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Nanotechnology for oral bioavailability of drugs and nutraceuticals: applications in neuroscience and well-being

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Low bioavailability limits the effectiveness of multiple drugs and nutraceuticals due to factors such as reduced aqueous solubility, restricted intestinal permeability, gastrointestinal degradation, and first-pass metabolism. Nanostructured technologies including liposomes, polymeric nanoparticles, and nanoemulsions consistently demonstrate gains in systemic exposure, stability, and release control, with potential dose reduction and fewer adverse events. This article contextualizes the problem and reviews mechanisms and delivery platforms, describing characterization methods and critical quality attributes, alongside an analysis of clinical and translational evidence. It also discusses regulatory requirements and challenges in industrial scalability, and explores applications in nutritional neuroscience and well-being, with emphasis on the gut–brain axis. Perspectives include systems responsive to biological stimuli, integration with biosensors, and lipid–polymer hybrid platforms, supported by a quality-by-design framework. Recent literature reinforces benefits when nanoencapsulation is rigorously characterized, with relevant increases in AUC for liposomal polyphenols and sustained release of fat-soluble vitamins in biodegradable matrices, while maintaining favorable safety profiles in in vitro and in vivo evaluations (GUTIERREZ et al., 2020; PANDEY et al., 2018; LIU et al., 2022).

1. Introduction

Bioavailability is a determining variable for therapeutic and nutritional effectiveness. Drugs and nutraceuticals with insufficient aqueous solubility, limited intestinal permeability, and susceptibility to gastrointestinal degradation often present reduced absorbed fractions, leading to dosing regimens with high doses and a greater likelihood of adverse events. Moreover, first-pass metabolism can inactivate a substantial fraction of the active ingredient, reducing the available systemic concentration and undermining clinical and functional outcomes. These obstacles make individual response predictability a challenge, impacting adherence, cost, and public health outcomes.

Nanotechnology changes this landscape by offering structures capable of modulating critical steps of the oral route. Through encapsulation in lipidic or polymeric environments and by creating colloidal interfaces with high surface area, it is possible to increase apparent solubility, protect the active from pH and enzymes, prolong mucosal residence, and direct release to the appropriate intestinal segment. These effects converge to measurable gains in AUC, adjustments in Cmax and tmax, and reduced interindividual variability—provided the formulation is designed from critical quality attributes and subjected to robust characterization that supports in vitro–in vivo correlation (GUTIERREZ et al., 2020; PANDEY et al., 2018).

Translational relevance expands in areas such as neuroscience and well-being. Polyphenols, fat-soluble vitamins, and polyunsaturated fatty acids can modulate low-grade inflammation, oxidative stress, and synaptic processes, but frequently face limited bioavailability due to lipophilicity and instability. The interface with the gut–brain axis adds another layer of complexity, as it requires luminal stability, appropriate interaction with mucus and microbiota, and release profiles that favor the production or preservation of bioactive metabolites. In this context, nanostructured platforms, when well characterized and controlled, can sustain consistent and clinically relevant exposures (LIU et al., 2022).

This article aims to contextualize the problem of bioavailability, review nanoencapsulation mechanisms and delivery platforms, describe characterization methods and quality criteria, integrate evidence of efficacy and safety, discuss regulatory framing and scalability, and explore perspectives focused on brain health and well-being. It adopts a quality-by-design and risk management approach aligned with harmonized guidelines and applicable regulatory frameworks (ICH, 2005; ICH, 2008; ICH, 2009; FDA, 2014).

2. Theoretical Framework and Pharmacokinetic Bases

Bioavailability reflects the fraction and rate at which an active ingredient reaches the systemic circulation unchanged. For Biopharmaceutics Classification System Class II molecules, dissolution is the rate-limiting step. Increased surface area through reduced particle size accelerates dissolution and raises the concentration gradient in the intestinal lumen, which favors absorptive flux across the unstirred water layer adjacent to the epithelium. In nanostructured systems, the presence of surfactants and lipid phases maintains the active in solubilized or partially solubilized states, enabling controlled supersaturation that increases the absorbed fraction, provided precipitation is managed by inhibitory polymers and release kinetics control.

