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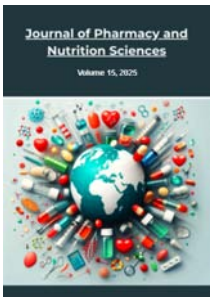

The Precision Nutraceutical Delivery Continuum: A Critical Review of Nanoencapsulation Strategies Bridging Pharmaceutical Engineering and Personalized Nutritional Therapy

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Abstract:

Most bioactive nutraceuticals and many oral pharmaceuticals share a common translational bottleneck: poor aqueous solubility, gastrointestinal instability, and low systemic bioavailability that blunt their clinical and nutritional benefit. Nanoencapsulation — the entrapment of a bioactive within a nanoscale lipid, polymeric, or hybrid carrier — has become the dominant engineering strategy to overcome this bottleneck, and the literature on individual carrier types (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric and chitosan-based nanoparticles, nanoemulsions) or individual bioactives (curcumin, resveratrol, quercetin, omega-3 polyunsaturated fatty acids, probiotics and postbiotics, micronutrients) has grown rapidly and largely in isolation. This review synthesises that fragmented evidence base into a single analytical frame. First, it summarises carrier chemistry, fabrication technologies (spray drying, electrospinning/ electrospraying, coacervation, ionic gelation, nanoprecipitation), and encapsulation-efficiency and bioavailability outcomes across five major bioactive classes, drawing on 50 verifiable primary and secondary sources published mainly between 2020 and 2026. Second, and as its principal novelty, the review proposes the Precision Nutraceutical Delivery Continuum (PNDC), a conceptual framework that cross-maps four generations of nanocarrier sophistication (conventional carriers, first-generation lipid/polymeric systems, stimuli-responsive smart carriers, and microbiome-/genotype-adaptive carriers) against four layers of inter-individual physiological variability (gastric pH-motility phenotype, gut-microbiome enterotype, pharmacogenomic and nutrigenomic polymorphism, and disease-specific metabolic state). The PNDC is offered as a hypothesis-generating design heuristic — not an empirically validated algorithm — intended to guide the next generation of "nanocarrier-phenotype matching" studies at the interface of pharmacy and nutrition science. Third, the review evaluates the regulatory and safety landscape governing nano-enabled nutraceuticals under the European Food Safety Authority, the United States Food and Drug Administration, and Indonesia's Food and Drug Authority (BPOM), including halal-assurance considerations relevant to Southeast Asian markets. We conclude that nanoencapsulation has matured from a bioavailability-enhancement tool into a platform technology with the potential to individualise nutritional therapeutics, but that its clinical translation is constrained by heterogeneous *in vitro-in vivo* correlation, insufficient long-term nanotoxicological data, and regulatory frameworks that have not yet caught up with stimuli-responsive and precision-oriented carrier designs.

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1. INTRODUCTION

Nutraceuticals — food-derived compounds credited with physiological benefit beyond basic nutrition — and a large proportion of orally administered pharmaceutical actives share a structural problem long recognised in the Biopharmaceutics Classification System: many of the most biologically interesting molecules (curcumin, resveratrol, quercetin, long-chain omega-3 polyunsaturated fatty acids, fat-soluble vitamins, and live or inanimate microbial biotherapeutics) are class II or class IV compounds, meaning their pharmacological promise *in vitro* is rarely matched by adequate absorption *in vivo* [1-3]. Nanoencapsulation, the packaging of such actives inside carriers with at least one dimension below one micrometre, has therefore evolved over the last two decades into the principal engineering response to this bottleneck, protecting labile cargo from gastric acid, digestive enzymes, and oxidative degradation while improving solubility, mucoadhesion, and epithelial uptake [1,2,32].

The resulting literature, however, is markedly siloed. Reviews tend to focus either on a single carrier chemistry — liposomes [13,15], solid lipid nanoparticles and nanostructured lipid carriers [10-12], polymeric and chitosan systems [21-26], or nanoemulsions [8,9] — or on a single bioactive class, most commonly curcumin [13-15], resveratrol and quercetin [16-20], omega-3 fatty acids [4-9], or probiotics and postbiotics [21,27-31]. Few works attempt to integrate carrier engineering, fabrication technology, gut-microbiome interaction, and regulatory science within a single analytical frame that speaks equally to a pharmaceutical formulator and a nutrition scientist — the dual audience this journal serves. This fragmentation matters because the same physicochemical design levers (particle size, surface charge, wall-material chemistry, and release trigger) recur across bioactive classes, and lessons learned in pharmaceutical nanocarrier design (e.g., stimuli-responsive release for oncology [36,37]) are frequently rediscovered rather than transferred into nutraceutical formulation, and vice versa.

This review therefore pursues three objectives. First, it consolidates the evidence on nanocarrier chemistry, fabrication technique, and bioavailability outcome across five major bioactive classes using 50 independently verifiable sources. Second, and as its central conceptual contribution, it proposes the Precision Nutraceutical Delivery Continuum (PNDC), a framework that explicitly cross-maps nanocarrier sophistication against layers of inter-individual physiological variability, intended to reframe nanoencapsulation not merely as a bioavailability fix but as a platform for individualised nutritional and pharmaceutical therapy. Third, it evaluates the regulatory and halal-assurance landscape relevant to translating these technologies into Indonesian and broader Southeast Asian markets, an aspect largely absent from the existing international literature. This explicit gap distinguishes the present review from recent (2020-2026) reviews on nanoencapsulation of nutraceuticals, which remain confined to describing carrier chemistry or single-bioactive evidence and do not propose a framework linking carrier sophistication to inter-individual physiological variability, nor an integrated regulatory and halal-assurance analysis for the Southeast Asian context (Section 2.2 details this comparison; Section 1.1 details the search methodology underlying this claim).

