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Surfactants as molecular architects of materials: from interfacial organization to function

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ABSTRACT

Surfactants are versatile molecular tools that control the formation, stabilization, organization and function of materials across multiple length scales, yet the literature treating them remains fragmented across colloid science, soft matter, nanomaterial synthesis, catalysis, energy materials, nanomedicine and sustainable materials chemistry. This Review develops a unifying, materials-centred framework positioning surfactants as molecular architects rather than passive additives, tracing a single causal chain: molecular design determines interfacial adsorption and organization; organization directs nucleation, growth and self-assembly; the resulting dynamic organization determines material formation and structure; and structure, in turn, determines function. We establish a physicochemical taxonomy of surfactant architecture, charge, functionality and origin, and examine the electrostatic, covalent, coordinate, hydrogen-bonding, hydrophobic, π–π and multivalent mechanisms governing interfacial adsorption. We analyze surfactants as active agents in nucleation, growth, templating and self-assembly across noble metals, oxides, semiconductors, silica, carbon materials and hybrid nanostructures, and develop a critical, correlative framework for characterizing the resulting interfaces. We then ask, property by property, what these interfaces are demonstrably known to control – optically, catalytically, electronically, mechanically and energetically – before examining how this control is exploited in catalysis, energy conversion, sensing, environmental technologies, nanomedicine and manufacturing, what it costs biological and environmental systems, how sustainability and regulation constrain it, and what artificial intelligence can and cannot yet contribute to predictive design. Throughout, we distinguish mechanistically established structure–function relationships from those still assumed by empirical analogy, providing a transferable basis for designing next-generation materials with programmable interfaces, controlled functionality and improved sustainability.

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1. Introduction: surfactants as molecular architects of materials

1.1. From colloidal stabilizers to active materials-design agents

Surfactants are among the most versatile molecular tools available for controlling the formation, stabilization, organization and function of materials across multiple length scales. By combining chemically distinct hydrophilic and hydrophobic domains within a single molecule, they regulate interfacial energies, direct nucleation and crystal growth, induce self-assembly, stabilize colloidal dispersions, mediate ligand exchange, and dynamically remodel material surfaces in response to environmental stimuli. Historically, however, surfactants have most often been treated as formulation additives: agents introduced after the fact to stabilize a dispersion, adjust a surface charge, or extend a shelf life, rather than as active participants in the design of the material itself. Three transitions mark the shift away from that view. Classical colloidal stabilization, formalised in the DLVO framework of the 1940 s, treated the amphiphile as a means of controlling interparticle forces. Ligand-directed synthesis emerged in the 1990 s and early 2000 s, when facet-selective capping in noble-metal and semiconductor nanocrystal growth showed that the surfactant determines morphology rather than merely preserving it, and when surfactant-templated mesoporous silica established the same principle for extended solids. Predictive, data-driven design is the most recent and least consolidated of the three, dating from the past decade. This Review adopts a different premise. We treat surfactants as molecular architects of materials: molecules whose structure translates directly into interfacial organization and, through it, into the composition, morphology, hierarchical organization and ultimately the functional performance of the material with which they interact.

1.2. Why surfactant–material interfaces matter across length scales

The consequences of this architect role are visible wherever a surfactant meets a material surface, from the nucleation of a metal nanocrystal in solution to the self-assembly of a lipid bilayer or the stabilization of an industrial emulsion, and they cross freely between fields that rarely cite one another: colloid and interface science, soft matter physics, catalysis, energy materials, nanomedicine and sustainable materials chemistry. Few settings document these consequences as directly, or connect them as tightly to translational stakes, as the engineering of surfactant coatings for colloidal nanoparticles. We use it below as a detailed, heavily characterized illustration of principles that recur, in modified form, across every material class discussed later in this Review.

Nanoparticles have become a cornerstone platform in biomedical, pharmaceutical, and industrial applications, owing to the unique physicochemical properties that arise from their nanoscale dimensions. However, their synthesis and use are constrained by colloidal instability, aggregation, and nonspecific interactions with surrounding biomaterials. To address these challenges, surface

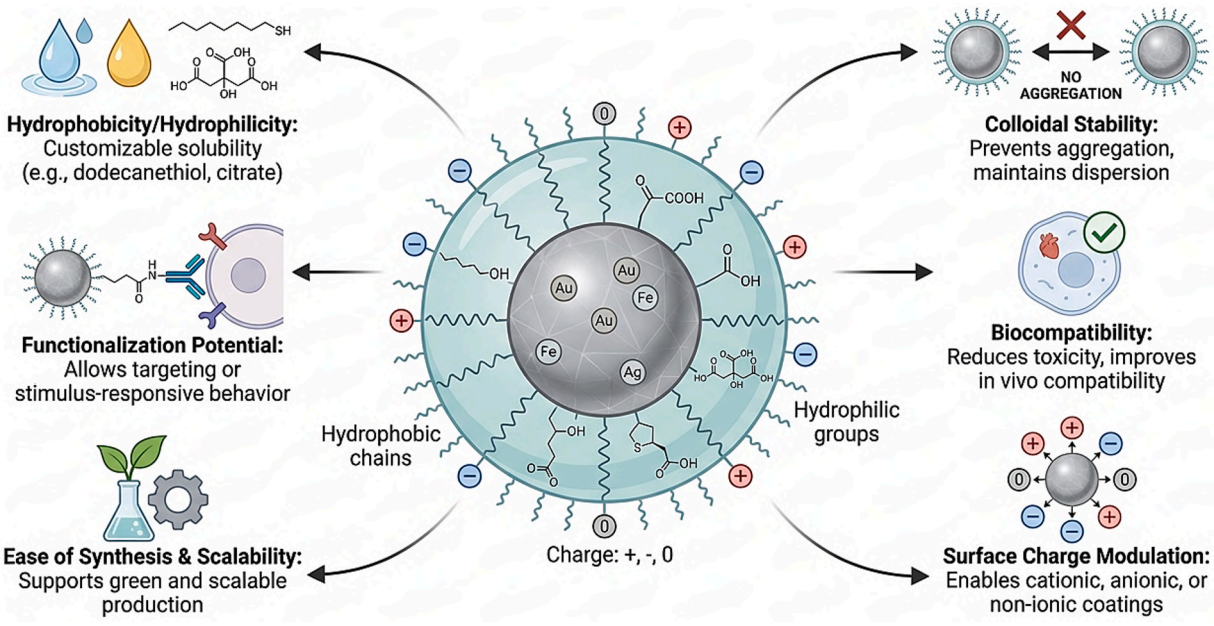

Fig. 1. Molecular design of surfactant-coated nanoparticles and the resulting interfacial functions. Schematic representation of a colloidal nanoparticle comprising an inorganic core and a multifunctional surfactant shell. The molecular composition and organization of the interfacial coating – including hydrophobic/hydrophilic balance, functional-group chemistry, surface charge and ligand architecture – define the physicochemical properties of the nanoparticle interface and thereby regulate its behavior in complex environments. These interfacial features collectively govern colloidal stability, surface-charge modulation, solubility and dispersibility, chemical functionalization and targeting, and biocompatibility, while also influencing the scalability and sustainability of material production. The figure illustrates the central concept of this review: surfactants are not passive stabilizers but molecular architects that translate interfacial chemistry into nanoparticle structure, stability and function.

functionalization with surfactants has been extensively investigated, yielding significant improvements in colloidal stability and biological compatibility [1].

In recent years, the literature on nanoparticle coatings has expanded rapidly, and several coatings have reached the market, offering diverse options across various applications. However, a major limitation is that several coatings are difficult to reproduce, owing to complex synthesis and the cost of the monomers and reagents required, which also raise green chemistry and sustainability concerns, given their potential harm to the environment and human health [2].

The ongoing focus on developing new nanomaterials has prompted researchers to design surfactants that prevent colloidal instability. Specifically, surfactants can be small molecules or macromolecules, such as polymers, that coat the nanoparticle surface with an affinity that varies based on the nanoparticle's chemical nature. Surfactants used to coat colloidal nanoparticles should ideally exhibit the following characteristics (Fig. 1) [3].

Surfactants suitable for coating colloidal nanoparticles should ideally combine several properties. They should be easy to synthesize and scalable, ideally through eco-friendly, aqueous routes with simple, rapid coating procedures [4–6]. They should confer biocompatibility, reducing cytotoxicity and immune responses – as with chitosan, which improves cell viability and biodistribution *in vivo* [7,8]. Their primary function is to increase colloidal stability by lowering surface energy and preventing aggregation, thereby preserving properties such as optical response [9]. By tuning surfactant charge (cationic, anionic or non-ionic) they also modulate surface charge, controlling dispersion, interactions with cells and tissues, and mechanisms such as charge-induced endosomal escape [2,10–13]. The choice of hydrophobic (e.g., dodecanethiol) or hydrophilic (e.g., citrate, glutathione, lipoic acid) moieties tunes solubility in different media [14]. Finally, surfactants provide functionalization potential: their chemical groups can anchor to surfaces or bind cellular receptors and proteins for targeting, and stimuli-responsive compositions (pH, temperature) enable triggered drug release, making a given coating either application-specific or highly versatile – a feature increasingly valuable for sustainable design [15–20]. Overall, surfactant properties are fundamental to optimizing nanoparticle behavior in suspension and *in vivo*, making them versatile and essential tools for advanced nanoparticle design [21–23].

Given the increasing use of metals, especially at the nanoscale, the study of new surfactants remains a highly relevant topic in current scientific research [5,24].

Across this literature, however, surfactant selection has remained overwhelmingly empirical: coatings are chosen by analogy to prior success rather than predicted from first principles, and their performance is too often reported without the mechanistic, analytical, or toxicological evidence needed to justify the choice. This review therefore takes a deliberately critical stance. Rather than cataloguing surfactant chemistries application by application, we interrogate a paradigm now widely proclaimed but rarely tested – the shift from empirical selection toward rational, regulation- and data-driven design. For each dimension of the field – including classification, interfacial mechanism, characterization, application, manufacturing, sustainability, and computation – we ask not only what has been achieved but what remains assumed, unreproducible, or unproven, and we identify the specific evidence that must be generated before surfactant engineering of nanoparticles can be called rational rather than customary.

1.3. The central design chain: Molecular structure → interface → dynamic organization → material formation → structure–function → functionality

Across the sections that follow, this Review is organized around a single causal chain: molecular structure dictates interfacial adsorption and organization; interfacial organization directs nucleation, growth and self-assembly; the resulting dynamic organization determines material formation and structure; and material structure, in turn, determines function. We return to this chain (molecular design → interfacial chemistry → dynamic organization → material formation → structure–function → functionality) at the opening and closing of every subsequent section, using it as the test against which we judge whether a given finding constitutes genuine design knowledge or merely an empirically successful recipe.

1.4. Scope and conceptual framework of the Review

The Review is organized in fourteen sections. Sections 2–4 establish the molecular design space of surfactants and the physical mechanisms by which they adsorb, organize and direct material formation. Section 5 addresses self-assembly across length scales, from individual micelles to hierarchical, functional architectures. Section 6 develops a critical, technique-by-technique framework for characterizing the resulting interfaces. Section 7 asks, material class by material class and property by property, what these interfaces are actually known to control – optically, catalytically, electronically, mechanically and energetically. Sections 8–11 then examine how this control is exploited in technology, what it costs the surrounding biological and environmental systems, how sustainability and regulation constrain it, and what artificial intelligence and molecular simulation can and cannot yet contribute to predicting it. Sections 12–14 close the Review with manufacturing and translation, a forward-looking assessment of adaptive and programmable interfaces, and our overall conclusions. Throughout, applications are treated as illustrations of the underlying design chain rather than as self-contained topics, consistent with the Review's central aim: to position surfactants as molecular architects of materials rather than as passive formulation components.

1.5. Operational use of the term "surfactant" in this Review

Because this Review deliberately compares molecules that are not conventionally grouped together, it is necessary to state at the outset how the term surfactant is used here and where that usage departs from the strict physicochemical definition. In the classical

sense, a surfactant is a low-molecular-weight amphiphile that adsorbs at an interface, lowers interfacial tension and self-assembles above a critical micelle concentration (CMC). Many of the interfacial agents discussed in the following sections satisfy some but not all of these criteria, and treating them as interchangeable would weaken rather than strengthen the argument. We therefore distinguish four categories throughout.

(i) True surfactants: low-molecular-weight amphiphiles with a defined hydrophilic head and hydrophobic tail, a measurable CMC and demonstrable interfacial-tension reduction (*e.g.*, SDS, CTAB, Triton X-100, sorbitan and polysorbate esters, rhamnolipids). Statements about CMC, packing parameter and HLB apply strictly to this class.

(ii) Amphiphilic polymers and block copolymers: macromolecules that adsorb and self-assemble by the same thermodynamic driving forces but without a sharply defined CMC, and whose interfacial behaviour is additionally governed by chain conformation, grafting density and molecular-weight distribution (*e.g.*, Pluronics, PEG–PLGA, poly(phosphoester)s, polysaccharide derivatives). Micellar concepts transfer only approximately to this class.