Intestinal permeability is another determinant. Tight junctions limit the paracellular route for larger or poorly lipophilic molecules, while efflux transporters such as P-gp reduce intracellular residence of certain substrates. Surface engineering and moderate mucoadhesion of nanoparticles can increase contact time with the epithelium and favor internalization via endocytosis or transcytosis, modulating absorption pathways. These mechanisms influence plasma concentration–time curves and enable profiles with moderated peaks and sustained plateaus, which may reduce peak-related events and improve the benefit–risk balance in chronic use (PANDEY et al., 2018).

Gastrointestinal stability also conditions outcomes. Acidic environments and digestive enzymes degrade sensitive molecules, reducing the absorbable fraction. Enteric coatings and biodegradable polymeric matrices protect against premature degradation and schedule release in more favorable environments, such as the small intestine. Consistency of systemic exposure benefits from in vitro–in vivo correlations based on biorelevant media, with variations in pH, bile, and lipases that mimic the digestive process. Reducing interindividual variability depends on standardized manufacturing, control of size, content, and particle–medium interactions.

In nutraceuticals, pharmacokinetic effects translate into functional outcomes. Polyunsaturated fatty acids require efficient emulsification and lipid digestion to form mixed micelles that facilitate absorption and subsequent incorporation into neuronal membranes. Polyphenols require protection against degradation and early conjugation to preserve active fractions. Fat-soluble vitamins demand vehicles that maintain plasma levels within target ranges. Nanostructured strategies, when calibrated for each class of active, can yield observable clinical gains with greater consistency in healthy and special populations, particularly for interventions aimed at well-being and brain health (LIU et al., 2022).

3. Nanotechnology Delivery Platforms

3.1 Liposomes

Liposomes are vesicles with one or more phospholipid bilayers surrounding an aqueous core, capable of simultaneously encapsulating hydrophilic and lipophilic actives. The architecture mimics cell membranes and supports bioavailability gains through mechanisms such as solubilizing hydrophobic compounds in the bilayer, protection against acidic pH and enzymes, and facilitation of interaction with biological membranes via fusion or endocytosis. Performance depends on attributes such as hydrodynamic diameter, polydispersity index, and zeta potential, which inform uniformity and colloidal stability. The active-to-lipid ratio and encapsulation efficiency define effective dose and interlot reproducibility, whereas phospholipid oxidative stability conditions shelf life.

Evidence with polyphenols such as curcumin shows relevant increases in AUC for liposomal formulations compared to the free form, suggesting that bilayer organization and luminal protection reduce losses and increase the absorbed fraction (GUTIERREZ et al., 2020). Clinical translation requires confirming stability in biological fluids, compatibility with excipients, and robustness to thermal and mechanical stresses. Techniques such as lyophilization with cryoprotectants can preserve size and bilayer integrity during distribution and storage. Functionalization with ligands adds targeting potential, but increases analytical complexity and regulatory requirements.

Limitations include susceptibility to phospholipid oxidation and hydrolysis, and risks of coalescence and fusion under improper processing conditions. Selecting stable lipids, compatible antioxidants, and controlled processes mitigates these effects. Costs of raw materials and specialized equipment also factor into feasibility. In summary, liposomes are particularly promising for lipophilic and labile actives, provided critical quality attributes are rigorously monitored and linked to in vivo performance.

3.2 Polymeric Nanoparticles

Nanoparticles made of biodegradable polymers such as PLGA, chitosan, and alginate offer release control based on hydrolytic degradation, diffusion, and matrix erosion. Matrix or core–shell architectures allow modulation of release kinetics, mucoadhesion, and epithelial interaction. The choice of molecular weight, monomer ratio, and degree of deacetylation in the case of chitosan influences mechanics, hydration, surface charge, and degradation rates. Surface engineering via hydrophilic coatings can reduce opsonization and favor transit through mucus, whereas functional groups direct specific interactions with transporters.

For vitamin D3, PLGA systems present sustained release over 24 hours and maintenance of plasma levels with reduced fluctuation, suggesting dosing convenience and potentially superior adherence in prolonged use (PANDEY et al., 2018). Characterization includes measurements of size and polydispersity by dynamic light scattering, zeta potential, morphology by electron microscopy, encapsulation efficiency by chromatography, and release profiles in biorelevant media. Cytotoxicity, hemocompatibility, and genotoxicity assays are essential to anchor safety, particularly for sensitive populations.