1.1. Review Methodology

This review is a narrative (non-systematic) critical review; nonetheless, source identification followed a structured protocol to ensure transparency and reproducibility. The literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for records published between January 2020 and February 2026, using combinations of the terms "nanoencapsulation", "nanocarrier", "nutraceutical delivery", "bioavailability", "liposome", "solid lipid nanoparticle", "nanostructured lipid carrier", "polymeric nanoparticle", "chitosan", "nanoemulsion", "stimuli-responsive carrier", "probiotic encapsulation", "postbiotic", "curcumin", "resveratrol", "quercetin", "omega-3", "precision nutrition", "nanotoxicology", and "regulatory framework", combined with Boolean operators. Records were screened first by title and abstract and then by full text against the following inclusion criteria: (i) peer-reviewed original research, systematic or narrative reviews, or authoritative regulatory/guidance documents; (ii) explicit reporting of a nanoscale (<1 μm) delivery system for a nutraceutical or a closely related oral pharmaceutical active; (iii) quantitative or clearly described qualitative outcome data (encapsulation efficiency, particle size, bioavailability, stability, survival, or safety endpoint); and (iv) publication in English, or, for Indonesian regulatory instruments, official BPOM text. Exclusion criteria were conference abstracts without a peer-reviewed full text, non-oral delivery studies outside the nutraceutical-pharmaceutical scope of this review, and

studies whose full text could not be independently verified against a DOI, PMID, or PMCID. Of the records identified, 50 sources meeting these criteria were retained and independently verified prior to inclusion, prioritising 2023-2026 primary literature while retaining a smaller number of foundational or regulatory sources published earlier. Source selection and synthesis were performed by the sole author; because this is a narrative rather than systematic review, no formal risk-of-bias tool or PRISMA flow diagram was applied, a limitation acknowledged in Section 9.

2. THE PRECISION NUTRACEUTICAL DELIVERY CONTINUUM: A NOVEL INTEGRATIVE FRAMEWORK

The novelty of this review rests on reframing nanoencapsulation along two orthogonal axes rather than describing carriers and bioactives as parallel, unconnected lists. The first axis, carrier sophistication, spans four generations: (i) conventional/ unencapsulated or simple emulsion delivery; (ii) first-generation nanocarriers (liposomes, solid lipid nanoparticles, basic polymeric nanoparticles) engineered chiefly for protection and passive bioavailability enhancement [10-15,21,22]; (iii) stimuli-responsive "smart" carriers that release cargo in response to pH, enzymatic, or redox triggers along the gastrointestinal tract [8,25,36,37]; and (iv) microbiome- or genotype-adaptive carriers, an emerging class designed to interact deliberately with the gut microbiome or to be selected according to an individual's metabolic or genetic profile [27-31,42].

The second axis, physiological variability, comprises four layers that determine how a given carrier will actually behave once ingested by a specific person: gastric pH and motility phenotype; gut-microbiome enterotype and its enzymatic repertoire [32-35]; pharmacogenomic and nutrigenomic polymorphisms affecting absorption and metabolism [42-44]; and disease-specific metabolic states (e.g., inflammatory bowel disease, metabolic syndrome) that alter gastrointestinal barrier integrity and microbial composition [21,34,35]. The PNDC (Figure **1**) cross-tabulates these two axes, generating sixteen conceptual cells that describe the degree of "carrier-phenotype matching" achievable with current technology. Most published nutraceutical nanoencapsulation studies to date cluster in the intersection of generation-ii carriers with a physiologically "average" (non-stratified) recipient — that is, formulation optimisation has outpaced recipient