(iii) Capping and anchoring ligands: species that bind a nascent or preformed inorganic surface through a specific coordinating group and thereby control nucleation, facet growth and colloidal stability, but that are not necessarily surface-active in the bulk sense (*e.g.*, oleylamine, oleic acid, alkanethiols, citrate, phosphonates, catechols). Their action is coordination chemistry rather than interfacial-tension reduction, even when the same molecule can also behave as a surfactant.

(iv) Broader surface modifiers: dendrimers, proteins, peptides, zwitterionic brushes and biomimetic membrane coatings, which are included only where they illuminate the same molecular design → interfacial organization → function logic, and which we do not claim to be surfactants.

Where a statement holds for all four categories we refer to interfacial agents or surface-active species; where it holds only for classical amphiphiles we retain the term surfactant. This distinction matters because the unification proposed here is conceptual – a shared causal chain from molecular architecture to material function – and not a claim that these chemically diverse species obey a single physicochemical formalism.

2. The molecular design space of surfactants

We begin with the chemical and physical descriptors that define a surfactant's architecture, and that determine how it adsorbs,

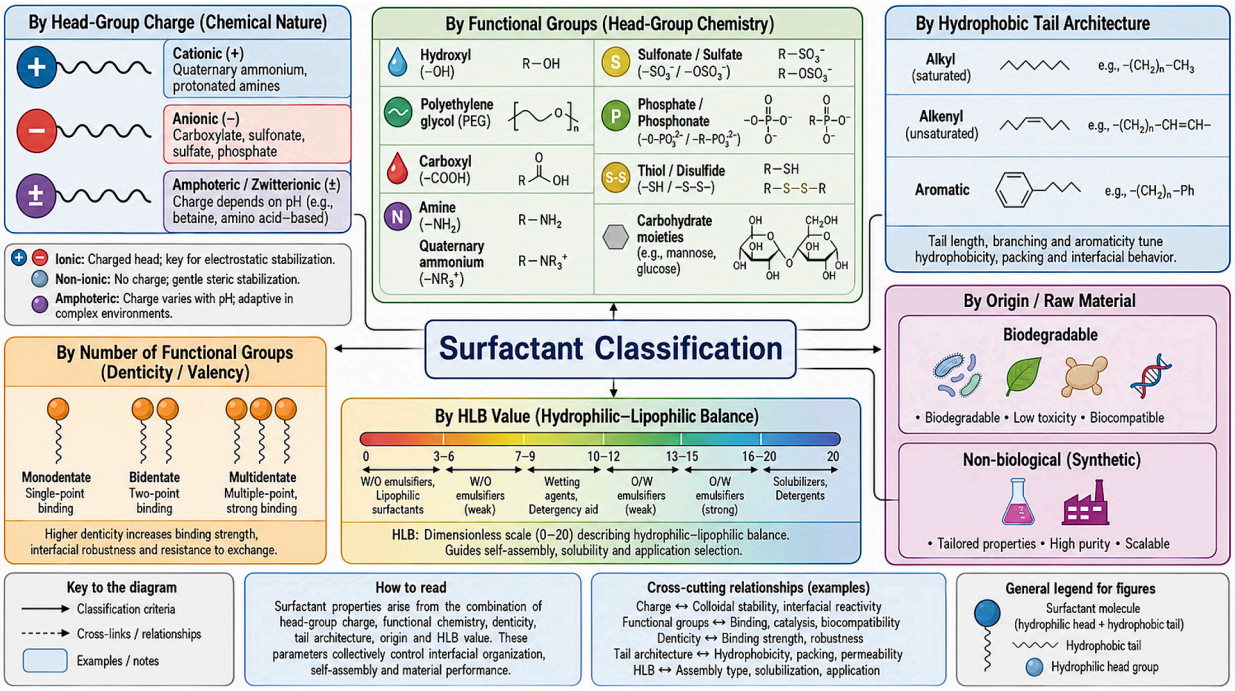

Fig. 2. Comprehensive classification of surfactants based on molecular structure and physicochemical properties. Surfactants can be classified according to multiple complementary criteria, including the chemical nature and charge of the hydrophilic head group, the functional groups and molecular architecture, their natural or synthetic origin, molecular weight, and hydrophilic–lipophilic balance (HLB). This multidimensional classification highlights the broad chemical diversity of surfactants and the structural parameters that govern their interfacial behavior, self-assembly, solubility, and interactions with inorganic, organic, and biological interfaces. The HLB scale provides an additional functional descriptor of the relative hydrophilic and lipophilic character of surfactant molecules and helps rationalize their propensity to form different assemblies and stabilize specific dispersed phases. Together, these classification criteria provide a framework for linking surfactant molecular identity and architecture to interfacial organization and material function.

Table 1
Representative surfactants per class. Feedstock and production route are reported separately, because the two are independent attributes and neither predicts biodegradability or toxicity on its own.

	Advantages of the class	Common surfactant	Functional group	Origin (feedstock; production route)	Uses	Molecular weight (g/mol)	HLB value	References
Non-ionic surfactants	Generally good tolerability and stability over a wide pH range; biocompatibility is compound- and dose-specific and can be compromised by peroxide and aldehyde degradation products	Polysorbate 80 (PS-80)	−COOR −O- –OH	Bio-based feedstock; chemically synthesized	Oil/water emulsifier in cosmetics; Stabilizer in drug delivery systems and in food additives	1310.00	15	[38]
		Sorbitan Monolaurate 20	−COOR −O- –OH	Bio-based feedstock; chemically synthesized	Skin permeation enhancer in cosmetics	346.46	8.6	[39]
Cationic surfactants	Head-group diversity allows for chemical modification; strong antibacterial and antimicrobial activity, which is mechanistically linked to the membrane-disruptive action that also underlies their cytotoxicity; high affinity for the phosphate backbone of DNA and for anionic groups of cell membranes.	Cetyltrimethyl-ammonium bromide (CTAB)	$-NR_4^+$	Petrochemical feedstock; chemically synthesized	Template in nanoparticle synthesis and antimicrobial agents, since it is cytotoxic and induces oxidative stress	364.46	10	[40]
		Lauric arginate (LAE)	−COOR –CONH- $-N(NH_2)^+$	Bio-based feedstock; chemically synthesized	Food preservative, antimicrobial compound and drug (E243)	421.02	10	[41]
Anionic surfactants	High capability of reducing surface tension in water; excellent foaming properties; readily biodegradable for linear alkyl chains, though branched and highly ethoxylated homologues degrade more slowly.	Sodium Lauryl Ether Sulfate (SLES)	$-OSO_3^-$ −O-	Bio-based or petrochemical feedstock; chemically synthesized	Emulsifier, cleanser and foaming agent in cosmetics and household cleaning products	332.43	>20	[42,43]
		Sodium Lauryl Sulfate (SLS)	$-OSO_3^-$	Bio-based or petrochemical feedstock; chemically synthesized	Emulsifier agent in household cleaning products and in cosmetics	288.38	>20	[44,45]
Amphoteric surfactants	Good solubility in water; pH-dependent net charge; generally lower irritancy than comparable cationic surfactants, although biodegradability and toxicity vary widely with head-group and chain structure; capability of decreasing surface tension in water.	Betaine	$-NR_4^+$ $-COO^-$	Naturally occurring; obtained by extraction from sugar beet or by chemical synthesis	Food additive	117.15	13.4	[46]
		Phosphatidylcholine	$-PO_4^-$ −COOR $-NR_4^+$	Biological; extracted from soy or egg lecithin	Liposome preparation for drug delivery	≈ 776	7–8	[47]
Zwitterionic surfactants	Highly tunable properties by altering their chemical structure; Large dipole moment and high affinity with anions, promoting micelles formation; High capability of biomolecules chemical stabilization; High catalityc activity. [48]	Cocamidopropyl Betaine	–CONH- $-NR_4^+$ $-COO^-$	Bio-based feedstock (coconut oil); chemically synthesized	Skin sensitizers and mild surfactants used in shampoos and other cosmetics	342.52	13.4	[49]
		Phosphatidylserine	$-PO_4$ −COOR $-NH_2$ –COOH	Biological; extracted or enzymatically derived from phosphatidylcholine	Liposomal carriers for brain-targeted drug delivery.	385.31	7–8	[50]

organizes and directs material formation in the sections that follow.

Considering that a taxonomy is only as useful as its predictive power, the classification schemes surveyed below – by head-group charge, functional moiety, denticity, origin, molecular weight and hydrophilic–lipophilic balance (HLB) – are necessary for organizing a sprawling chemical space. However, it is worth asking at the outset how much of a nanoparticle's colloidal and biological fate any of them actually predicts. HLB, for instance, was formalized for emulsion systems and transfers imperfectly to solid nanoparticle

interfaces; charge class predicts electrostatic stabilization but not biological identity. We therefore present these categories not as ends in themselves but as a scaffold whose predictive limits we test in the sections that follow.

2.1. General overview of the different types of surfactants

Surfactants can be classified by chemical structure, origin/environmental impact, functionality, hydrophilic–lipophilic balance and molecular weight (Fig. 2). The most common scheme is based on the amphiphilic chemical structure, which divides them by the nature of the hydrophilic head into ionic, non-ionic and amphoteric [25]. Classification by functional group and by number of ligands (mono-, bi- or multidentate), rather than by overall structure, better captures the specific interactions relevant to rational coating design; surfactants are further distinguished as biological *vs*. non-biological and as low- or high-molecular-weight (typically polymers/macromolecules) [26].

Surfactants can be differentiated from one another based on their HLB value, which expresses the balance between the size and strength of hydrophilic and lipophilic moieties of the molecule [25].

2.2. Chemical structure classification

Table 1 reports the complete classification of the most well-known surfactants per class.

2.2.1. Non-ionic surfactant

Non-ionic surfactants are characterized by a polar, neutral head group and interact with the environment mainly through hydrogen bonding. The main advantage of this type of molecule is its ability to stabilize inorganic nanoparticles, preventing aggregation and ensuring high colloidal stability [25]. Moreover, non-ionic surfactants are generally less toxic than other types of surfactants, as their chemical reactivity toward biological components is weak or moderate [27].

2.2.2. Ionic surfactant

Ionic surfactants can have a positive or negative total charge, which is balanced by a simple counterion; they are called cationic or anionic surfactants, respectively [25].

Cationic surfactants.

The positively charged head group confers a strong affinity for negatively charged cell membranes and DNA on cationic surfactants, making them attractive for gene delivery applications [28]. However, this positive charge can lead to cytotoxicity and unwanted interactions with biological materials, such as serum proteins, which may trigger immune responses or cause rapid clearance from the bloodstream [29]. Moreover, when coating inorganic nanoparticles, cationic surfactants provide electrostatic stabilization, generally yielding a comb-like coating, but their toxicity must be carefully balanced [30,31].

Anionic surfactants.

The negatively charged head group provides electrostatic repulsion between anionic surfactant-coated nanoparticles, preventing aggregation in aqueous environments [32]. Their charge facilitates the dispersion of nanoparticles in water but can also lead to challenges in biological applications, as negatively charged particles may have reduced cellular uptake, lower stability depending on the pH of the environment and may be rapidly cleared from the bloodstream [33]. However, these surfactants can be useful in specific applications where negatively charged surfaces are advantageous, such as targeting proteins or receptors with an affinity for anionic species [34].

Magnetic surfactants.

Ionic surfactants can exhibit different properties depending on the chemical nature of the charged groups. Indeed, a subset of this class comprises magnetic surfactants, in which the charged group contains a magnetic atom, resulting in magneto-responsive properties. These surfactants have lower critical micelle concentrations and are more effective at reducing surface tension than conventional surfactants [35].

2.2.3. Amphoteric and zwitterionic surfactant

Amphoteric surfactants change their net charge with solution pH, behaving as cationic species in acidic media and anionic species at higher pH [36]. This switchability makes them valuable in nanomedicine, where they can operate across compartments of differing pH, interact with biomolecules in a controlled manner, and provide both electrostatic and steric stabilization in complex biological environments while causing lower cytotoxicity than purely cationic or anionic surfactants [17,37].

A subset of amphoteric surfactants is represented by zwitterionic surfactants, which are characterized by the presence of both positive and negative charges in their chemical structure that balance each other, making the overall molecule neutral, independent of solution pH. These surfactants are particularly useful for nanoparticle coatings because of their unique ability to resist protein adsorption, thereby reducing immune recognition and extending circulation time in the bloodstream, key advantages for drug delivery systems [51,52].

2.3. Emerging surfactants

Increasing demand for environmentally and biologically safe stabilizers is shifting attention toward molecules that not only stabilize nanostructures but also direct their interaction with biological media via molecular recognition. Natural polysaccharides (starch,

cellulose, pectin, alginate, chitosan) are widely explored as tunable stabilizers, and are commonly reported to combine ready biodegradability with low toxicity, although both properties depend on the degree of substitution, molecular weight and residual reagents of the specific derivative used [53]. Chitosan, a cationic chitin derivative, is among the most used: it enhances cellular uptake through electrostatic affinity for negatively charged membranes and prevents aggregation of silver and gold nanoparticles while adding antimicrobial, mucoadhesive activity [54–59]. Anionic alginate and cellulose derivatives (carboxymethyl-, hydroxypropyl-cellulose) stabilize metal and polymer nanoparticles through hydrogen-bonding networks and steric effects.[53] Where finer control is needed, synthetic biocompatible polymers such as PLGA are preferred for their tunable, hydrolysis-controlled degradation and sustained release by hydrolysis [60]. Polyethylene glycol is commonly grafted onto nanoparticles to provide a stealth effect, minimizing opsonization and prolonging circulation [60,61]. A more recent class of multifunctional polymers acts not merely as templates but as active interfacial agents, binding surfaces through multidentate coordination, electrostatic or covalent interactions [60,62]. Examples include poly(acrylic acid), catechol-functionalized polymers and dendrimers; multidentate PEG-phosphonate surfactants, for instance, stabilize iron oxide nanoparticles even in highly ionic biological fluids while minimizing the organic mass per unit surface, reducing toxicity and oxidative damage, and allowing conjugation of targeting ligands for theranostic designs [62].