Scalability challenges include preserving a narrow size distribution and encapsulation efficiency when moving from bench to pilot and industrial scales. High-shear processes and microfluidics provide uniformity but require process controls and specific cleaning validation. Early adoption of quality-by-design and risk management, with definition of critical attributes and process variables, reduces uncertainty and strengthens production reproducibility.

3.3 Nanoemulsions

Oil-in-water nanoemulsions with sub-100 nm droplets increase interfacial area and accelerate dissolution of lipophilic actives. Surfactants and cosolvents stabilize the interface, while the composition of the oil phase and surfactant profile modulate lipid digestion and mixed micelle formation—key steps for absorption. Performance depends on droplet size, polydispersity index, zeta potential, and robustness to pH, dilution, and temperature. Coalescence and Ostwald ripening must be mitigated through appropriate choices of oil, surfactant, and antioxidants.

For omega-3 fatty acids, nanoemulsions show superior absorption to conventional forms and consistency of clinical response, with implications for cardiometabolic markers and neuroinflammatory pathways relevant to brain health and well-being (LIU et al., 2022). Characterization includes measurements of size and viscosity, accelerated stability, in vitro digestion simulating gastrointestinal conditions, and permeation tests in cell models. Industrially, high-pressure homogenization and microfluidics are common, requiring rigorous qualification and calibration. Safety and palatability of surfactants and antioxidants must be carefully demonstrated for prolonged use.

4. Characterization Methods and Quality-Oriented Criteria

Translating in vitro performance to in vivo requires an analytical framework linking critical quality attributes to pharmacokinetic and functional outcomes. Size and polydispersity by dynamic light scattering inform uniformity and colloidal stability. Zeta potential offers a proxy for electrostatic repulsion and aggregation propensity. Morphology by electron microscopy elucidates bilayer or matrix architecture. Encapsulation efficiency and active loading, determined by chromatography, support dose calculation and interlot control. Release profiles in biorelevant media, with kinetic modeling and construction of in vitro–in vivo correlations when possible, guide prototype selection.

Stability should be evaluated under accelerated and shelf conditions, monitoring size, zeta potential, active content, and degradation indicators. For liposomes, phospholipid oxidation and hydrolysis are critical. For nanoemulsions, resistance to coalescence and Ostwald ripening is determinant for shelf life. In polymeric nanoparticles, matrix degradation rate and active integrity merit attention. The safety dossier integrates cytotoxicity, hemocompatibility, genotoxicity, endotoxins, and evaluation of residual surfactants and solvents. A quality-by-design and risk management approach, per harmonized guidelines, structures the definition of critical attributes, process variables, and in-process controls, promoting reproducibility and regulatory compliance throughout the product life cycle (ICH, 2005; ICH, 2008; ICH, 2009; ISO, 2012).

5. Translational Applications in Neuroscience and Well-Being

Bidirectional gut–brain communication involves neural, endocrine, immune, and metabolic routes that are modifiable by nutritional and pharmacological interventions. Polyphenols with antioxidant and anti-inflammatory properties, when nanoencapsulated, tend to exhibit greater luminal stability and absorbed fraction, potentially amplifying systemic effects on markers of low-grade inflammation and oxidative stress. Preserving active fractions and delivering to strategic intestinal segments contribute to generating bioactive metabolites and modulating pathways relevant to synaptic plasticity and neurotransmitter signaling.

Nanoemulsions of polyunsaturated fatty acids optimize digestion and micellation, increasing incorporation into neuronal membranes and influencing fluidity and signaling that support cognitive and mood functions. The consistent responses observed compared to conventional forms suggest that pharmaceutic gains translate into functional outcomes, especially when accompanied by adequate adherence and biomarker monitoring. In the case of fat-soluble vitamins such as D3, sustained-release polymeric nanoparticles may reduce plasma fluctuations and support neuromuscular and neurocognitive functions dependent on micronutrient homeostasis (PANDEY et al., 2018; LIU et al., 2022).

The biological plausibility of these interventions is strengthened when formulation design is integrated with relevant clinical and functional endpoints. Evaluations combining pharmacokinetic measures with markers of inflammation, oxidative stress, and cognitive functions help build chains of evidence. Trials incorporating variations in food matrix and physiological states, such as postprandial and fasting, enhance the applicability of results. Integration of biosensors and remote monitoring can provide adherence and response data in near real time, enabling dose adjustments and chronotherapy.