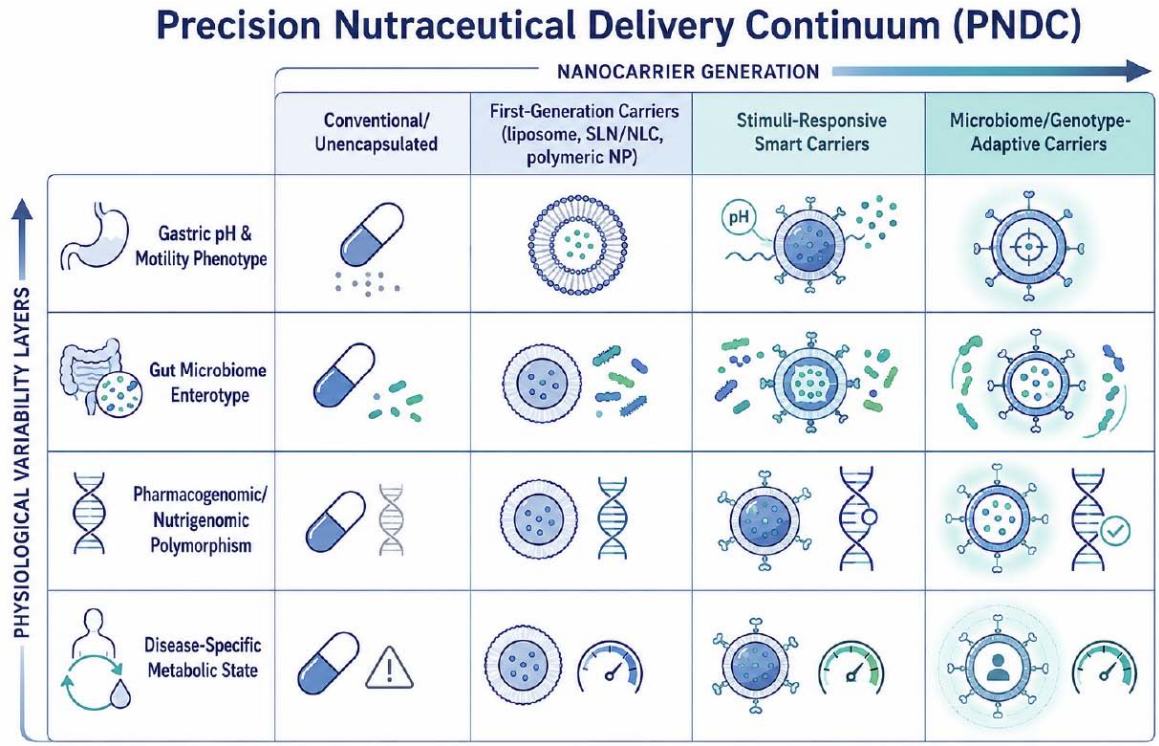

Figure 1: Conceptual schematic of the Precision Nutraceutical Delivery Continuum (PNDC), cross-mapping four generations of nanocarrier sophistication against four layers of inter-individual physiological variability. The framework is proposed as a hypothesis-generating design heuristic synthesised from the evidence reviewed in Sections 3-6 [1-3,8,10-15,21,22,25,27-37,42-44], not as an empirically validated predictive tool.

stratification. We propose the PNDC explicitly as a hypothesis-generating design heuristic to guide future formulation-genotype and formulation-enterotype matching studies; it is not itself an empirically validated predictive algorithm, and its predictive value will need prospective testing before clinical or regulatory application.

2.1. Justification of the Framework's Granularity

The choice of four carrier generations and four physiological-variability layers is not arbitrary: each axis was bounded by the granularity actually reported in the reviewed literature rather than expanded to a finer taxonomy that current evidence could not support. Carrier sophistication was limited to four generations because the reviewed literature clusters coherently into these tiers — passive/simple-emulsion delivery, first-generation protective nanocarriers, stimuli-responsive smart carriers, and microbiome-/genotype-adaptive carriers — with no consistently reported intermediate class; collapsing this into three generations would conflate mechanistically distinct stimuli-responsive and adaptive designs, while expanding to five or more would fragment the evidence base into cells with too few studies to support meaningful synthesis. Similarly, the four physiological-variability layers were selected because they are the host-level determinants of nanocarrier fate most consistently measured or discussed in the reviewed evidence (Section 6); other candidate layers, such as circadian variation in gastrointestinal transit or sex-specific differences in microbiome composition, were considered but excluded because they are not yet addressed with sufficient consistency in the nanoencapsulation literature to populate a matrix cell.

2.2. Advancement Beyond Existing Precision-Nutrition Models

The PNDC differs from existing precision-nutrition models — such as nutrigenomics-based dietary-stratification frameworks and microbiome-informed dietary-response models [42-44] — in that those frameworks stratify the recipient (genotype, enterotype, metabolic phenotype) without addressing how the delivery vehicle itself should be engineered to match that stratification; conversely, nanocarrier design reviews [10-15,21,22,25,36,37] optimise the vehicle without systematically referencing recipient variability. The PNDC's specific contribution is therefore the explicit cross-mapping of these two previously separate literatures into a single matrix, making visible which carrier-phenotype combinations are already supported by evidence and which remain unstudied (Section 7); it does not claim algorithmic or predictive novelty beyond this organisational and hypothesis-generating function, and its cells will require prospective validation before any clinical or regulatory application, as already noted above.

3. FUNDAMENTALS AND CLASSIFICATION OF NANOCARRIER SYSTEMS

3.1. Lipid-Based Carriers

Liposomes remain the most clinically mature nanocarrier class, with phospholipid bilayers that protect hydrophobic cargo such as curcumin while enabling both hydrophilic and lipophilic loading. A randomized, double-blind pharmacokinetic trial of a double-layered chitosan/alginate-coated nano-liposomal curcumin (BNT-C060) reported a 23.2-fold higher plasma area-under-curve relative to an equivalent dose of free curcumin in healthy volunteers [14], while earlier liposomal curcumin formulations using different lecithin sources produced 5-10-fold bioavailability gains in comparative pharmacokinetic reviews [13,15]. Solid lipid nanoparticles (SLN) and their second-generation counterpart, nanostructured lipid carriers (NLC), extend this protection using a solid or mixed solid/liquid lipid matrix; NLC in particular combine higher drug-loading capacity with improved storage stability relative to SLN because their imperfect crystal lattice accommodates more active compound without expulsion during storage [10,12]. Comparative reviews of oral antioxidant nutraceutical delivery report that lipid nanoparticles enhance gastrointestinal transport chiefly by increasing loading capacity, improving physicochemical stability, and prolonging residence time at the absorptive mucosa [11].