In addition to new surfactants, another promising direction concerns the development of biosurfactants derived from natural sources. Biosurfactants synthesized by the activity of microorganisms, such as bacteria, fungi, and yeast, or some plants and animals are built from sugars, lipids and proteins, a composition that is frequently associated with good biocompatibility, although this must be established for each compound and exposure rather than inferred from the biogenic building blocks [63].

Low-molecular-weight biosurfactants (*e.g.*, rhamnolipids, sophorolipids, surfactins) are most effective at lowering surface tension and forming micelles or vesicles, whereas high-molecular-weight species (fatty acids, biopolymers) are better suited to emulsion stabilization [64]. Their stability across temperature, pH and concentration ranges enables multifunctional nanosystems; the main drawback is the high cost of synthesis and purification, which emerging routes based on industrial waste feedstocks may mitigate [65,66].

2.4. Classification of surfactants based on functionality

2.4.1. Hydroxyl groups (–OH)

Hydroxyl groups increase the hydrophilicity of surfactants and promote hydrogen bonding with water, contributing to the formation and stabilization of interfaces in aqueous environments. When exposed to water, they form hydrogen bonds, thereby increasing the solubility of drug-loaded nanoparticles and enabling controlled release [38].

2.4.2. Polyethylene glycol (PEG) chains (–$[CH_2CH_2O]_n$–)

PEG chains are highly hydrophilic, thus enabling them to form a “hydration” shell around nanoparticles. The polymer conformation depends on PEG chain length and grafting density [67]. PEGylation reduces immune recognition, prevents protein adsorption, prolongs circulation time, and enables functionalization via surface modifications [68,69].

2.4.3. Carboxyl groups (–COOH)

The carboxyl groups are polar and therefore can act as hydrogen-bond donors to other molecules. This functionality is exploited because it is pH-sensitive and exhibits interesting chemical reactivity. In the field of nanomedicine, nanoparticles may be engineered to present carboxylate groups on their surfaces, imparting a negative surface charge and colloidal stability, as well as chemical reactivity that can be exploited for further functionalization [70].

2.4.4. Amine (–NH_2) and quaternary ammonium (–NR_4^+) groups

The amino group can be positively charged under physiological conditions, whereas the quaternary ammonium group has a permanent positive charge. Since they primarily act as nucleophiles in chemical reactions, these groups are often exploited to modify surfactants and introduce new properties through functionalization [51].

2.4.5. Sulfonate (–SO_3^-) and sulphate (–OSO_3^-) groups

The negatively charged sulfonate and sulphate groups enhance nanoparticle stability in biological fluids and minimise nonspecific protein adsorption [52].

2.4.6. Phosphate (–PO_4^{3-}) and phosphonate (–RPO_3^{2-}) groups

The phosphate and phosphonate groups are negatively charged and can form stable complexes with cations. Moreover, they are critical in the formulation of nanoparticles that mimic the cell membrane, since it is composed of phospholipids, for facile particle encapsulation and release of both hydrophobic and hydrophilic drugs [71,72].

2.4.7. Thiols (–SH) and disulfide (–S-S–) bonds

Thiolated surfactants exhibit different advantages in the biomedical field. First, the chemical reactivity of the thiol group enables redox activation, under the elevated glutathione concentrations characteristic of cancer cells. This strategy has been used for the controlled release of drugs in tumor environments [52]. In addition, the high affinity of the Sulphur atom for metals makes thiol- or disulfide-based surfactants ideal for stabilizing metal nanoparticles, providing high colloidal stability [73].

2.4.8. Carbohydrate moieties (e.g., mannose and glucose)

The presence of carbohydrate groups in the structure of the surfactant enhances the hydrophilicity of the structure. Thus, these surfactants are used to facilitate interactions within the biological system and enhance biocompatibility [74]. For instance, glycosylated surfactants can be used to target biological systems that express receptors for carbohydrate groups [75]. Moreover, carbohydrate surfactants can be used to guide crystal formation during the synthesis of metal nanoparticles [76].

2.4.9. Hydrophobic chains (alkyl or aromatic hydrocarbons)

Hydrophobic chains confer structural properties on the surfactant, enabling it to form lipid bilayers or micelles in specific environments. For instance, in water, these surfactants align toward the core of the structure, allowing encapsulation of hydrophobic drugs [77]. For this reason, such surfactants are widely used in drug delivery strategies. For example, in lipid nanoparticles used for mRNA vaccines, the surfactant's hydrophobic tail stabilizes the encapsulated RNA [78]. Lipid nanoparticles are also employed in the cosmetic field to alleviate cutaneous inflammations [79] or as photoprotective agents [80].

2.5. Classification of surfactants based on the number of functional groups

Monodentate surfactants, with only one type of functional group in their hydrophilic head, interact with water or other polar solvents and display basic surfactant activity, which includes surface tension reduction and colloid stabilization. Bidentate surfactants, with two functional groups in their hydrophilic head, display increased surface activity and solubilization ability. The increased interaction with other compounds at two points enhances adhesion and solubilization [81].

Multidentate surfactants, bearing multiple functional groups in the hydrophilic head, are valued where enhanced stability and interaction are required, including the formation of self-assembled micelles and vesicles. Through multivalent binding they stabilize inorganic nanoparticles against degradation and aggregation in physiological media, typically outperforming mono- and bidentate analogues in stability, biocompatibility and function [73,82]. The metal-to-ligand ratio must nonetheless be controlled to avoid multiparticle bridging and aggregation [83].

2.6. Classification of surfactants based on feedstock and production route

Surfactant origin is frequently reported as a binary choice between "biological" and "synthetic", but this dichotomy conflates two independent attributes: the feedstock from which the molecule is derived (petrochemical, bio-based or mixed) and the route by which it is manufactured (extraction from a biological source, microbial fermentation, or chemical synthesis). The two are not correlated. Sodium lauryl sulfate, sorbitan esters and cocamidopropyl betaine are all commonly produced from renewable oleochemical feedstocks yet are unambiguously products of chemical synthesis; conversely, betaine occurs naturally in sugar beet and is obtained both by extraction and by synthesis. Because environmental and toxicological behaviour follows the molecular structure and the impurity profile of the finished material rather than the provenance of its carbon, we report both attributes separately in Table 1 and avoid inferring safety or biodegradability from origin alone.

Four adjectives are used throughout this Review in senses that are frequently conflated in the literature, and we fix them here. Biological (or biogenic) describes a molecule produced by a living system and recovered from it, whether by extraction or by fermentation; biosurfactant is reserved for surface-active molecules of microbial origin, such as rhamnolipids, sophorolipids and lipopeptides, and is not used for chemically synthesised molecules that merely derive from renewable carbon. Bio-based refers to feedstock only and carries no implication about the production route or the properties of the product. Biodegradable denotes a measured extent of mineralisation under a specified test protocol and time frame, and is meaningful only when both are stated. Biocompatible describes an absence of adverse response in a defined biological system at a defined exposure, and is therefore a property of a material–context–dose combination rather than of a molecule.

2.6.1. Biosurfactants

The term biosurfactant primarily refers to surfactants produced by microorganisms and has been effectively used in various applications due to their surfactant-like properties [84,85]. The hydrophilic part of the biosurfactant consists of groups such as esters, hydroxyls, phosphates, and carboxyl groups, whereas the hydrophobic part consists of fatty acid and alcohol compounds [85]. Biosurfactants are frequently described as non-toxic, readily biodegradable and of low environmental impact, and many display high emulsifying ability. These properties, however, are structure-dependent rather than a consequence of biological origin: rhamnolipids and sophorolipids, for example, show measurable aquatic toxicity at concentrations comparable to some synthetic non-ionic surfactants, and fermentation-derived products carry residual substrate and by-product burdens that are rarely reported. Claims of superior safety therefore require compound-specific data generated to the same standards applied to the incumbents they aim to replace [86].

2.6.2. Non-biological surfactants

Non-biological surfactants are also called synthetic surfactants. Here the term "synthetic" denotes the production route rather than the feedstock: many large-volume synthetic surfactants are manufactured from renewable oleochemical precursors such as coconut or palm-kernel oil, and are therefore both bio-based and synthetic. The synthesis of non-biological surfactants occurs through industrial-scale chemical reactions, in which the compounds are produced for specific purposes [87].

2.7. HLB: A convenient metric of limited predictive validity at the nanoscale

The hydrophilic character of a surfactant is commonly described by the Hydrophilic–Lipophilic Balance (HLB), introduced by Griffin and estimated from the mass ratio of hydrophilic to lipophilic portions [88]. On its 0–20 scale, higher values indicate greater water solubility. The metric is empirical and limited: it does not apply to all classes and ignores factors such as counterions in ionic surfactants and the influence of substituents along the hydrophobic chain.

However, the HLB scale helps in identifying the suitability of non-ionic surfactants for a particular purpose. Through HLB values, it is possible to distinguish: defoamers (HLB 1.5–3); water-in-oil emulsifiers (HLB 3–6); wettings (HLB 7–9); oil-in-water emulsifiers (HLB 8–18); detergents (HLB 13–15); peptize-solubilizers (HLB 15–18) [25].

In sum, no single classification axis surveyed here predicts nanoparticle behavior on its own; charge, functionality, denticity, origin and HLB are complementary descriptors, not design rules. The practical consequence is that surfactant selection still cannot be reduced to a lookup table, and claims that a coating was chosen "rationally" should state which property was optimized and against which measured endpoint.

2.8. From molecular descriptors to interfacial behavior

The classification schemes of this section – by charge, functional group, denticity, origin, molecular weight and hydrophilic–lipophilic balance – are ultimately useful only insofar as they predict how a surfactant behaves at an interface. Each taxonomic axis maps, imperfectly, onto an interfacial consequence: head-group charge governs the electrostatic component of adsorption, functional-group chemistry sets the specific binding mode, denticity determines attachment strength and exchange resistance, and the balance of hydrophilic and hydrophobic domains fixes the packing geometry that dictates aggregate and layer structure. The central limitation, developed throughout this review, is that none of these single-parameter descriptors predicts interfacial behavior on its own, because the relevant quantity – *i.e.*, how the molecule actually organizes on a given surface in a given medium – depends on their combination and on the environment. This is why the classification problem and the interface problem cannot be separated: the molecular descriptors catalogued here acquire predictive meaning only when translated into the interaction mechanisms and interfacial organization examined in the next section.

3. The surfactant–material interface: Molecular mechanisms of interaction

Having established what a surfactant is, we turn to what it does at a material surface: the largely non-covalent mechanisms by which molecular structure is converted into interfacial organization, which is the first link between molecular design and material formation.

The interfacial chemistry between a surfactant head-group and an inorganic surface is frequently described with more confidence than the underlying evidence warrants. Binding modes – covalent, coordinative, electrostatic, hydrogen-bonding, hydrophobic, π–π and multivalent – are often assigned by analogy or inferred from bulk behavior rather than measured directly at the interface, and their thermodynamic signatures and dependence on pH, ionic strength and temperature are seldom quantified for the specific core–ligand pair in question. In this section we distinguish mechanisms supported by direct, quantitative evidence from those that remain plausible assumptions, because the reliability of every downstream rational design choice rests on this distinction.

Beyond their interfacial role, surfactants also function as sophisticated structure-directing agents (SDAs) and molecular architects during nanoparticle synthesis. Their amphiphilic nature allows them to modulate the energy landscape of crystalline surfaces, tune reaction kinetics, and generate soft templates that dictate the final size, shape, phase, and self-assembled hierarchy of nanomaterials [16,89]. Through selective adsorption on specific crystal facets and control of precursor diffusion, surfactants can steer nucleation and

Table 2
Mechanism of interaction between functional groups and metals.

Material class	Representative materials	Surface characteristics	Typical interactions with organic functional groups	Key applications	References
Noble metals	Au, Ag, Pt, Pd	Low oxide coverage, high polarizability, soft Lewis acids	Strong affinity for thiols (Au-S, Ag-S); coordination with amines; weak interaction with –OH/–COOH	Plasmonics, drug delivery, catalysis	[3]
Transition metals	Fe, Cu, Ni	Surface oxides/hydroxides, variable oxidation states	Strong coordination with carboxylates, phosphates; electrostatic interactions	Catalysis, magnetic nanoparticles	[81]
Metal oxides	Fe_3O_4, TiO_2, ZnO, Al_2O_3	Hydroxylated surfaces, pH-dependent charge	Hydrogen bonding, coordination (M−O−C, M−O−P), electrostatic interactions	Drug delivery, photocatalysis	[16]
Carbon-based materials	Graphene, CNTs, carbon dots	π-conjugated surfaces, hydrophobic domains, surface defects	π-π stacking, hydrophobic interactions, weak electrostatic interactions	Sensing, drug delivery	[92–94]
Semiconductors	CdSe, CdTe, perovskites	Surface defects, ligand-dependent stabilization	Coordination with ligands (amines, phosphines, thiols)	Optoelectronics, bioimaging	[95]
Silica-based materials	SiO_2, mesoporous silica	Silanol groups (−SiOH), tuneable surface	Hydrogen bonding, covalent functionalization via silanes	Drug delivery, coatings	[96]

Table 3
Dependence of interaction characteristics on environmental conditions.