Safety remains central. The more intense interaction of sub-100 nm particles with epithelium and immune cells demands robust demonstrations of absence of relevant cytotoxicity, hemolysis, and genotoxicity, as well as control of endotoxins and residual surfactants. The balance between effect magnitude and safety margin should guide development and labeling decisions.

6. Dietary Supplements: Use Contexts, Bioavailability Challenges, and Nanotechnology Opportunities

Dietary supplements complement the diet and support physiological functions without intending to replace therapies. In Brazil, RDC No. 243 of 2018 consolidated the regulatory framework, defining positive lists, use limits, and rules for labeling and claims, which increased predictability for responsible innovation (ANVISA, 2018). Nonetheless, bioavailability challenges persist for highly functional ingredients such as polyphenols, fat-soluble vitamins, carotenoids, and polyunsaturated fatty acids. These compounds face limitations in solubility, gastrointestinal instability, and first-pass metabolism that restrict the absorbed fraction and the consistency of outcomes. In this context, food-grade nanostructures can improve luminal solubilization, protect against degradation, and modulate release, provided safety, compliance, and good manufacturing practices are respected.

Polyphenols such as curcuminoids, catechins, and resveratrol display lipophilicity and lability that hinder achieving effective systemic concentrations in conventional uses. Liposomes with food-grade phospholipids and oil-in-water nanoemulsions have been used to increase solubilization and stability, with reports of higher AUC than free forms when the system is rigorously characterized and stable over shelf life. These pharmaceutic gains align with functional effects related to modulation of inflammation and oxidative stress, directly relevant to well-being interventions and potential support for cognitive functions (GUTIERREZ et al., 2020; MCCLEMENTS, 2020).

Long-chain omega-3 fatty acids, such as EPA and DHA, depend on emulsification and digestion to form mixed micelles and cross the intestinal barrier. Stable nanoemulsions with sub-100 nm droplets, food-grade surfactants, and suitable oils can accelerate lipid digestion and increase solubilization in digestive colloids, yielding absorption superior to conventional presentations under biorelevant conditions. In applications aimed at brain health and well-being, this greater efficiency tends to produce more consistent responses, provided physicochemical stability is preserved against coalescence, Ostwald ripening, and lipid oxidation, and the palatability and safety of excipients are demonstrated (LIU et al., 2022; MCCLEMENTS, 2020).

The interface with the microbiome broadens opportunities. Probiotics require viability up to the site of action and protection against gastric pH and bile salts. Micro- and nanoencapsulation with enteric coatings can improve delivery to the small and large intestines. Prebiotics, as selective substrates benefiting host microorganisms, can be formulated in particles that modulate release and distal fermentation. Postbiotics, composed of inactivated microbial components and bioactive molecules, offer alternatives where stability and safety under variable environmental conditions are critical. In all cases, validating strain identity, effective dose, safety, and, when pertinent, endotoxins and cell wall components is indispensable to support claims and consumer protection, in line with international consensus (HILL et al., 2014; GIBSON et al., 2017; SALMINEN et al., 2021).

The design of nanotechnology-based supplements should follow guiding principles. First, select excipients with a history of safe use in foods and avoid solvents without consumption precedents. Second, adopt characterization methods adapted to the food context, including measurements of size and polydispersity by dynamic light scattering in biorelevant media, zeta potential, accelerated stability, and in vitro digestion simulating gastrointestinal conditions. Third, recognize that evidence for supplement claims is anchored in functional outcomes and validated markers, requiring pragmatic and field studies when superiority is intended. Fourth, apply quality-by-design from the outset, defining critical attributes, process variables, acceptance limits, and cleaning validation strategies for equipment in the presence of lipids and surfactants. These guidelines enable products with real bioavailability gains and consistent responses, preserving safety, transparency, and regulatory compliance (ANVISA, 2018; MCCLEMENTS, 2020; MCCLEMENTS; XIAO, 2014).

