or droplet size, pH, and appearance may be monitored depending on the formulation. Appropriate process controls reduce batch-to-batch variability and facilitate scale-up from laboratory to industrial manufacturing. Scale-up is particularly important for semisolids because equipment geometry, shear patterns, heat transfer, and mixing efficiency can change when moving to larger vessels. Therefore, process development should focus on scientifically meaningful parameters rather than simply reproducing laboratory settings.

Quality evaluation of soft pharmaceutical dosage forms includes physical, chemical, microbiological, and performance-related tests. Appearance, homogeneity, pH, viscosity, spreadability, drug content, content uniformity, microbial quality, and stability are commonly considered according to the product and applicable standards.

Rheological analysis is particularly valuable because viscosity and flow behavior can influence manufacturing, filling, application, and drug release. Oscillatory and rotational rheological measurements can provide information about structural strength, shear-thinning behavior, thixotropy, and recovery after application. In vitro release testing can help evaluate the rate at which an active ingredient leaves the formulation. For topical products, additional studies may investigate permeation through suitable membranes or skin models. Modern characterization may also include microscopy, spectroscopy, particle-size analysis, thermal analysis, and chemical stability studies.

Quality by Design provides a structured framework for formulation development. The process begins with defining a Quality Target Product Profile and identifying Critical Quality Attributes. Formulation and process variables are then assessed through scientific knowledge and risk analysis. Design of Experiments can be used to investigate interactions between factors and define an appropriate design space.

For semisolid formulations, potential critical quality attributes include viscosity, droplet or particle size, pH, drug content, microstructure, physical stability, chemical stability, and in vitro release. Critical material attributes may include polymer grade, emulsifier properties, particle size, and drug form. Critical process parameters may include temperature, mixing speed, homogenization time, and cooling rate.The systematic QbD approach can reduce formulation variability and support more robust manufacturing. A recent systematic review specifically emphasizes the value of QbD, Design of Experiments, and control strategies for topical semisolid formulations.

Semisolid dosage forms can experience physical instability, including phase separation, creaming, sedimentation, crystallization, changes in viscosity, and changes in microstructure. Chemical degradation may also occur through oxidation, hydrolysis, photodegradation, or interaction with excipients. Stability testing should therefore assess both

active pharmaceutical ingredient integrity and preservation of formulation performance. Packaging can influence product stability and usability. Tubes, jars, pumps, and other dispensing systems may provide different levels of protection against air, light, moisture, and microbial contamination. The packaging system should be compatible with the formulation and should support accurate and convenient dosing.

Modern development increasingly considers the interaction between formulation, packaging, storage conditions, and patient use. This integrated approach helps maintain quality throughout the product life cycle.

Modern soft dosage forms offer several advantages, including direct application to the target area, flexibility in drug delivery, potential reduction of systemic exposure, improved local drug concentration, and convenient administration. Their formulation can also be adapted to different drug solubility characteristics and therapeutic objectives. However, challenges remain. Topical absorption can vary between individuals and anatomical sites. Formulations may be sensitive to temperature, pH, microbial contamination, and mechanical stress. Complex semisolid systems may also present difficulties in scale-up, reproducibility, bioequivalence assessment, and regulatory characterization. Recent work emphasizes that microstructure and rheology are closely connected with product performance and therefore require careful control.

Future development of soft pharmaceutical dosage forms is expected to emphasize personalized therapy, advanced nanocarriers, stimuli-responsive systems, digital formulation development, and more precise manufacturing control. Computational modeling and artificial intelligence may assist in predicting formulation behavior and identifying optimal combinations of materials and process conditions.

Patient-centric design will also become increasingly important. Products may be optimized for sensory characteristics, ease of spreading, reduced residue, convenient packaging, and appropriate dosing. Advanced analytical technologies can provide a more detailed understanding of microstructure and help establish relationships between formulation properties and clinical performance. Sustainable pharmaceutical manufacturing is another emerging consideration. The development of safer excipients, lower-energy processes, reduced solvent use, and environmentally responsible packaging may contribute to more sustainable semisolid medicines.

Conclusion: Modern pharmaceutical technologies have significantly expanded the possibilities for designing and manufacturing soft dosage forms. Traditional creams, ointments, gels, and pastes can now be developed using advanced emulsification, controlled rheology, nanocarriers, novel structured lipid systems, and systematic Quality by Design approaches. These technologies allow formulation scientists to optimize drug release, stability, spreadability, patient acceptability, and therapeutic performance. The future of semisolid pharmaceutical technology will depend on stronger integration of formulation science, process engineering, advanced analytical characterization, and patient-centered development. Robust control of microstructure and manufacturing parameters is essential for producing reproducible products. Although challenges related to stability, scale-up, bioequivalence, and regulation remain, continued innovation is likely to produce safer, more effective, and more convenient soft pharmaceutical dosage forms.

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