Interaction type	Physical origin	Typical strength (kJ/mol) (Atkins)	pH dependence	Ionic strength effect	Temperature effect	Reference
Covalent bonds	Orbital overlap (σ bonds)	150–1000	Weak, high stability across pH ranges	Independent	Very stable	[97]
Coordination bonds	Lewis acid-base interaction	50–200	Strong, ligand protonation state may change	Dependent, competitive ions reduce binding	Moderate stability	[3]
Electrostatic interactions	Coulombic attraction	5–50	Strong, ionization state may change	Dependent, strong screening effect	Strength decreases with T	[98]
Hydrogen bonds	Dipole-dipole interaction	5–30	Strong, high sensitivity for donor/acceptor functionalities	Weak dependency	Strength decreases with T	[98]
Hydrophobic interactions	Entropy driven interaction	2–20	Weak, high stability across pH ranges	Dependent, strengthened by salts	Complex dependency	[99]
Van der Waals	Induced dipoles	0.5–5	pH independent	Independent	Strength decreases with T	[100]
π-π stacking	π orbital overlap	1–50	Weak, high stability across pH ranges	Weak dependency	Strength decreases with T	[101]
Multivalent interactions	Cooperative binding	>200 (effective)	Depends on individual interaction	Dependent, weakened by salts	Very stable	[82]
Steric stabilization	Entropic repulsion	–	pH independent	Dependent, weakened by salts	Strength decreases with T	[3]

growth pathways with sub-nanometer precision, enabling the rational design of nanoparticles with tailored morphologies and functionalities.

3.1. Mechanisms of surfactant coating on nanoparticles

Surfactant adsorption at solid–liquid interfaces lowers surface free energy, limits aggregation and forms protective interfacial layers, while the shell simultaneously governs surface charge, hydrophobicity, steric hindrance and chemical accessibility – and hence interactions with biomolecules and cells. Coating efficacy depends on nanoparticle composition and surface charge, surfactant structure, and conditions such as pH, ionic strength and temperature, so understanding the underlying binding mechanisms is central to rational design.

3.1.1. Interaction between surfactant functional groups and inorganic nanoparticles

The most common elemental composition of inorganic nanoparticles is the following [90,91]:

Iron (Fe): Main component in magnetic nanoparticles in the form of iron oxides such as Fe_3O_4 and γ-Fe_2O_3, used for magnetic resonance imaging, hyperthermia treatment, and drug delivery.

Gold (Au): Often used in photothermal treatments, biosensing, and therapeutic agent delivery systems because of the superior plasmonic and biocompatibility features.

Silver (Ag): Traditionally used in antimicrobial treatments and in the development of wound healing and infection-resistant materials.

Palladium (Pd): Used in catalysis, photothermal treatments, and multifunctional drug delivery systems.

Platinum (Pt): Known for its catalytic ability and is used in cancer treatments, especially in combination with chemotherapeutic agents.

Carbon (C): Carbon-based nanoparticles consist of carbon nanotubes, graphene, graphene oxide, nanodiamonds, and fullerenes. They exhibit unique physical, chemical, and mechanical properties.

Depending on the material's elemental composition, the type of interaction between the surfactant and the particle surface varies, as reported in Table 2.

Surfactant adsorption is dynamic, governed by functional group/surface affinity and by external parameters that reshape charge distribution and interfacial energy, thereby altering binding strength, reversibility, colloidal stability and aggregation. As summarized in Table 3, strong covalent and multivalent bonds confer high stability, whereas weaker hydrogen-bonding, electrostatic, van der Waals and hydrophobic interactions are more sensitive to the surrounding medium – dependencies central to rational design.

3.2. Covalent attachment and surface grafting

Covalent attachment provides the strongest and most durable surfactant–surface bond, with bond energies of roughly 150–1000 kJ/mol that are essentially independent of pH and ionic strength (Table 3) [97]. The archetype is the thiol–gold bond (Au–S) exploited throughout the gold-nanoparticle literature, but covalent grafting extends to silane coupling on oxides and to click-type conjugation of pre-formed ligands. Because the bond does not rely on the surrounding medium, covalently grafted layers offer the reproducibility and stability that electrostatic or physisorbed coatings lack at the cost of a more demanding, often less scalable, attachment chemistry and

of a shell that cannot be reconfigured once formed.

3.3. Coordination and metal–ligand interactions

Coordination bonds, formed by Lewis acid–base donation from a ligand head-group to a surface metal atom, occupy an intermediate regime (≈50–200 kJ/mol) and, unlike covalent bonds, are sensitive to the medium: the ligand protonation state shifts binding strongly with pH, and competing ions can displace the ligand (Table 3) [3]. Carboxylate, amine, phosphine and phosphonate head-groups bind transition-metal and oxide surfaces through this mechanism, which is why these functional groups dominate the coatings of iron oxide and other transition-metal nanoparticles (Section 3.1.1). The medium-dependence that makes coordination bonds tunable is also what makes them vulnerable to the competitive, ion-rich environments encountered in biological and industrial media.

3.4. Hydrogen bonding

Hydrogen bonding contributes weaker, more numerous interactions (≈5–30 kJ/mol) whose strength is highly sensitive to the availability of donor and acceptor groups but only weakly dependent on ionic strength (Table 3) [98]. Individually labile, hydrogen bonds acquire significance through multiplicity – the cooperative network formed by hydroxyl-, amide- and PEG-type head-groups on hydroxylated oxide and silica surfaces. Because each bond is weak and thermally reversible, hydrogen-bonded layers are readily disrupted by temperature and by competition with water, making them a supporting rather than a primary anchoring mechanism for most nanoparticle coatings.

3.5. Hydrophobic interactions

Hydrophobic interactions (≈2–20 kJ/mol) are entropically driven, arising from the exclusion of ordered water around apolar chains rather than from a specific bond, and are consequently strengthened rather than weakened by added salt (Table 3) [99]. They govern the association of alkyl tails, underpinning bilayer and admicelle formation on hydrophobic surfaces such as carbon materials, as well as the double-layer organization observed in surfactants such as CTAB. Their non-specific, medium-sensitive nature makes hydrophobic assembly easy to induce but difficult to control precisely, a recurring limitation for coatings that rely on tail–tail association for their integrity.

3.6. π–π stacking and aromatic interactions

π–π stacking between aromatic head-groups or tails and conjugated surfaces (≈1–50 kJ/mol) provides the principal non-covalent route to functionalizing carbon-based materials, including graphene, carbon nanotubes and related sp^2-carbon surfaces, which offer no reactive sites for covalent or coordinate bonding [101]. The interaction is largely pH-independent but relatively weak, so aromatic surfactants such as pyrene-terminated amphiphiles are used precisely because they combine adequate binding to an otherwise inert surface with preservation of the underlying material's electronic structure. As with hydrogen bonding, strength here is achieved through extended, multivalent contact rather than through any single strong bond.

3.7. Multivalent and cooperative binding

Multivalent anchoring converts individually modest interactions into a highly stable attachment: multiple anchoring groups binding cooperatively produce effective binding energies exceeding 200 kJ/mol and coatings that resist desorption far better than their monovalent counterparts (Table 3) [82]. This is the principle behind multidentate polymers and branched surfactants, and it is central to the rational-design argument of this Review – denticity is a molecular design variable that can be tuned deliberately to trade attachment strength against surface accessibility. The cooperative binding that confers stability, however, also slows exchange and can lock in a shell configuration, coupling the benefits of multivalency to reduced reconfigurability.

3.8. Steric and hydration forces

Distinct from the attractive mechanisms above, steric and hydration forces are primarily repulsive and stabilizing: extended polymeric or hydrated head-groups generate an entropic repulsion that opposes the van der Waals attraction (≈0.5–5 kJ/mol) driving aggregation (Table 3) [3,100]. Steric stabilization is pH-independent but weakened by high salt, which compresses the extended chains. This is the dominant stabilization mechanism for non-ionic and PEGylated coatings, where colloidal stability derives not from surface charge but from the physical, entropic barrier that the hydrated layer presents to close approach – the structural basis of the colloidal stability discussed in Section 7.1.

3.9. Competitive adsorption and ligand exchange

Adsorption is rarely a one-time, exclusive event. In any realistic medium, surfactants, ions and biomolecules compete for the same surface sites, and a bound ligand can be displaced or exchanged for another of higher affinity – the basis of post-synthetic ligand exchange (Section 4.5) and of protein-corona formation (Section 9.1). The susceptibility of a coating to competitive displacement

follows directly from its binding mechanism: covalent and multivalent attachments resist exchange, whereas electrostatic, hydrogen-bonded and hydrophobic layers are readily overwritten (Table 3). Competitive adsorption is therefore where the mechanistic distinctions of this section acquire their practical consequences, determining whether a designed interface survives contact with its working environment.

3.10. Thermodynamics and kinetics of adsorption

The mechanisms above differ not only in equilibrium binding strength but in the kinetics that determine whether that equilibrium is reached. Adsorption reflects a balance between the enthalpic gain of binding and the entropic costs and gains of confining the ligand and releasing ordered water, and the same coating can be under kinetic rather than thermodynamic control, trapped in a metastable configuration that never reaches its lowest-energy arrangement. This distinction matters for reproducibility: coatings assembled far from equilibrium depend on preparation history (mixing, concentration, time), which is a principal, and under-reported, source of the batch-to-batch variability discussed in Sections 6 and 12.

3.11. Environmental variables controlling interfacial organization: pH, ionic strength, temperature, solvent composition, surface curvature, defect density, crystal facet, surface charge and potential

Finally, none of these mechanisms operates independently of the medium. As Table 3 makes explicit, pH shifts the protonation and therefore the binding of coordinate and electrostatic interactions; ionic strength screens electrostatic repulsion while strengthening hydrophobic association; and temperature weakens most physisorbed layers. To these solution variables must be added the properties of the surface itself – including curvature, crystal facet, defect density and surface charge – which set the local density and geometry of binding sites. The practical implication, which recurs throughout this Review, is that an interfacial structure characterized under one set of conditions cannot be assumed to persist under another, and that specifying the medium is inseparable from specifying the coating.

4. Surfactants as directors of material formation

Interfacial organization is not an end in itself: adsorbed surfactants actively steer how a material nucleates, grows and acquires its final morphology, converting the interfacial chemistry established in Section 3 into the structural outcomes examined here.

Bottom-up synthesis controls nucleation, growth and self-assembly at the molecular level, and surfactants act here not merely as stabilizers but as structure-directing agents that tune reaction kinetics, surface energies and interparticle interactions. Through facet-selective adsorption, micelle templating, coordination and ligand-mediated assembly they govern nanoparticle size, shape, phase and hierarchical organization. This section covers the underlying mechanisms, class-specific strategies, sustainable and surfactant-free routes, and post-synthetic ligand exchange/removal.

4.1. Fundamental mechanisms of nucleation, growth, and morphological control

Nanoparticle formation in liquid-phase synthesis proceeds through classical stages of nucleation, seed growth, and ripening or aggregation-based coalescence, with surfactants, polymers, and ligands modulating each step to prevent agglomeration and encode morphology [89]. Coarse-grained dissipative particle dynamics simulations of gold nanoparticle formation reveal that nucleation itself is relatively insensitive to surfactant identity, whereas growth trajectory, final size, and shape depend critically on headgroup

Table 4
Representative surfactant classes, their structure-directing mechanisms, and resulting nanoparticle morphologies.

Surfactant Class	Representative Examples	Primary SDA Mechanism	Resulting Morphologies	Key References
Cationic	CTAB, CTAC, TOAB, DDAC	{100} facet stabilization; soft template for nanoreactors; halide-mediated oxidative etching	Nanorods, nanowires, nanocubes, hollow structures	[3,6,89]
Polymeric (non-ionic)	PVP, PEG, Pluronic F127, polysaccharides	{100} protection via C=O coordination; mild reduction; mesoporous templating with lyotropic LCs	Nanocubes, nanoplates, nanospheres, mesoporous oxides (2–50 nm pores)	[102–104]
Anionic	SDS, SDBS	Soft template for oxide growth; electrostatic stabilization	MnO_2 nanosheets, SnO_2 nanoflowers	[16,89]
Organic ligand shells (oleic acid, oleylamine, alkanethiols)	Oleic acid, oleylamine, dodecanethiol	Tail-tail interactions modify surface energy and crystallization thermodynamics; ensure monodispersity	Monodisperse spheres, superlattice films; controlled assembly	[104,109]
Biosurfactants	Rhamnolipids, surfactin, sophorolipids	Dual role: reduction and stabilization from renewable feedstocks; strong hydration, with reported absence of toxic residues in the systems examined	Ag, Au, ZnS nanoparticles for biomedical/environmental use	[58]
Biomolecules (DNA, peptides)	Thiol-DNA, peptide amphiphiles	Programmable, sequence-specific assembly; facet recognition	fcc/bcc/hcp superlattices, tetrahedral nanocrystals	[16]

chemistry, alkyl chain length, and the nanoparticle-to-surfactant molar ratio [6]. Four interconnected mechanisms underlie surfactant-directed morphological control:

Selective facet adsorption. Surfactants bind preferentially to specific crystallographic facets, reducing their surface energy and suppressing growth normal to those faces. In gold nanorod synthesis, cetyltrimethylammonium bromide (CTAB) selectively passivates {100} facets, driving anisotropic elongation along {111} to yield high-aspect-ratio structures. Analogously, polyvinylpyrrolidone (PVP) coordinates via its carbonyl groups to {100} faces of face-centred cubic metals, yielding nanocubes and nanoplates with exceptional face uniformity [3,102].