7. Results and Integrative Discussion

A synthesis of recent publications indicates that liposomes, polymeric nanoparticles, and nanoemulsions can significantly increase systemic exposure of actives with low solubility and limited stability. In liposomal curcumin, increases in AUC compared to free forms are observed, consistent with hypotheses of greater solubilization and protection against degradation, with the possibility of maintaining efficacy with lower doses, provided the bilayer is stabilized against oxidation and fusion (GUTIERREZ et al., 2020). In vitamin D3 encapsulated in PLGA, 24-hour sustained release reduces plasma fluctuations and may improve adherence in continued use, with emphasis on controlling residual solvents, polymer consistency, and process repeatability (PANDEY et al., 2018).

In omega-3 nanoemulsions, superior absorption and response consistency versus conventional presentations are explained by larger interfacial area, facilitated digestion, and efficient micellation, aligned with biorelevant in vitro digestion models and clinical outcomes. Stability against Ostwald ripening and lipid oxidation is critical to preserve performance over shelf life, requiring appropriate choices of oil phase, surfactants and antioxidants, and rigorous control of processing and storage (LIU et al., 2022). When translated to the domain of well-being and nutritional neuroscience, these pharmaceutic improvements support interventions with greater predictability of effect, especially when integrated with adherence strategies and monitoring of functional markers.

Safety accompanies efficacy in the integrative analysis. Lipid systems and biodegradable polymers tend toward favorable profiles when impurities, endotoxins, and process residues are controlled, and when size and surface attributes are maintained within safe ranges. The intensified interaction of sub-100 nm particles with epithelium and immune elements reinforces the need for comprehensive safety packages. Building in vitro–in vivo correlations and selecting relevant clinical endpoints strengthen result reliability and regulatory decision-making.

8. Regulatory Challenges and Industrial Scalability

Regulatory evaluation of products involving nanotechnology requires a quality, safety, and performance dossier with greater granularity than that required for conventional formulations, given the critical role of nanoscale physicochemical attributes in in vivo behavior. Authorities require detailed characterization of size and distribution, morphology, zeta potential, encapsulation efficiency, polydispersity, porosity when applicable, and release profile in biorelevant media, in addition to stability studies capturing phenomena such as coalescence, Ostwald ripening, and lipid oxidation. Scientific justification for selecting excipients, process routes, and analytical methods must demonstrate the connection between critical quality attributes and clinical/nutritional performance, with dossier transparency and traceability throughout the product life cycle, per international reference guidelines (FDA, 2014; ISO, 2012).

A quality-by-design and risk management approach constitutes the recommended framework for development and control. From ICH Q8, Q9, and Q10, explicit definition of critical quality attributes and critical process parameters is expected, the construction of a design space supported by design of experiments, and the implementation of a pharmaceutical quality system that supports continuous improvement and change governance. In nanotechnology, this implies simultaneously controlling variables such as shear energy, thermal gradients, interfacial composition, and residence times that directly impact size, polydispersity, and encapsulation efficiency, with sampling plans and acceptance criteria anticipating process drift and interlot variation. Real-time analysis strategies via process analytical technologies can strengthen the ability to keep the process within the design space, reducing variability and rework (ICH, 2005; ICH, 2008; ICH, 2009).

Scaling nanoformulations imposes unique challenges. High-shear and microfluidic processes that generate narrow size distributions at bench scale may exhibit nonlinearities when translated to pilot and industrial scales, with sensitivity to small deviations in viscosity, temperature, and feed rate. Maintaining narrow size distribution and high encapsulation efficiency requires instrumentation with fine control, periodic calibration, and inline monitoring of critical variables, as well as robust cleaning strategies that consider the presence of surfactants and lipids. In parallel, CAPEX and OPEX decisions should balance costs of raw materials and specialized equipment with the direct impact of formulation quality on efficacy, safety, and market competitiveness, considering product life cycle and traceability requirements (FDA, 2014; ISO, 2012).

In the CMC domain, comparability and change management are central. Since seemingly discrete variations in inputs, polymer supplier, shear force, or homogenization temperature can shift particle size or alter interfacial composition, defining comparability protocols and change management plans is indispensable. The dossier should establish measurable criteria to assert product similarity after changes and include data preserving the relationship between critical attributes and performance in biorelevant tests. Building in vitro–in vivo correlations, when feasible, and adopting specifications based on performance attributes strengthen predictability and reduce the need for redundant clinical studies in scale and manufacturing site changes, within the quality-by-design and pharmaceutical quality system frameworks (ICH, 2008; ICH, 2009).