3.2. Polymeric Carriers

Chitosan — a cationic, mucoadhesive, biodegradable polysaccharide — is the most widely used natural polymer for oral nanoparticle design because its positive surface charge favours electrostatic interaction with the negatively charged intestinal mucus layer, prolonging transit time and promoting paracellular and transcellular uptake [25]. Poly(lactic-co-glycolic acid) (PLGA), an FDA-approved synthetic polymer, offers tunable degradation kinetics through its lactide:glycolide ratio and has been used to co-encapsulate resveratrol and quercetin for pH-sensitive colorectal delivery, achieving encapsulation efficiencies

exceeding 80% with particle sizes of 174-177 nm [19]; single-agent resveratrol-PLGA nanoparticles have separately achieved encapsulation efficiencies above 97% [18]. Plant-protein carriers such as zein are gaining traction for co-delivering multiple polyphenols in layered nanostructures, exploiting zein's amphiphilic self-assembly behaviour [20].

3.3. Nanoemulsion-Based Systems

Oil-in-water nanoemulsions are the delivery system of choice for lipophilic, oxidation-prone actives such as omega-3 polyunsaturated fatty acids, where droplet-size reduction below roughly 200 nm increases the interfacial surface area available for lipase action, accelerating micellar solubilisation and intestinal uptake, though this can also accelerate premature hydrolysis if not stabilised with an appropriate emulsifier or protein coating [8]. A systematic review and data-mining analysis of 23 controlled studies confirmed that nanoencapsulation consistently reduces oxidative degradation of unsaturated omega-3 fatty acids relative to bulk oil across storage conditions [6].

3.4. Stimuli-Responsive Carriers

A growing subset of nanocarriers is engineered to remain stable under physiological conditions but to disassemble in response to a specific trigger — reduced pH, elevated glutathione/redox potential, or site-specific bacterial or digestive enzymes — thereby restricting cargo release to a target gastrointestinal segment or diseased tissue [36,37]. Although this design logic originated largely in oncology drug delivery, the same pH- and enzyme-responsive chemistries are now being adapted for colon-targeted probiotic and postbiotic release [25,35].

4. MANUFACTURING AND FABRICATION TECHNOLOGIES

The choice of fabrication technique governs particle morphology, encapsulation efficiency, and scalability, and is therefore inseparable from carrier selection. Spray drying remains the industrial workhorse owing to its continuous, solvent-minimal, and cost-effective operation, converting a liquid feed containing the bioactive and a protein or carbohydrate wall material into a dry powder in a single step [46,48]. Electrospinning and electrospraying use a high-voltage electric field to draw a polymer solution into nanofibres or nanoparticles respectively, offering finer morphological control and gentler processing conditions suited to heat-labile peptides and bioactives, though at lower throughput than spray drying [38,39]. Complex coacervation exploits electrostatic interaction between oppositely charged biopolymers (commonly a

Table 1: Comparative Summary of Major Nanocarrier Platforms Used for Nutraceutical and Pharmaceutical Delivery

Carrier class	Typical size / EE range	Representative bioactive(s)	Principal advantage	Principal limitation	Key source(s)
Liposomes	80-400 nm; EE 60-95%	Curcumin, vitamin C/glutathione	Amphiphilic loading; clinically validated	Phospholipid oxidation; scale-up cost	[13-15,17]
Solid lipid nanoparticles (SLN)	50-300 nm; EE 40-90%	Antioxidant polyphenols	Biocompatible, solvent-free production	Drug expulsion on storage (crystallisation)	[10,11]
Nanostructured lipid carriers (NLC)	50-300 nm; EE up to ~95%	Antioxidants, lipophilic vitamins	Higher loading than SLN; better stability	Complex lipid-blend optimisation	[10,12]
Polymeric NP (chitosan)	100-400 nm; EE 70-91%	Probiotics, bioactive peptides	Mucoadhesive; pH-responsive natural polymer	Batch-to-batch polymer variability	[21-26]
Polymeric NP (PLGA)	150-250 nm; EE 78-97%	Resveratrol, quercetin	FDA-approved; tunable release kinetics	Organic-solvent residues; acidic microenvironment on degradation	[18,19]
Nanoemulsions	20-200 nm droplet size	Omega-3 PUFA, curcumin	High interfacial area; food-compatible	Oxidative instability without coating	[6,8,9]
Stimuli-responsive carriers	Variable (50-300 nm)	Colon-targeted probiotics/postbiotics; oncology actives	Site-specific, triggered release	Complex synthesis; limited regulatory precedent	[25,36,37]