Soft templating and micellization. Above the Critical Micelle Concentration (CMC), surfactants self-assemble into nanometer-scale compartments (*i.e.*, spherical, cylindrical, or lamellar micelles) that serve as nanoreactors confining inorganic precursors and controlling their local concentration. Inverted micelle microemulsions, characterized by ultralow interfacial tension and large interfacial area, produce size- and morphology-controlled metal nanoparticles through spatially restricted growth. Lyotropic liquid crystals formed by triblock copolymers (*e.g.*, Pluronic F127) direct the mineralization of silica or titania precursors around the surfactant scaffold, generating highly ordered mesoporous frameworks with pore diameters of 2–50 nm upon post-synthetic calcination [58,89].

Kinetic modulation and weak reduction. Certain surfactants, such as PVP and oleylamine, act simultaneously as mild reducing agents. By forming stable coordination complexes with metal ions and releasing them at controlled rates, they shift the synthesis from thermodynamic to kinetic control, enabling non-equilibrium morphologies such as concave nanocubes, hexapods, or pentagonally twinned structures that are inaccessible under rapid, uncontrolled reduction [103]. This dual reducing/capping capacity is exploited in one-step green syntheses [89].

Oxidative etching. In aerobic conditions, halide counter-ions of cationic surfactants (Cl^- from CTAC; Br^- from CTAB) act as etching agents, selectively dissolving unstable, high-energy surface atoms. Combined with growth, this produces hollow nanostructures, high-index facet particles, or twinned intermediates depending on the etching/deposition balance [3].

Organic ligand shells, in a broader sense, behave as surfactant-like assemblies whose collective tail–tail interactions modify nanocrystal thermodynamics, surface energy, and assembly kinetics, thereby indirectly defining shape and superlattice structure even in the absence of classical SDA behavior [104].

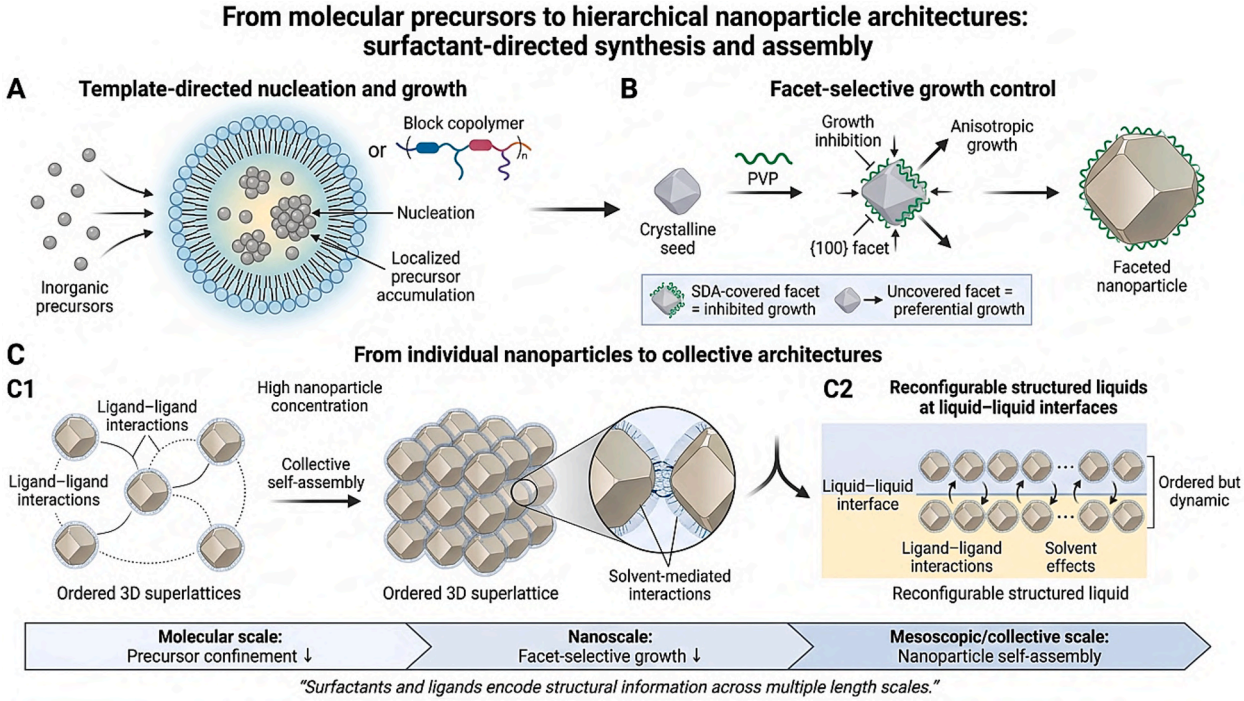

Fig. 3. Surfactant-directed control of nanoparticle synthesis and hierarchical self-assembly. Surfactant-directed agents (SDAs) regulate nanoparticle organization across multiple length scales, from molecular precursor confinement to collective assembly. **(A)** Inorganic precursors are concentrated within the cores of surfactant micelles or domains of block-copolymer templates, where spatial confinement promotes localized nucleation and growth. **(B)** Selective adsorption of SDAs onto specific crystallographic facets (e.g., PVP on {100} facets) suppresses growth in selected directions and thereby drives anisotropic growth and the formation of well-defined faceted nanostructures. **(C)** From individual nanoparticles to collective architectures: **(C1)** At high nanoparticle concentrations, ligand–ligand and solvent-mediated interactions direct the collective self-assembly of individual nanoparticles into ordered three-dimensional superlattices. **(C2)** At liquid–liquid interfaces, these inter-particle ligand and solvent-mediated interactions assemble nanoparticles into dynamic, reconfigurable structured liquids characterized by an ordered yet flexible packing. The scheme illustrates the hierarchical role of surfactants and ligands as structure-directing agents, linking molecular-scale interactions to nanoparticle morphology and ultimately to collective nanoscale architectures.

4.2. Class-specific synthesis strategies across material families

4.2.1. Noble metal nanoparticles

The synthesis of Au, Ag, Pt, and Pd nanoparticles exploits the Hard-Soft Acid-Base (HSAB) principle to guide ligand selection, with binding affinity typically following C < O < N < S. Cationic surfactants such as CTAB, CTAC, and TOAB dominate gold nanorod synthesis through the bilayer passivation of {100} faces and the establishment of a positively charged diffusion barrier that controls Au^{n+} flux toward the growing tip. For palladium nanodisks, cationic surfactants (CTAB, CTAC, TOAB) markedly slow hydrogen sorption/desorption kinetics, while PVP coatings accelerate hydrogen sorption, illustrating how surfactant identity directly tunes sensor response and catalytic reactivity [105]. Multidentate, high-avidity surfactant systems confer superior colloidal stability upon removal of excess surfactant, facilitating robust conjugation for drug delivery and imaging [73,106].

4.2.2. Oxides and mesoporous materials

Block copolymer and ionic surfactant templates are indispensable for the synthesis of mesoporous silica, titania, and related frameworks. Soluble oxide precursors co-assemble around the surfactant scaffold in an evaporation-induced or solution-phase process, condensing into an ordered inorganic matrix whose pore geometry faithfully replicates the mesophase (hexagonal, cubic, or lamellar). Post-synthetic calcination removes the organic template, yielding materials with high specific surface areas (>1000 $m^2\ g^{-1}$) and tunable pore connectivity for catalysis, drug delivery, and sensing [89].

4.2.3. Luminescent lanthanide nanoparticles

For rare-earth-doped nanoparticles, surfactants, long-chain hydrocarbons, and chelating ligands collectively govern nucleus growth rate, crystallographic phase (cubic *vs*. hexagonal), and surface passivation, while simultaneously balancing colloidal dispersibility with photoluminescence efficiency. The choice of surfactant determines whether nanoparticles maintain their emission properties after ligand exchange for aqueous biomedical applications [107].

4.2.4. Higher-order architectures and cooperative self-assembly

Beyond individual nanoparticle control, SDAs guide the cooperative self-assembly of nanoparticles into ordered two- and three-dimensional superlattices. Thiol-DNA ligands act as highly specific programmable SDAs directing nanoparticles into fcc, bcc, or hcp geometries based on linker length and sequence. Surfactant-decorated nanoparticles can also function as “colloidal surfactants” at liquid–liquid interfaces, where stimuli-responsive ligands enable triggered assembly and disassembly, driving macroscopic phase transformations and reconfigurable all-liquid devices [16,108] (Table 4).

4.3. Sustainable and surfactant-free synthesis strategies

Despite their structural benefits, conventional surfactants can passivate catalytic sites, complicate downstream analysis, and raise environmental concerns regarding persistence and ecotoxicity [89,110]. Three complementary strategies address these limitations:

Biosurfactants. Microbially or plant-derived amphiphiles, including rhamnolipids, surfactin and sophorolipids, are reported to combine good biocompatibility with ready biodegradability in the systems studied to date, with the caveats set out in Sections 2.6 and 10. They frequently fulfil a dual role as both reducing and stabilizing agents, enabling the “green” fabrication of Ag, Au, and ZnS nanoparticles from aqueous precursor solutions. Biosurfactant-stabilized nanoparticles show stable colloidal behaviors across extended storage periods, positioning them as sustainable alternatives for environmental remediation and nanomedicine [58,110].

Surfactant-free colloidal synthesis. A unified theoretical framework for gold nanoparticle shape control bypassing all conventional surfactants delivers nanostars, nanospheres, nanorods, and nanoplates via green syntheses that exploit preferential facet reduction kinetics without SDA additives, outperforming surfactant-coated analogues in SERS and catalysis [111]. Complementary approaches use laser ablation, solution plasma, polyols, or monoalcohols to generate “naked” precious-metal nanoparticles with unobstructed surface sites [112].

Table 5
Comparison of post-synthetic surfactant removal and exchange strategies.

Method	Mechanism	Key Advantages	Principal Drawbacks	References
Thermal annealing	Thermal decomposition of organic chains	High cleanliness; scalable; no solvents	Sintering and nanoparticle growth; loss of high-SA/V ratio	[102]
Solvent washing / centrifugation	Physical desorption by “good/poor” solvent cycles	Simple equipment; widely applicable	Incomplete chemisorbed ligand removal; large solvent waste	[103]
Chemical stripping ($NOBF_4$)	Nitrosonium ion displaces bulky organics with BF_4^-	Preserves morphology; restores metal accessibility	Requires specific reagents; limited substrate scope	[103,109]
Ligand exchange	Competitive displacement by shorter/functional molecules	tuneable surface chemistry; reduces interparticle spacing	May induce aggregation; incomplete exchange possible	[73,109]
UV-Ozone (UVO) irradiation	Ozone oxidises organic species (PVP, alkyls)	Effective for PVP and alkyl chains; no solvents	Ineffective for amines (e.g. oleylamine on Pt)	[102]
Electrochemical cleaning	Potential cycling desorbs surfactants in inert electrolyte	In-situ; preserves electrocatalytic surface	Limited scalability; instrument-dependent	[112]

Non-ionic biocompatible stabilizers. For polymeric drug delivery nanoparticles – particularly those based on phytochemicals or hydrophobic active pharmaceutical ingredients – non-ionic surfactants such as polysorbates (Tween 20/80), poly(vinyl alcohol), and poloxamers serve as colloidal stabilizers that prevent irreversible aggregation while modulating interactions with biological barriers and pharmacokinetics. Their low toxicity and regulatory acceptance make them the preferred choice for nanomedicine formulations [38,113].

4.4. Ligand shells: From synthesis to post-synthetic functionality

The ligand shell fixed during synthesis dictates final size and shape; post-synthetic ligand engineering subsequently modulates colloidal stability, electronic properties, and biological or catalytic function [16,103] (Fig. 3).

Long-chain ligands such as oleic acid ensure monodispersity but form thick, insulating shells that impede charge transport, motivating exchange to short-chain organic or inorganic ligands (halides, thiocyanates) to improve conductivity [109]. Conversely, polymer ligands can convert dense surfactant coatings into brush-type colloids that retain dispersibility while exposing accessible metal surface for catalysis [114]. Multidentate ligands with two or more anchors are far more stable than monodentate analogues under dilution or solvent exchange, which is critical for biomedical conjugation [73].