Chemical and biological safety at the nanoscale requires a comprehensive data package. Cytotoxicity, hemocompatibility, and genotoxicity assays should be aligned with the use profile and route of administration, with attention to endotoxins, residual surfactants, residual solvents when applicable, and degradation products of polymers and phospholipids. Accelerated and shelf-life studies should monitor the emergence of oxidative byproducts in lipid systems and the evolution of size and polydispersity in nanoemulsions and liposomes. In polymeric nanoparticles, matrix degradation rate and potential alteration of release kinetics over shelf life need to be captured by validated methods. Adoption of standards and technical reports for physicochemical characterization at the nanoscale assists data comparability and regulatory interpretation (ISO, 2012; FDA, 2014).

International harmonization and early dialogue with authorities are accelerators of translation. Early scientific consultations and phased submissions allow aligning expectations on evidence sufficiency, avoiding rework and dossier gaps. In borderline areas such as dietary supplements and nutraceuticals, adherence to specific regulatory frameworks, such as Brazil's RDC No. 243, should be reconciled with best practices in characterization and safety for nanostructured systems, even when the evidence path relies predominantly on functional outcomes. Harmonizing methods and building shared databases on safety and performance reinforce predictability and confidence in the use of nanostructured platforms in public health (ANVISA, 2018; FDA, 2014).

Operationally, sustainable industrialization of nanoformulations incorporates metrics of energy efficiency, solvent minimization, and selection of excipients with a history of safe use, while preserving performance and regulatory compliance. Implementing continuous processes with inline monitoring, coupled with predictive maintenance strategies and qualification of sensitive equipment such as homogenizers and microfluidic devices, reduces variation and process deviations. Integrating design of experiments from early development through process validation allows establishing robust and scalable operating windows, maintaining product quality across different production campaigns within the approved design space (ICH, 2009; ISO, 2012).

Finally, post-marketing demands a pharmacovigilance and technovigilance system tailored to the specificities of nanostructures. Field quality monitoring plans, deviation investigation, and recall management should consider the risk of particle size drift, coalescence under storage conditions, and raw material variations that impact critical quality attributes. Systematic collection of performance and safety data, associated with internal product review processes and continuous improvement, closes the life cycle with a focus on quality-by-design, user safety, and consistency of response in real use, strengthening the evidence base that supports regulatory and clinical decisions in the long term (ICH, 2008; FDA, 2014).

9. Future Perspectives

Systems responsive to biological stimuli emerge as a natural evolution of nanostructured formulations, adding a spatiotemporal selectivity layer to active release. Platforms sensitive to gastrointestinal pH variations, digestive enzyme activity, and redox gradients in inflammatory microenvironments enable modulation of release kinetics closer to physiology, with potential to reduce unnecessary systemic exposure and, consequently, adverse events. In pharmaceutic design terms, this responsiveness can be achieved by incorporating polymers with ionizable groups, enzyme-cleavable linkages, or moieties sensitive to reactive species, integrated into established lipidic or polymeric matrices. Adoption of such mechanisms remains aligned with quality-by-design logic, in which critical attributes such as size, zeta potential, and encapsulation efficiency remain central, while new attributes related to triggers and response thresholds become equally critical for clinical and nutraceutical performance (ICH, 2009; ICH, 2005; FDA, 2014).

Lipid–polymer hybrid platforms represent another frontier of interest, combining the functional flexibility of lipid bilayers with the structural stability and programmability of biodegradable polymers. In core–shell configurations, a lipid core may favor solubilization of highly hydrophobic actives, while a polymer shell controls release and mucus interaction, reducing opsonization and aggregation. Alternatively, lipids can act as sealing layers or fusion domains over polymer matrices, expanding compatibility with biological membranes and optimizing transepithelial permeation. This hybrid architecture also facilitates anchoring surface ligands, when applicable, without sacrificing manufacturability and robustness, provided development integrates criteria of physicochemical stability, controlled degradation, and excipient safety per harmonized guidelines (ISO, 2012; ICH, 2008).