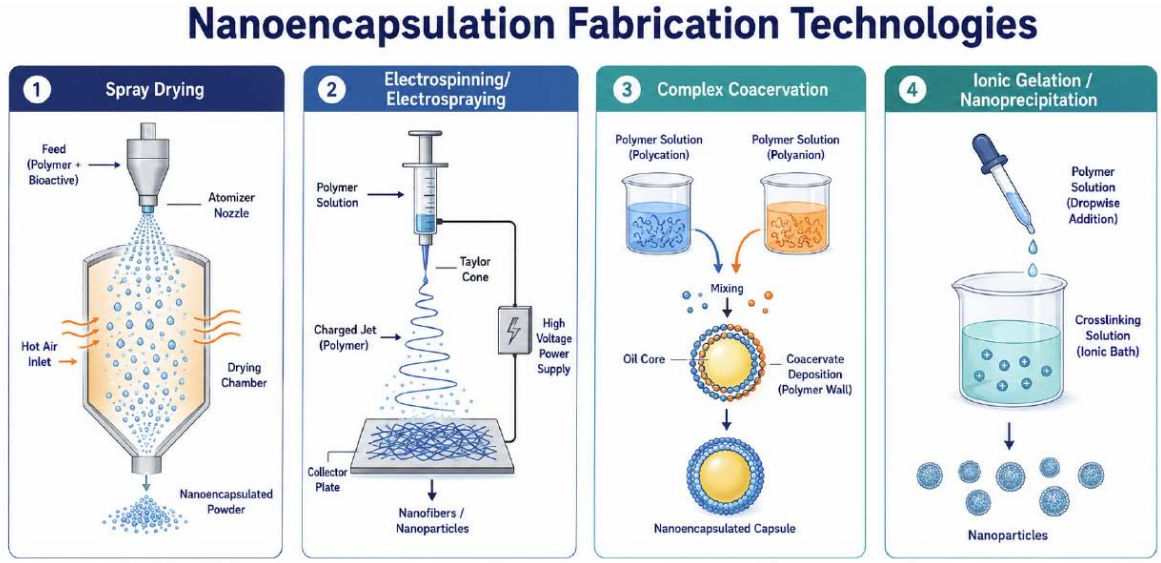

Figure 2: Schematic overview of the four principal fabrication technologies used to manufacture nutraceutical and pharmaceutical nanocarriers: spray drying, electrospinning/electrospraying, complex coacervation, and ionic gelation/nanoprecipitation [24-26,38-40,46,48].

protein and a polysaccharide) to form a wall around an oil or aqueous core, and is particularly favoured for probiotic microencapsulation because processing can be conducted near ambient temperature, preserving microbial viability [40]. Ionic/ionotropic gelation and nanoprecipitation, meanwhile, are the methods of choice for chitosan- and PLGA-based nanoparticles respectively, offering simple, scalable, solvent-light protocols [24-26].

5. BIOACTIVE-SPECIFIC EVIDENCE SYNTHESIS

The quantitative outcomes synthesised below derive from evidence of markedly different strength, spanning randomized double-blind human clinical trials, rodent and other animal experiments, *in vitro* cell-based assays, simulated gastrointestinal-fluid models, and food-matrix (food-system) models; because these evidence levels are not interchangeable, the evidence type is stated explicitly alongside each quantitative claim in Sections 5.1-5.4 and summarised in the "Model" column of Table **2**, and the reader is cautioned against extrapolating rodent- or in-vitro-derived magnitude estimates directly to expected human outcomes.

5.1. Curcumin and Polyphenols

Curcumin is the most extensively nanoencapsulated nutraceutical in the literature, reflecting both its well-documented anti-inflammatory and antioxidant pharmacology and its notoriously poor native bioavailability. Beyond the pharmacokinetic gains already noted for liposomal formulations [13-15], curcumin-loaded liposomal nanoparticles consistently demonstrate high encapsulation efficiency, controlled release, and improved physicochemical stability relative to free curcumin (evidence base predominantly *in vitro* physicochemical characterisation), setting the stage for expanded clinical evaluation, including an ongoing Phase I/II trial combining intravenous liposomal curcumin with radiotherapy and temozolomide in high-grade glioma [16]. Resveratrol and quercetin, two structurally related polyphenols with overlapping anti-inflammatory and anticancer signalling effects, face a similar bioavailability ceiling; PLGA and casein-based nanoparticle formulations have achieved 2- to 10-fold increases in oral bioavailability in rodent models [17-19], while pH-sensitive PLGA/Eudragit co-delivery systems allow simultaneous, site-targeted release of both compounds [19].

5.2. Omega-3 Polyunsaturated Fatty Acids

Long-chain omega-3 fatty acids (EPA and DHA) are highly susceptible to oxidative degradation, a problem nanoencapsulation addresses by physically isolating the unsaturated lipid from oxygen and prooxidant metal ions [6]. Whey-protein-based micro- and nanoencapsulation improves both oxidative stability and gastrointestinal bioaccessibility of omega-3 PUFA in food-matrix applications [5], while metal-organic-framework and other advanced nanoparticle platforms are being explored specifically for cardiovascular indications, given the substantial global burden of

cardiovascular disease — this application remains at a preclinical/conceptual stage and has not yet been evaluated in human cardiovascular-outcome studies [4]. Nanoemulsion and microgel comparisons show that delivery-system architecture materially changes the rate and extent of *in vitro* lipolysis, underscoring that carrier choice affects not only stability but also the kinetics of release within the simulated gastrointestinal tract [7,8].

5.3. Micronutrients and Vitamin Delivery

Deficiencies of vitamins D, A, E, K, B12, and folate remain a persistent global public-health problem despite widespread supplementation efforts, in part because conventional oral formulations do not adequately address individual variation in mucosal uptake. Nanoparticle-based vitamin delivery systems — spanning lipid nanoparticles, polymeric carriers, liposomes, and protein/peptide-based carriers — are increasingly framed explicitly as a precision-nutrition tool, with authors calling for integration of artificial intelligence and stimuli-responsive materials to tailor vitamin delivery to individual metabolic needs; at present, this remains largely conceptual and early-stage *in vitro*/formulation work rather than validated human outcome data [42].

5.4. Probiotics and Postbiotics

Encapsulation of live probiotic bacteria addresses the central challenge of viability loss during gastric transit; chitosan-based and chitosan/alginate composite nanoparticles have improved survival of Lactobacillus species under simulated gastrointestinal fluid from roughly 29% (unencapsulated) to 52-91% depending on wall-material composition [21-26]. Postbiotics — inanimate microbial cells, cell fragments, or metabolites that retain bioactivity without requiring viability — represent a more recent and arguably more nanoencapsulation-compatible category, since formulation no longer needs to preserve a living organism; postbiotic nanoparticles have demonstrated enhanced antimicrobial potency (up to four-fold against resistant Enterococcus strains, based on *in vitro* antimicrobial assay data) and expanded application into topical, food-preservative, and functional-food formats [27-31].