4.5. Post-synthetic surfactant removal and ligand exchange: An often-ignored source of hidden variability

Whilst SDAs are indispensable during synthesis, their persistent presence on the nanocrystal surface frequently constitutes a liability in downstream applications: blocking active catalytic sites, creating insulating barriers that hinder charge transport in electronic

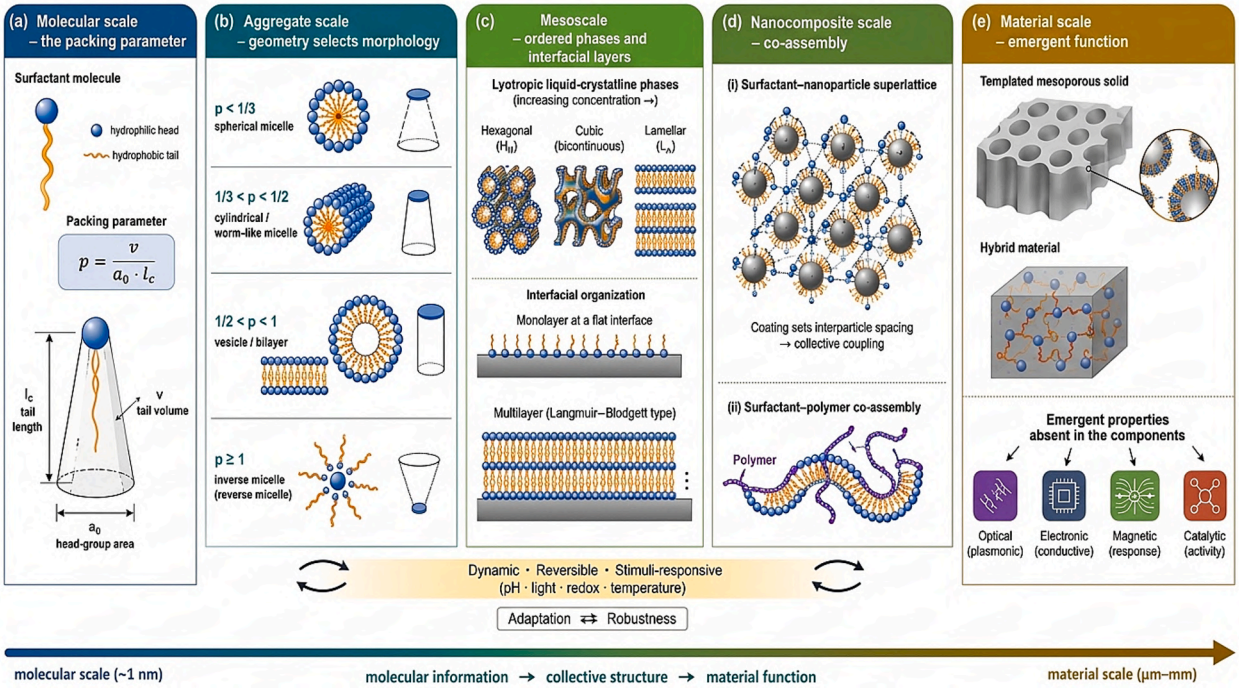

Fig. 4. Surfactant self-assembly across length scales: from molecular packing to emergent material function. Surfactant molecular geometry encodes information that propagates across hierarchical levels of self-organization, linking molecular structure to collective architecture and ultimately to material function. **(a) Molecular scale: packing parameter.** The balance between hydrophilic head-group area and hydrophobic tail volume and length is captured by the packing parameter, $p = v/(a_0 l c)$, where v is the hydrophobic tail volume, a_0 is the effective head-group area, and lc is the critical tail length. **(b) Aggregate scale: geometry selects morphology.** Changes in packing parameter favor distinct aggregate architectures, ranging from spherical micelles ($p < 1/3$) and cylindrical or worm-like micelles ($1/3 < p < 1/2$) to bilayers and vesicles ($1/2 < p < 1$) and inverse micelles ($p \gtrsim 1$). **(c) Mesoscale: ordered phases and interfacial organization.** Increasing surfactant concentration and changes in molecular packing promote the formation of ordered lyotropic phases, including hexagonal, bicontinuous cubic and lamellar structures, together with organized interfacial monolayers and multilayer assemblies. **(d) Nanocomposite scale: co-assembly.** Surfactants direct the organization of inorganic nanoparticles and polymers into higher-order architectures. Ligand shells can define interparticle distances and mediate collective coupling within nanoparticle superlattices, while surfactant aggregates can template or organize polymer chains into hybrid structures. **(e) Material scale: emergent function.** Molecularly programmed self-assembly can generate mesoporous and hybrid materials whose collective architectures give rise to optical, electronic, magnetic and catalytic properties that are not present, or are qualitatively different, in the individual components. Across these hierarchical levels, self-assembly remains dynamic, reversible and stimuli-responsive, with structures adapting to changes in pH, light, redox conditions and temperature, thereby coupling structural organization with the balance between adaptability and robustness.

films, and sterically masking recognition motifs in biological assays. Developing removal strategies that restore surface accessibility without compromising morphology or introducing new contaminants is therefore a major research priority.

4.5.1. Physical and thermal methods

Thermal annealing decomposes organic ligands at elevated temperatures but risks uncontrolled sintering, irreversible nanoparticle aggregation, and loss of high surface-area-to-volume ratio [115]. Rapid "flash" annealing protocols partially mitigate grain growth.

UV-Ozone (UVO) irradiation generates ozone that oxidises PVP and alkyl chains efficiently [116]; however, it proves ineffective against strongly chemisorbed amines such as oleylamine on platinum surfaces. Plasma cleaning (oxygen or argon plasma) removes organic components from thin films while creating porous surface textures, but risks altering the chemical oxidation state of the nanoparticle core [117].

4.5.2. Chemical methods

Repeated centrifugation and solvent washing disperse and reprecipitate nanoparticles using good/poor solvent pairs (*e.g.*, ethanol/cyclohexane or acetone/water). Simple and versatile, this approach nonetheless fails to remove chemisorbed ligands and generates substantial solvent waste.

Chemical stripping with $NOBF_4$. Nitrosonium tetrafluoroborate replaces bulky organic surfactants with the small, weakly coordinating BF_4^- anion, restoring metal surface accessibility while preserving nanoparticle morphology – avoiding the aggregation typical of thermal methods [103,109].

Ligand exchange displaces original surfactants with shorter or more functional molecules (*tert*-butylamine, hydrazine, inorganic ligands), reducing interparticle distances, improving conductivity, and, in biomedical contexts, introducing targeting moieties or enabling aqueous dispersibility [73,109].

4.5.3. Electrochemical cleaning

Potential cycling through cyclic voltammetry in inert electrolyte oxidatively or reductively desorbs surfactants from electrode-supported nanoparticles. While precise and in-situ compatible for electrocatalysis studies, electrochemical cleaning is difficult to scale for bulk material production [112] (Table 5).

The primary challenge across all removal strategies remains colloidal destabilization: once the protective shell is stripped, NPs tend to aggregate irreversibly. Furthermore, complete removal is rarely achieved, leaving residual impurities that can impair reproducibility. Surfactant-free colloidal synthesis using weakly stabilizing solvents (dimethylformamide, polyols) represents a compelling alternative, yielding "naked" surfaces immediately ready for application [110,111].

The recurring theme of this section is inference outpacing measurement. Where binding mode, coverage and conformation have been resolved directly, structure–property relationships are robust; where they are assumed, apparent design rules frequently fail to transfer between cores, solvents or biological media. Prioritizing interface-resolved, in situ measurement over bulk proxies is, in our view, the single most consequential step toward genuinely mechanistic surfactant design.

4.6. Soft and hard templating

Templating represents the most literal expression of the architect metaphor: surfactant assemblies act as molds that guide the formation of the material, which is subsequently cast around or within them. In soft templating, a surfactant mesophase or micellar array serves as a removable organic scaffold around which an inorganic precursor condenses, so that the pore architecture of the product replicates the geometry of the assembly – the mechanism established for ordered mesoporous silicates, in which a liquid-crystalline surfactant phase directs the framework [118]. In hard templating, a pre-formed rigid solid (itself often surfactant-synthesized) is infiltrated and then removed, transferring its inverse structure to the replica [89]. The two strategies trade control against fidelity: soft templates are versatile and tunable but sensitive to the co-assembly conditions, whereas hard templates reproduce a defined structure faithfully at the cost of additional synthetic steps. In both, the structural information originates in the surfactant assembly discussed in Section 5, making templating the operational bridge between molecular self-assembly and solid-state architecture.

4.7. Mesoporous materials and hierarchical architectures

The best-developed application of soft templating is the synthesis of ordered mesoporous materials, where the symmetry of the lyotropic surfactant phase (Section 5.3) is transcribed directly into the pore lattice (hexagonal, cubic or lamellar) of silicas, titanias and related oxides [119]. Control is exerted through the same molecular variables that govern the parent mesophase: the surfactant's packing parameter sets the pore geometry, its chain length sets the pore diameter, and block-copolymer templates extend the accessible pore sizes into the large-mesopore range. Combining templates across length scales – micellar and colloidal, or multiple block copolymers – yields hierarchical architectures with porosity at several scales simultaneously. The reliability of this transcription is precisely why mesoporous synthesis is the clearest success of surfactant-directed design; its principal caveat is the one common to all templated materials, namely that template removal (Section 4.5) can distort or partially collapse the very structure it was used to create.

4.8. Surfactant-assisted phase transformation

Beyond directing initial formation, surfactants influence which crystalline phase a material adopts and how it transforms between polymorphs. By binding selectively to the surfaces of a particular polymorph, a surfactant alters the relative interfacial energies that determine phase stability at the nanoscale, and can stabilize a phase that would be metastable in the bulk or bias a transformation toward a desired product [3]. Because phase governs function – catalytic, optical, magnetic and electronic properties frequently differ sharply between polymorphs of the same composition (Section 7) – this facet-selective control of phase is a direct extension of the structure-directing role, operating on crystal structure rather than on external morphology. It remains, however, among the least predictable aspects of surfactant-mediated synthesis, since the same surface-binding selectivity that enables it is difficult to anticipate a priori for a new surfactant–material pair.

4.9. Surfactant-mediated assembly of hybrid materials

Finally, surfactants organize not only single-component materials but multi-component hybrids, co-assembling inorganic, polymeric and molecular constituents into a single architecture. Acting as the common organizing medium, the surfactant reconciles components that would otherwise phase-separate, positioning them with nanoscale registry – the same co-assembly principle that produces nanoparticle superlattices (Section 5.5) applied to chemically dissimilar building blocks [120]. The resulting hybrids combine properties that no single constituent provides, and they represent the upper end of the complexity that surfactant direction can reach. As with hierarchical templating, the achievement is structural control across components and scales; the persistent limitation is that the multi-component assembly amplifies the sensitivity to conditions already noted for single-component systems, so that reproducibility becomes correspondingly harder to guarantee (Sections 6 and 12).

5. Self-assembly across length scales

Beyond directing the formation of individual nanoparticles or surfaces, surfactants can organize themselves – and the materials or interfaces they decorate – into structures spanning from single molecules to hierarchical, functional architectures; this section extends the design chain from single-interface adsorption to collective, multi-scale organization.

Self-assembly is the step in the design chain where the properties of a single molecule become the properties of a collective structure. Everything covered so far – including molecular architecture (Section 2), interfacial adsorption (Section 3) and the direction of material formation (Section 4) – feeds into a small set of geometric rules that determine how amphiphiles organize, from individual aggregates to hierarchical, functional materials. We treat lipid nanoparticles and liposomes, the most consequential self-assembled surfactant systems in current practice, as a worked example in Section 8.6, and concentrate here on the general principles: what governs which structure forms, how that structure spans length scales (Fig. 4), and how far the process can be made dynamic, reversible and responsive rather than merely spontaneous.

5.1. Micelles, vesicles and bilayers

The first-order predictor of aggregate shape is geometric. The dimensionless packing parameter, $p = v/(a_0 l_c)$ – relating the hydrophobic tail volume v and length l_c to the effective head-group area a_0 – divides amphiphiles into those that form spherical micelles ($p < 1/3$), cylindrical micelles ($1/3 < p < 1/2$), vesicles and flexible bilayers ($1/2 < p < 1$) and planar or inverse structures ($p \approx 1$ and above) [121,122]. This framework is remarkable for how much it explains from so little, and it is the clearest instance in surfactant science of a molecular descriptor mapping directly onto a supramolecular outcome. Its limits, however, are equally instructive: a_0 is not a fixed molecular constant but a thermodynamic quantity that responds to ionic strength, temperature, co-surfactants and the state of the tail, so that the "neglected role of the surfactant tail" can shift the predicted geometry entirely [121]. The packing parameter is therefore best read not as a lookup table but as the paradigm case of a structure-predicting rule whose inputs are themselves environment-dependent.