Convergence with biosensors and digital ecosystems introduces a dimension of continuous monitoring and dynamic dose adaptation. Wearable devices and point-of-care sensors can provide signals of adherence, physiological variables, and biomarkers that feed back into dosing schemes, opening room for chronotherapy and fine release adjustments in prolonged regimens. In nutraceuticals targeting well-being and brain health, combining data on sleep, heart rate variability, inflammatory markers, and mood parameters with controlled-release profiles may enable more precise and responsive interventions, while preserving safety margins and respecting the food nature of products where applicable. Feasibility of this integration requires cross-validation between digital measures and clinical outcomes, as well as an analytical framework connecting critical formulation attributes to reproducible field metrics, maintaining traceability and regulatory compliance (FDA, 2014; ICH, 2008).

Personalization based on metabolic, inflammatory, and microbiological profiles tends to benefit from the versatility of nanostructures, especially when combined with decision-support algorithms incorporating population pharmacokinetics and interindividual variability. In contexts of brain health and well-being, differences in lipid digestion, bile composition, and microbiota profile influence absorption and biotransformation of polyphenols, polyunsaturated lipids, and fat-soluble vitamins. In this direction, systems offering adjustable windows of loading, size, and interfacial hydrophobicity, coupled with biorelevant in vitro digestion tests and in vitro–in vivo correlations, can accelerate iteration cycles between formulation and clinical response. The goal is to align release with the individual's chronotype, habitual diet, and baseline inflammatory state, maintaining ease of use and manufacturing robustness to enable large-scale adoption (LIU et al., 2022; PANDEY et al., 2018).

In manufacturing and scalability, next steps include consolidating continuous routes under microfluidics and high-pressure homogenization with inline monitoring of particle size, polydispersity, and zeta potential, enabling statistical process control and interlot reproducibility. Integrating design of experiments from early phases, together with specifications based on critical quality attributes, can reduce variability and rework costs. In parallel, sustainability metrics and circular economy principles will likely guide selection of excipients and processes with lower carbon footprint and solvent consumption, without compromising safety and efficacy. This technical evolution should remain aligned with guidelines for physicochemical characterization of nanomaterials, ensuring comparable safety and performance assessments across the life cycle (ISO, 2012; ICH, 2009).

Lastly, regulatory and scientific advancements should deepen evaluation criteria for products involving nanotechnology, including standardization of in vitro lipid digestion assays, in vitro–in vivo correlation models for the oral route, and frameworks to demonstrate when stimulus-responsiveness adds measurable clinical benefit. Early dialogue with authorities, use of phased dossiers, and building shared databases on safety and performance can accelerate translation and reduce redundancies. In nutraceuticals and supplements in particular, harmonizing requirements for claims and validating functional markers will favor comparability across products, while the adoption of responsive and hybrid systems will demand transparency regarding mechanisms, critical attributes, and safe use limits, preserving consumer trust and the scientific integrity of claims (FDA, 2014; ICH, 2005; ICH, 2008).

10. Conclusion

Nanotechnology platforms offer concrete solutions to overcome solubility, permeability, and stability limitations that restrict the bioavailability of drugs and nutraceuticals. Liposomes, polymeric nanoparticles, and nanoemulsions demonstrate consistent gains in systemic exposure and release control compared to conventional forms, with potential to reduce doses and adverse events when development is guided by critical quality attributes and supported by robust characterization. Challenges in scalability and regulatory harmonization remain and require quality-by-design strategies, risk management, and early interaction with authorities. Incorporation of responsive systems, hybrid platforms, and biosensor-based monitoring points to a phase of greater precision and personalization, especially relevant for applications targeting the gut–brain axis and well-being.

- **Production Cost and Scalability:** The development and production of nanocarriers and personalized formulations are complex and currently high-cost processes. Research and development of new nanosystems, optimization of encapsulation processes, and industrial-scale manufacturing require significant investments in technology and infrastructure. This can make final products inaccessible to most consumers, limiting their widespread adoption (GOYAL et al., 2020).

- **Standardization and Quality Control:** The complexity of nanotechnological formulations and the variability of plant bioactives make standardization and quality control difficult. Ensuring the uniformity of nanoparticle size, encapsulation stability, purity of bioactives, and reproducibility of personalized formulation across different batches is a considerable technical challenge (MOHANTY; SAHOO, 2020).

- **Consumer Acceptance:** Despite growing interest in natural and personalized products, there may be resistance or distrust from consumers regarding nanotechnology, due to the perception of "chemicals" or a lack of understanding about what nanomaterials are and how they work. Transparent communication and public education are essential to build trust (PATIL et al., 2018).

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