6. GASTROINTESTINAL FATE, GUT-MICROBIOME INTERACTION, AND BIOACCESSIBILITY

Once ingested, a nanocarrier's fate is co-determined by the host digestive physiology and the resident gut microbiota, a bidirectional relationship that is often underweighted in formulation-centric reviews.

Table 2: Summary of Representative Bioavailability, Stability, or Efficacy Outcomes for Nanoencapsulated Bioactives, Organized by Class

Bioactive class	Carrier used	Reported outcome	Model	Source(s)
Curcumin	Double-layered nano-liposome (BNT-C060)	23.2-fold higher plasma AUC vs. free curcumin	Randomized double-blind human trial	[14]
Curcumin	Liposome (varied lecithin source)	5-10-fold bioavailability increase	Human pharmacokinetic review	[13,15]
Resveratrol	Casein nanoparticle	10-fold oral bioavailability increase (26.5%)	Rat model	[18]
Resveratrol + quercetin	PLGA/Eudragit S100 pH-sensitive NP	EE > 80%; targeted colorectal release	*In vitro* colorectal cancer model	[19]
Omega-3 (EPA/DHA)	Whey-protein nano/microcapsule	Improved oxidative stability & bioaccessibility	Food-system model	[5]
Omega-3 (flaxseed oil)	Nanoemulsion vs. microgel	76% vs. 65% FFA release in 5 min (delivery-system dependent)	Simulated GIT digestion	[8]
Lactobacillus plantarum	Alginate/nano-chitosan wall	Survival increased from ~29% to ~58%	Simulated gastrointestinal fluid	[24]
Postbiotic (Enterococcus bacteriocin)	Liposome	4-fold increase in antimicrobial activity	*In vitro* antimicrobial assay	[27]

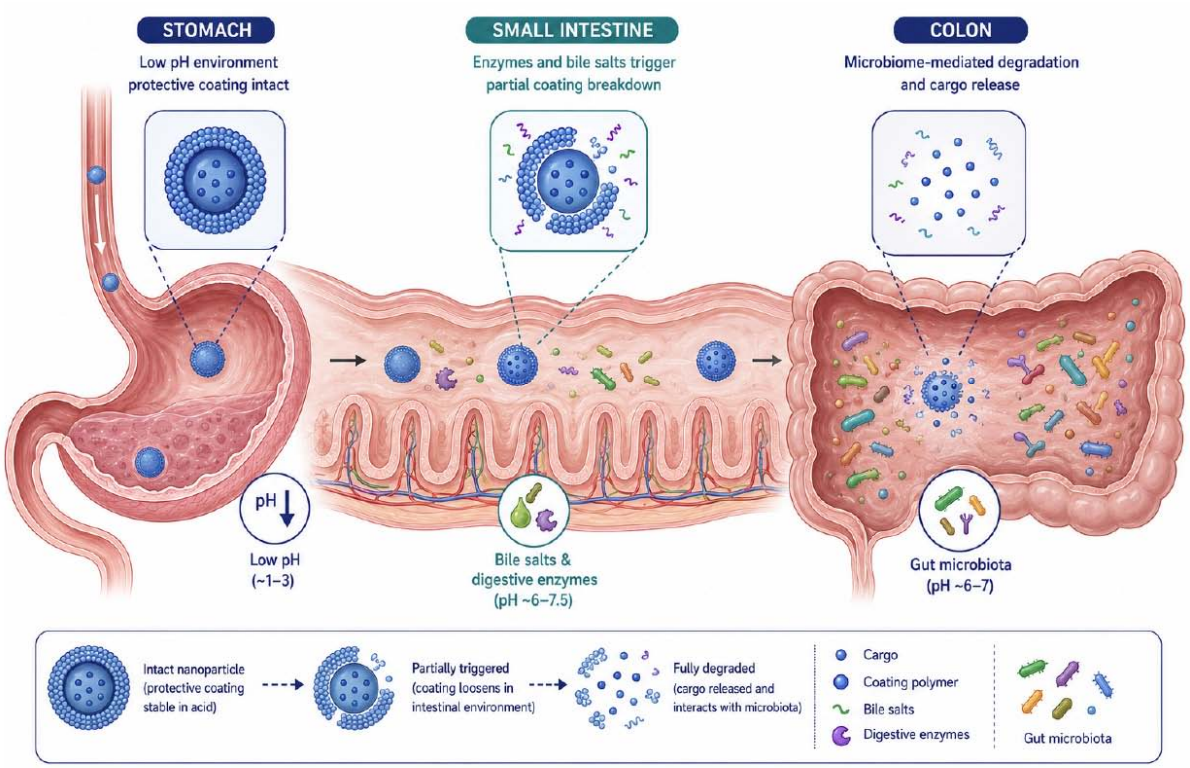

Figure 3: Schematic representation of nanocarrier transit and triggered cargo release along the gastrointestinal tract, and its bidirectional interaction with the gut microbiome [32-35].