5.2. Interfacial monolayers and multilayers

At an interface rather than in bulk, the same amphiphiles organize into monolayers and, through successive deposition or adsorption, multilayers. The air–water interface has served as the canonical model system, where surface-tension and neutron-reflectivity measurements resolve how head-group chemistry and chain packing set the surface excess, the layer thickness and the in-plane order [123]. The organizing principles established there – that adsorption is governed by the balance of hydrophobic driving force and head-group repulsion, and that the resulting film thickness and density are molecular properties – carry over, with modification, to the curved and chemically heterogeneous surfaces of real materials discussed in Section 3. The key difference is that a planar interface permits the direct, quantitative structural measurement that the buried, curved interface of a coated nanoparticle largely denies (Section 6), which is one reason interfacial monolayers remain the reference point against which nanoparticle coatings are interpreted.

5.3. Liquid-crystalline phases

As amphiphile concentration increases, discrete aggregates give way to ordered lyotropic liquid-crystalline phases – hexagonal, cubic and lamellar mesophases whose symmetry follows the same packing-geometry logic that governs individual aggregates [122]. These mesophases matter to materials science for two reasons. First, they are functional in their own right, providing ordered, tunable media with anisotropic transport and optical properties. Second, and more importantly for this Review, they act as structure-directing templates: the geometry of a surfactant mesophase is transcribed into the pore architecture of the inorganic material grown within it, the mechanism underlying ordered mesoporous solids treated in Section 4. The liquid-crystalline phase is thus the bridge between molecular self-assembly and the hierarchical porous architectures that give many surfactant-templated materials their function.

5.4. Surfactant–polymer co-assembly

Combining surfactants with polymers expands the accessible structural space well beyond what either component reaches alone. Depending on the sign and strength of the polymer–surfactant interaction, co-assembly produces mixed micelles, polymer-decorated aggregates, and bulk or interfacial complexes whose composition and structure can be tuned continuously. This behavior is mapped in detail at the air–water interface for a range of polymer–surfactant pairs [123]. The practical significance is that the polymer adds mechanical robustness, responsiveness and multivalency to the intrinsic organizing tendency of the surfactant, which is exactly the combination exploited in the polymer–surfactant hybrid coatings discussed under sustainability (Section 10.4). Co-assembly is, in effect, a route to interfaces that are simultaneously ordered (from the surfactant) and durable (from the polymer).

5.5. Surfactant–nanoparticle co-assembly

When the assembling objects are themselves nanoparticles, the surfactant governs both the interparticle interactions and the symmetry of the resulting superstructure. Surfactants drive the cooperative organization of nanoparticles into ordered arrays and superlattices in which the coating sets the interparticle spacing and, with it, the collective coupling between neighbors [124]. The resulting nanocrystal solids are not merely close-packed powders: controlled coupling between building blocks gives rise to collective optical, electronic, magnetic and catalytic properties absent in the isolated nanoparticles, and the surfactant shell is the spacer and glue that makes this coupling reproducible [120]. This is the clearest demonstration in the Review that a surfactant can encode structure at a level above the individual nanoparticle, and that the molecular length of a ligand can be a design variable for a material's bulk physical properties.

5.6. Hierarchical organization and emergent properties

The preceding subsections describe organization at single length scales; their power lies in the fact that surfactant self-assembly operates across scales simultaneously, from molecular packing through mesophase symmetry to nanoparticle superlattice, so that order at one level constrains and templates order at the next [120,122]. It is this hierarchical, multi-scale character that produces emergent properties that belong to the assembled ensemble rather than to any component. The recurring caution, however, is that emergence is only as reliable as the weakest link in the hierarchy: a defect in packing propagates upward, and the sensitivity of each level to environment (temperature, ionic strength, evaporation rate) means that reproducible hierarchical assembly demands control over process conditions that is rarely fully reported.

5.7. Dynamic and reversible self-assembly

Because surfactant self-assembly is held together by weak, non-covalent forces, it is intrinsically dynamic: aggregates exchange molecules with their surroundings, and structures form, dissolve and reform in response to changing conditions. This reversibility is a feature rather than a defect. It underlies error-correction during assembly, permits structures to heal, and is the precondition for the responsive behavior exploited in the next subsection [125]. The same lability, however, underlies the fragility highlighted throughout this Review – the ease with which a well-defined structure can be disrupted when the surrounding environment changes (Sections 7.1 and 9). Dynamic self-assembly is therefore best understood as a trade-off rather than an intrinsic advantage: the reversibility that enables adaptation is also what constrains structural robustness.

5.8. Stimuli-responsive surfactant systems

Harnessing that reversibility deliberately gives stimuli-responsive systems, in which an external trigger, such as pH, light, redox potential, temperature or a magnetic field, switches the assembly between defined states [125]. Photoswitchable amphiphiles bearing azobenzene or arylazopyrazole groups reconfigure on illumination; redox-active surfactants assemble and disassemble on oxidation and reduction and can be cycled electrochemically; and pH-responsive systems track the protonation state of the head-group. The materials-design significance is that responsiveness converts a static coating into an actuator, the basis for triggered release and adaptive interfaces (Sections 8.5 and 13). The critical caveat, consistent with our treatment of responsive coatings elsewhere, is that most demonstrations establish switching in idealized media; whether the same switch operates within the crowded, competitive environment of a real application is far less often shown.

5.9. From molecular self-assembly to functional materials

Taken together, the mechanisms in this section define the route by which a molecular property becomes a material function: molecular packing selects an aggregate geometry, that geometry organizes into mesophases and superstructures, and those structures are either functional directly or transcribed into an inorganic material by templating (Section 4) [120]. This is the central claim of the Review made concrete: surfactants are architects precisely because the information encoded in a single amphiphile propagates, through self-assembly, into the structure and function of a bulk material. The gap between this principle and its reliable practice is the recurring subject of the sections that follow: self-assembly delivers exquisite structural control under controlled conditions, but translating that control into reproducible, scalable, application-ready materials remains the research field central unsolved problem (Sections 6 and 12).

6. Characterizing the dynamic surfactant–material interface

None of the structure–function claims made elsewhere in this Review are stronger than the techniques used to support them; before turning to what surfactant-organized interfaces can do (Section 7), we examine critically how (and how reliably) that organization can actually be measured.

No single technique reports the surfactant shell in full, and the multi-method toolkits assembled to compensate frequently disagree. Hydrodynamic size, grafting density, conformation and binding stoichiometry are each accessed by orthogonal methods whose assumptions and failure modes differ, and the absence of standardized, cross-validated protocols means that nominally identical coatings can be characterized to mutually incompatible conclusions across laboratories. We treat this issue not as a technical footnote but as a reproducibility gap that directly undermines claims of controlled, rational coating design, assessing where technique complementarity genuinely constrains the answer and where it merely multiplies uncertainty.

6.1. Why no single technique can define the interface

Characterization of surfactant-coated nanoparticles is essential to verify coating quality, functional performance and colloidal stability. Because no single technique fully describes these complex systems, complementary methods must be combined, grouped here into (1) size and colloidal-stability analysis, (2) surface chemical characterization, and (3) structural and morphological investigation [126,127].

6.2. Size, aggregation and colloidal stability (DLS, NTA, DCS, AFM)

Size and colloidal-stability methods probe how surface functionalization affects hydrodynamic behavior. Dynamic Light Scattering (DLS) is the usual first-line tool, giving hydrodynamic diameter (Dh) and polydispersity index (PDI) [128]; an increase in Dh after adsorption indicates an interfacial layer and low PDI (<0.2) a uniform coating. Coupled with electrophoretic light scattering it yields the zeta potential (ζ): $|\zeta| \geq 30$ mV signals electrostatic stabilization by charged surfactants (CTAB, citrate), whereas near-neutral ζ, typical of PEGylated systems, indicates steric stabilization. Being intensity-weighted, DLS is biased toward larger aggregates and requires complementary techniques [129–131].

In this context, Nanoparticle Tracking Analysis (NTA) provides number-based size distributions by tracking the Brownian motion of individual nanoparticles, enabling discrimination between coated nanoparticles and small aggregates or uncoated fractions [132,133]. This capability is particularly valuable for detecting heterogeneous surfactant coverage or partial desorption over time. Similarly, Differential Centrifugal Sedimentation (DCS) provides high-resolution size analysis by separating nanoparticles based on their sedimentation velocity within a density gradient. Because the effective density of nanoparticles is influenced by the presence of a surfactant shell, typically less dense than the inorganic core, DCS enables indirect estimation of coating thickness and composition via measurable shifts in apparent particle size [134,135].

Atomic Force Microscopy (AFM) adds direct morphological characterization of surface topography and coating integrity on immobilized nanoparticles [136,137]; combined with DLS it compares hydrated and dry dimensions to estimate corona thickness and conformation. UV–Vis stability and turbidity assays provide rapid, sensitive readouts of colloidal integrity [138], since changes in absorbance intensity or shifts in the localized surface plasmon resonance (LSPR) maximum can indicate successful surface modification or the onset of nanoparticle aggregation, making UV–Vis spectroscopy particularly useful for monitoring colloidal stability under varying ionic strength and pH conditions. [139–148].

6.3. Morphology and structure (TEM, cryo-TEM, SEM, SAXS/SANS, XRD)

Structural and morphological characterization techniques are essential for probing the architecture and integrity of surfactant-coated nanoparticles, providing direct and complementary insights into coating efficiency and colloidal stability [149,150].

Scanning and Transmission Electron Microscopy (SEM, TEM) assess size, shape and dispersion, giving initial evidence of surfactant-mediated stabilization or aggregation [151,152]: well-coated gold nanoparticles appear isolated in TEM, whereas poor coatings cluster [153,154]. High-Resolution TEM resolves the core–shell interface and can measure thin (1–2 nm) organic layers such as thiolate or polymeric shells, evidencing successful functionalization [155–158].

To preserve the native colloidal state, cryogenic electron microscopy (cryo-TEM) images nanoparticles in their hydrated

environment, making it especially suitable for soft or dynamic surfactant assemblies. It has directly visualized lipid bilayers around inorganic cores and micelle-like surfactant shells (often 4–6 nm thick), enabling assessment of coating uniformity without drying artifacts [159,160].

Small-Angle X-ray Scattering (SAXS) provides ensemble-averaged, in-solution structural data [161], determining core–shell dimensions, shell thickness and electron-density profiles under realistic conditions [162,163]. It has quantified silica/polymer shells on metal cores and distinguished monolayer from bilayer CTAB arrangements on gold nanorods [147], and reports interparticle spacing in concentrated dispersions [164,165].

Although not an imaging method, Thermogravimetric Analysis (TGA) plays a key role in structural characterization by quantifying the organic content associated with the nanoparticle surface [166]. By monitoring mass loss during controlled heating, TGA enables estimation of surfactant loading and surface coverage [167,168]. For instance, differences in weight loss profiles can distinguish

Table 6
Information, advantages, and limitations of surfactant characterization methods.

	Technique	Information provided	Relevance for coating	Advantages	Limitations	References
Size and Colloidal Stability	DLS	Hydrodynamic diameter, polydispersity, zeta potential	Indirect evidence of coating; stability prediction	Fast, facile, widely available	Limited resolution in polydisperse systems	[129,197,198]
	NTA	measuring distribution (particle-by-particle) and concentration	Resolves size heterogeneity due to coating	High resolution for polydisperse samples	Lower throughput, operator-dependent	[133,199,200]
	AFM	Topography, real particle size, coating thickness	Direct measurement of coating; surface forces	High resolution, 3D mapping	Slow, requires substrate immobilization	[136,137]
	DCS	Size and density distribution	Detect coating-induced density changes	High-resolution separation	Requires density assumptions	[134,135,201]
	UV–Vis stability assay/ turbidity	Aggregation kinetics	Monitors colloidal stability over time	Fast, real-time	Indirect, qualitative	[202,203]
Surface Chemical Characterization	FT-IR	Functional groups, chemical bonds	Confirms presence of surfactant molecules	Simple, fast	Limited surface specificity (bulk contribution)	[204,205]
	XPS	Elemental composition, oxidation states	Quantifies surface coverage, binding	Surface-sensitive, quantitative	Expensive, vacuum required	[192,196]
	NMR	Molecular structure, binding state	Distinguishes free *vs.* bound surfactant	Detailed molecular insight	Complex interpretation	[194,206]
	MS (MALDI-TOF, ESI-MS)	Molecular weight, composition	Identifies surfactant species	High sensitivity	Sample preparation critical	[207,208]
	ToF-SIMS	Surface elemental and molecular mapping	Distribution of surfactants on the nanoparticle surface	Extremely surface-sensitive	Expensive, complex	[209–211]
	Raman SERS	Vibrational modes, molecular fingerprint	Detects low-level coverage	Highly sensitive	Fluorescence interference	[184,187,190,212]
	UV–Vis Fluorescence	Optical properties, LSPR shifts	Monitors coating-induced surface changes	Fast, real-time analysis	Indirect, not specific	[213,214]
	ITC	Binding affinity, thermodynamics	Quantifies surfactant-nanoparticle interactions	Quantitative, mechanistic insight	Requires high sample purity	[215–217]
Structural and Morphological	SEM	Surface morphology	Visualises aggregation, morphology	Easy imaging	Limited coating visibility	[149,157]
	TEM HRTEM Cryo-TEM	Core-shell structure, coating thickness	Direct visualization of coating	High resolution	Sample preparation artifacts	[152,160]
	Cryo-electron tomography	3D structure of coating	Resolves multilayer and complex architectures	3D imaging in near-native state	Technically demanding	[218–220]
	SAXS	Layer thickness, structure (core–shell)	Determines coating architecture	Works in solution	Requires modelling	[162,164]
	TGA	Organic mass fraction	Quantifies coating amount	Quantitative	No structural detail	[167–169]
	Ellipsometry	Layer thickness, refractive index	Studies on coating on planar analogues	Non-destructive, precise	Requires planar model	[174,176]
	QCM-D	Mass adsorbed, viscoelastic properties	Monitors coating formation, rigidity	Real-time, quantitative	Requires planar surface	[172,175,178]

between sparsely grafted and densely packed coatings, or reveal the presence of multilayer adsorption [169]. In PEG-functionalized systems, TGA is often used to calculate grafting densities, providing quantitative information on the number of polymer chains per unit surface area [170,171].