Nanoparticles can alter microbial community composition, and conversely, the microbiome's enzymatic and fermentative activity can degrade or activate nanocarrier wall materials, particularly polysaccharide-based coatings designed for colonic release [32-35]. Comprehensive reviews of oral nanoparticle fate emphasise that absorption pathway (paracellular, transcellular, or M-cell-mediated transcytosis in Peyer's patches), together with mucus-layer interaction, jointly determine the fraction of an administered dose that reaches systemic circulation, and that current *in vitro* digestion models only partially capture this complexity [32,33]. In inflammatory bowel disease models, nanoparticle-based delivery has been shown to modulate gut-microbiota dysbiosis directly, in addition to delivering an encapsulated active, suggesting nanocarriers can function as therapeutic agents in their own right rather than purely as passive vehicles [34,35].

7. THE PNDC IN PRACTICE: TOWARD GENOTYPE- AND MICROBIOME-ADAPTIVE CARRIER DESIGN

Building on Sections 3-6, the PNDC introduced in Section 2 can be given concrete formulation correlates. At the intersection of stimuli-responsive carriers and gut-microbiome enterotype, pH- and enzyme-triggered chitosan or alginate coatings are already being tuned to specific colonic bacterial enzyme profiles for targeted probiotic or postbiotic release [25,35], illustrating one populated cell of the matrix. At the intersection of microbiome-adaptive carriers and nutrigenomic polymorphism, precision-nutrition scholarship has begun to call explicitly for artificial-intelligence-assisted, omics-informed tailoring of nutrient and vitamin delivery [42-44], but corresponding nanocarrier engineering work that operationalises this call remains scarce. Two cells of the PNDC matrix — carrier design explicitly stratified by pharmacogenomic profile, and carrier design explicitly stratified by disease-specific metabolic state beyond inflammatory bowel disease — are essentially unoccupied in the current literature and are proposed here as priority research gaps. We suggest that closing these gaps will require interdisciplinary study designs that pair standard nanocarrier characterisation (particle size, zeta potential, encapsulation efficiency, *in vitro* release) with individual-level covariates (16S/shotgun microbiome sequencing, relevant single-nucleotide polymorphism panels, and gastrointestinal transit-time phenotyping) within the same cohort — a design that neither the pharmaceutical nanotechnology literature nor the precision-nutrition literature currently performs routinely.

8. REGULATORY, SAFETY, AND HALAL-COMPLIANCE CONSIDERATIONS

8.1. International Frameworks

The European Food Safety Authority (EFSA) maintains dedicated guidance for risk assessment of engineered nanomaterials applied in the food and feed chain, requiring physicochemical characterisation, migration/exposure testing, and hazard data spanning genotoxicity, absorption-distribution-metabolism-excretion, and repeated-dose oral toxicity before a nanomaterial can be approved for use as a food additive, novel food ingredient, or food-contact material [46]. EFSA has since 2024 been developing New Approach Methodologies (NAMs) — in silico, in chemico, *in vitro*, and ex vivo alternatives to animal testing — specifically for nanomaterial risk assessment, reflecting the field's continued methodological evolution [45]. In the United States, the Food and Drug Administration regulates nanomaterials in food-contact applications through the Food Contact Notification process, requiring manufacturers to submit migration and toxicological data [47]. Independent nanomaterial reviews continue to flag insufficient long-term human toxicity data and inconsistent nanoparticle characterisation across the published literature as unresolved concerns for both regions [48].

8.2. The Indonesian Regulatory Landscape

BPOM regulates health supplements, traditional medicines, and processed food under a risk-based licensing framework that has been substantially updated through 2025-2026, including Peraturan BPOM Nomor 27 Tahun 2025 on risk-based business licensing standards for the drug and food subsectors and, specifically relevant to one bioactive class reviewed here, Peraturan BPOM Nomor 17 Tahun 2025 on the assessment guideline for probiotic-containing health-supplement products [49]. Unlike the EFSA and FDA frameworks, current Indonesian regulation does not yet contain a nanomaterial-specific risk-assessment pathway analogous to EFSA's nano-guidance, meaning nanoencapsulated nutraceutical products are currently evaluated under the general health-supplement or functional-food registration pathway. This represents both a translational opportunity — streamlined market entry relative to jurisdictions with dedicated nano-approval steps — and a regulatory-science gap, since carrier-specific safety endpoints (biodistribution of nanoscale wall material, chronic accumulation potential) are not explicitly required. For halal-sensitive Southeast Asian markets, an additional layer of assurance is required at the level of wall-material sourcing (e.g., gelatin, phospholipid, or surfactant origin) and processing aids, an area increasingly addressed through structured halal-assurance frameworks being proposed for the broader food and pharmaceutical sector [50]. We recommend that any nanoencapsulated nutraceutical intended for the Indonesian market undergo parallel BPOM risk-based licensing and halal-certification review from the earliest formulation stage, rather than treating halal assurance as a post-hoc labelling exercise.

8.3. Nanotoxicology and Long-Term Safety Considerations

The safety literature synthesised in Sections 8.1-8.2 addresses regulatory process rather than the

Table 3: Comparative Summary of Regulatory Frameworks Governing Nanoencapsulated Nutraceutical and Food-Grade Nanomaterials

Jurisdiction/Body	Governing instrument	Nano-specific requirement	Key gap	Source(s)
European Union (EFSA)	SC Guidance on Nano-RA; EU Reg. 10/2011 (food-contact)	Physicochemical characterisation, migration testing, genotoxicity/ADME/90-day oral toxicity	NAMs still under implementation (open until Oct 2026)	[45,46]
United States (FDA)	Food, Drug & Cosmetic Act; Food Contact Notification	Manufacturer-submitted migration & toxicological data	No unified nano-specific statute; case-by-case review	[47,48]
Indonesia (BPOM)	PerBPOM No. 27/2025; PerBPOM No. 17/2025 (probiotic supplements)	General risk-based licensing; no dedicated nano-pathway	Absence of nanomaterial-specific safety-data requirement	[49]
Halal assurance (Indonesia/ASEAN)	Sector-specific halal-assurance frameworks	Wall-material and processing-aid origin verification	Limited integration with nanocarrier-specific formulation review	[50]

underlying toxicological evidence base in depth, which merits closer treatment given that nutraceuticals, unlike most pharmaceuticals, are typically consumed chronically at low dose. Long-term oral administration is the least-studied exposure scenario: the great majority of nanotoxicological data derive from single-dose or short-duration (28- to 90-day) repeated-dose rodent studies, and chronic (>90-day) or lifetime oral-exposure data directly relevant to daily nutraceutical supplementation remain sparse across all carrier classes reviewed here [45-48]. Systemic exposure and biodistribution are a related concern: nanoscale carriers below approximately 200 nm can cross the intestinal epithelium via paracellular, transcellular, or M-cell-mediated transcytosis (Section 6), and wall-material components that are not fully metabolised may translocate into systemic circulation and accumulate in the liver, spleen, or other reticuloendothelial organs; such accumulation potential is acknowledged as a data gap in current EFSA and FDA guidance rather than a characterised risk with defined thresholds [45-48]. Carrier-material toxicity also differs materially by chemistry: lipid-based carriers (liposomes, SLN, NLC) are generally regarded as lower-concern because their components are frequently endogenous or GRAS-status lipids that are metabolised through native lipolytic pathways, whereas polymeric carriers can raise chemistry-specific concerns — for example, residual organic solvent in PLGA nanoparticle manufacture, or the degradation-product profile of synthetic polymers — that are less relevant to natural polysaccharide carriers such as chitosan or alginate [10-12,18,19,25]. Finally, food-grade and pharmaceutical-grade nanocarriers are not interchangeable from a safety standpoint: pharmaceutical nanocarriers are typically administered at defined, monitored doses under clinical supervision with formal pharmacokinetic and toxicological characterisation prior to approval, whereas food-grade nanocarriers in a nutraceutical supplement are self-administered, taken chronically without clinical monitoring, and evaluated against food-safety rather than drug-safety toxicological thresholds; this distinction underlies why several jurisdictions, including Indonesia, currently regulate nanoencapsulated nutraceuticals under general food/supplement pathways that do not yet require the carrier-specific systemic-exposure and accumulation data that would be expected of an equivalent pharmaceutical nanocarrier (Section 8.2). We consider closing this evidence gap — particularly chronic oral-exposure and biodistribution data disaggregated by carrier chemistry — a precondition for the confident clinical translation of the PNDC's more advanced carrier generations.

9. CHALLENGES AND FUTURE RESEARCH DIRECTIONS

Four challenges recur across the evidence synthesised here. First, *in vitro-in vivo* correlation remains weak: most encapsulation-efficiency and release-kinetics data derive from simulated gastrointestinal fluids or rodent models, and human pharmacokinetic confirmation exists for only a minority of formulations, most prominently curcumin [13-15]. Second, long-term nanotoxicological data are sparse relative to the pace of formulation innovation, particularly for chronic, low-dose oral exposure typical of a daily nutraceutical supplement rather than an acute pharmaceutical intervention [45-48]. Third, manufacturing scale-up frequently degrades the encapsulation efficiency and particle-size uniformity achieved at laboratory scale, a translational gap rarely addressed quantitatively in the reviewed literature. Fourth, and central to the argument advanced here, formulation science and precision-nutrition/nutrigenomic science remain largely disconnected disciplines; realising the PNDC's microbiome- and genotype-adaptive quadrant will require deliberate interdisciplinary trial designs, harmonised regulatory pathways of the kind BPOM and EFSA are each independently developing, and — specific to the Indonesian and broader Southeast Asian context — halal-assurance integration from the earliest stage of formulation design rather than as a downstream certification step.

10. CONCLUSION

Nanoencapsulation has matured from a narrow bioavailability-enhancement technique into a platform technology capable, at least in principle, of individualising nutritional and pharmaceutical therapy. The evidence reviewed here across liposomal, lipid-nanoparticle, polymeric, nanoemulsion, and stimuli-responsive carrier classes consistently demonstrates multi-fold improvements in the stability, bioaccessibility, and, where human data exist, bioavailability of otherwise poorly absorbed nutraceuticals. The Precision Nutraceutical Delivery Continuum proposed in this review offers a structured way to identify where the field's next advances are most needed — chiefly at the underexplored intersection of smart-carrier engineering with individual gut-microbiome and genomic variability — while the regulatory analysis underscores that Indonesian and international

frameworks alike have not yet fully caught up with the sophistication of the carriers now entering the literature. Closing both gaps will require formulation scientists, nutrition scientists, and regulators to work from a shared conceptual map rather than parallel, discipline-specific literatures.

AUTHOR CONTRIBUTIONS

A.S. conceived the review, performed the literature search and verification, developed the Precision Nutraceutical Delivery Continuum framework, and wrote and approved the final manuscript.

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CONFLICT OF INTEREST

The author declares no conflict of interest. The views expressed are the author's own and do not represent the official position of the Indonesian Food and Drug Authority (BPOM).

DATA AVAILABILITY

No new data were generated; all sources synthesised are cited in the reference list and independently verifiable via the indicated DOI, PMID, or PMCID.

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