Surface-sensitive ellipsometry and Quartz Crystal Microbalance with Dissipation (QCM-D) probe coating formation and interfacial properties [172]. Ellipsometry gives sub-nanometer film thickness and refractive index on planar substrates, allowing real-time monitoring of, *e.g.*, PEG-layer growth across grafting regimes [173–176]. QCM-D tracks resonance-frequency and dissipation changes to report adsorbed mass and viscoelasticity, distinguishing rigid monolayers from soft, hydrated brushes and following adsorption/desorption kinetics [177–181].

6.4. Surface chemistry (XPS, FTIR, Raman, NMR)

Surface chemical characterization plays a central role in understanding the composition, binding mechanisms, and interfacial organization of surfactant-coated nanoparticles [16]. Given the complexity of nanoparticle–surfactant systems, a combination of complementary techniques is required to achieve a comprehensive description of the surface chemistry and its impact on nanoparticle behavior [182].

Vibrational spectroscopies – FT-IR and Raman, including Surface-Enhanced Raman Spectroscopy (SERS) – identify surfactant functional groups and confirm adsorption [183,184]. ATR-FT-IR detects bands such as C=O or C–O–C in polymeric coatings like PEG, evidencing functionalization [185,186], while SERS provides high sensitivity on plasmonic nanoparticles, resolving molecular fingerprints at low coverage – for example thiolated aromatic ligands on gold or silver, whose signals report coverage, orientation and stability over time [187–190].

X-ray Photoelectron Spectroscopy (XPS) further strengthens surface chemical analysis by providing quantitative and surface-sensitive information on elemental composition and chemical states. This technique is particularly valuable for confirming binding mechanisms [191–193]. For instance, the presence of S_{2p} signals in thiol-functionalized gold nanoparticles is indicative of sulfur-containing surface ligands, while S_{2p} binding energies around $\sim$ 162 eV are characteristic of thiolate species chemisorbed to gold. Similarly, shifts in binding energy can reveal changes in the local chemical environment and electronic state of the surface-bound species [194,195]. Additionally, XPS depth profiling, often achieved through controlled ion sputtering, enables investigation of layer thickness and the interface between the nanoparticle core and the surfactant shell, offering insights into coating uniformity and integrity [196].

Complementary to XPS, Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) provides highly surface-sensitive chemical mapping with excellent spatial resolution [210,221]. This technique enables the detection of characteristic molecular fragments at the outermost surface, allowing detailed analysis of surfactant distribution and heterogeneity across nanoparticle assemblies or supported systems. Such information is particularly useful for identifying non-uniform coatings or phase segregation within mixed surfactant layers [222–224].

Nuclear Magnetic Resonance (NMR) spectroscopy provides molecular-level insights by probing the structure and dynamics of surfactants at the nanoparticle interface [225,226]. Solution NMR can distinguish between free and bound molecules by changes in chemical shifts and peak broadening, while solid-state techniques, such as magic-angle spinning (MAS) NMR, provide insights into immobilized species, ligand packing, and molecular organization on the surface. These approaches are especially valuable for understanding the strength and nature of surfactant–nanoparticle interactions [51,206,227].

Mass spectrometry (MS), including Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) and Electrospray Ionization (ESI-MS), enables precise identification and characterization of surfactant molecules, both before and after interaction with nanoparticles [228,229]. For example, MALDI-TOF is commonly used to analyze polymeric coatings such as PEG, while ESI-MS is well-suited for studying small ionic surfactants and monitoring ligand exchange processes in solution [207]. These techniques can also provide information on the integrity of the surfactant layer and possible degradation or desorption phenomena [208].

Optical methods (UV–Vis, fluorescence) give real-time insight into surface modification and stability [230,231]. In plasmonic systems, LSPR shifts track refractive-index changes from adsorption or aggregation [232,233]: thiolate functionalization of gold typically red-shifts and stabilizes the plasmon band, whereas aggregation broadens it [212,234]. With labelled surfactants, fluorescence follows adsorption/desorption and exchange, with quenching or enhancement reporting fluorophore–surface proximity [235,236].

Finally, Isothermal Titration Calorimetry (ITC) offers a thermodynamic perspective on surfactant–nanoparticle interactions by directly measuring binding enthalpy, affinity constants, and stoichiometry [217,237]. This technique is particularly powerful for distinguishing between physisorption and chemisorption processes and for identifying cooperative effects in multilayer formation. For example, ITC can be used to quantify the energetics of surfactant adsorption onto metal or metal oxide nanoparticles, providing a deeper understanding of the forces governing coating formation and stability [237–243].

6.5. Adsorption, binding and interfacial dynamics (ITC, QCM-D, ellipsometry, SPR/LSPR)

The methods grouped here differ in kind from the imaging and spectroscopy of Sections 6.3–6.4: rather than reporting the static structure of a coating, they measure the interaction itself – its energetics, its kinetics and its evolution in situ. Isothermal titration calorimetry resolves the thermodynamics of surfactant–nanoparticle binding, returning the enthalpy, stoichiometry and affinity of adsorption directly and without labels [215,217,244,245]. Quartz crystal microbalance with dissipation follows the adsorbing layer in real time, reporting both the coupled mass and the viscoelasticity – and hence the hydration and softness – of the film as it forms

[175,177]. Ellipsometry returns the thickness and refractive index of thin coatings, including their swelling in situ [173,174,246,247], while surface plasmon resonance and its localized analogue track binding kinetics through the refractive index change at the interface [212,232]. Their shared value, and the reason they complement the structural methods, is that they capture the dynamic, solvated interface – the state in which the coating actually operates – that ex-situ, high-vacuum techniques cannot access (Section 6.1). Their shared limitation is model-dependence: each converts a measured signal into an interfacial quantity through assumptions (a binding model, a viscoelastic model, an optical model) whose validity is rarely tested against an independent measurement (Table 6).

6.6. *Thermal and compositional analysis (TGA, DSC)*

Thermal methods answer a question the others largely leave open: how much surfactant is actually present. Thermogravimetric analysis quantifies the organic fraction from the mass lost on controlled heating, providing one of the few direct routes to grafting density and coating completeness [166,167], while differential scanning calorimetry reports the thermal transitions of the shell – *i.e.*, melting, phase changes and the order of packed alkyl chains – that bear on its stability and permeability. The information is quantitative and ensemble-averaged, which is its strength; its weakness, developed in Section 6.8, is that thermal analysis alone cannot identify the molecules it weighs. Mass loss establishes that a given quantity of organic material is bound, but not what it is or how it is arranged, which is why thermal methods are informative only in combination with the compositional and structural techniques above — the point generalized in the following subsection.

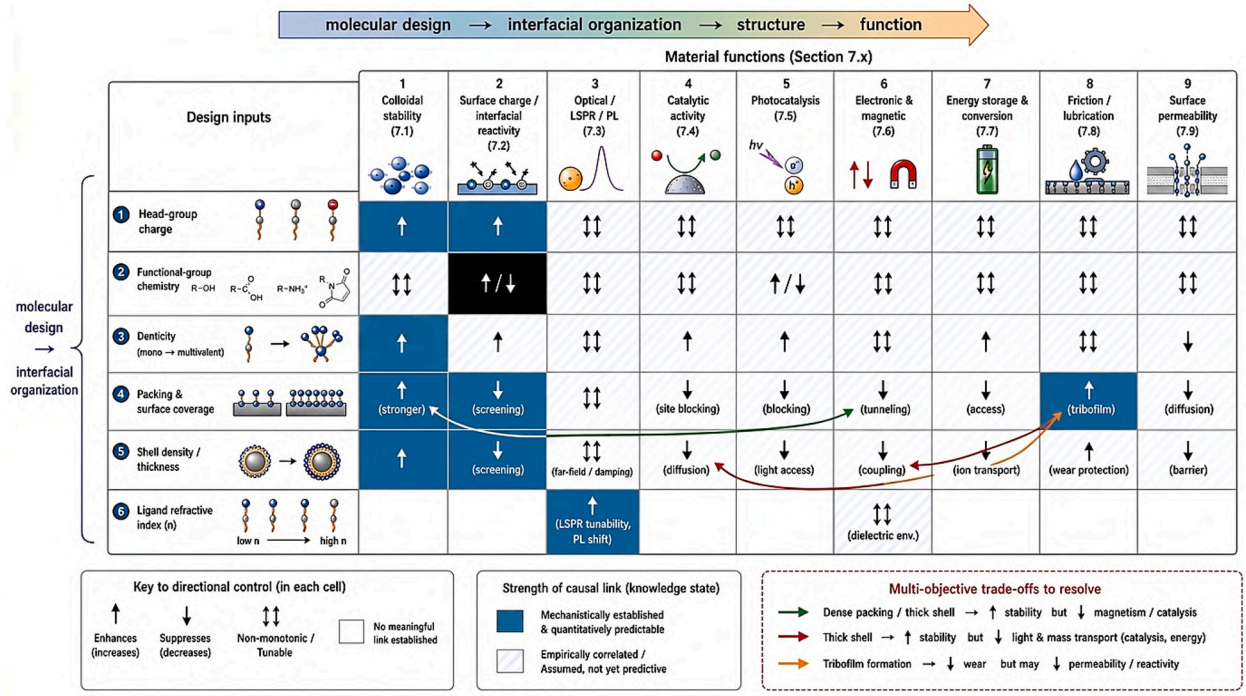

Fig. 5. From interface to function: structure–property relationships and the current state of predictability. The functional properties of surfactant-coated materials emerge from a hierarchical causal chain linking molecular design, interfacial organization, material structure and macroscopic function. The matrix maps six key design variables – head-group charge, functional-group chemistry, denticity, packing and surface coverage, shell density/thickness, and ligand refractive index – against nine classes of material function considered in Section 7: colloidal stability, surface charge and interfacial reactivity, optical properties, catalytic activity, photocatalysis, electronic and magnetic properties, energy storage and conversion, friction and lubrication, and surface permeability. Arrows indicate the qualitative direction of control: ↑ enhancement, ↓ suppression, and ↑↓ non-monotonic or tunable behavior; blank cells indicate that no sufficiently general or meaningful relationship can currently be assigned. The solid/saturated cells denote relationships that are mechanistically established and sufficiently understood to support quantitative prediction under defined conditions, whereas pale/hatched cells indicate relationships that remain primarily empirical, system-dependent, or insufficiently predictive. The matrix highlights a central challenge in surfactant-enabled materials design: the same interfacial parameter can improve one function while compromising another, giving rise to multi-objective trade-offs. For example, increasing surface coverage or shell density may improve colloidal stability and wear protection while restricting catalytic-site accessibility, mass transport, magnetic coupling, or optical interactions. The figure therefore distinguishes between established structure–property relationships and assumed or incompletely resolved causal links, emphasizing that predictive materials design requires quantitative understanding of the interfacial organization that mediates between molecular structure and collective function.

6.7. Correlative and multimodal characterization

The recurring conclusion of this section – that no single technique defines the interface (Section 6.1) – is not a counsel of despair but a specification for how characterization should be designed. The productive response is not to accumulate methods but to match specific questions to the minimal complementary set that answers them, and to cross-check the answers [150]. In practice the questions fall into four families, each with a natural technique combination. How much surfactant is bound is answered by thermal and calorimetric quantification (TGA, ITC; Sections 6.5–6.6). How thick and how organized the layer is requires ensemble scattering combined with an in-situ interfacial probe (SAXS/SANS with ellipsometry or QCM-D; Sections 6.3, 6.5). What the coating is chemically, and how it is bound, is the province of surface spectroscopy (XPS, FTIR, Raman, NMR; Section 6.4). In what physical state the coating exists (hydrated, solvated, intact) demands methods that preserve the native environment (cryo-TEM, in-situ optical and QCM-D measurements; Sections 6.3, 6.5). The decisive distinction is between merely parallel characterization, in which methods are applied to different samples and their results assumed to concur, and genuinely correlative characterization, in which complementary methods interrogate the same sample so that their disagreements become visible and informative. It is precisely these disagreements – a hydrodynamic size that contradicts an electron-microscopy diameter, a grafting density that a binding model cannot reproduce – which expose the assumptions hidden in each technique and that a single-method study conceals. A characterization strategy built on deliberate, cross-validated complementarity, rather than on an accumulation of individually plausible measurements, is therefore the practical precondition for the reproducibility this section has argued the field still lacks, and for the standardized reporting taken up next.

6.8. Standardization, reproducibility and reporting requirements

Numerous characterization methods are employed to investigate the size, distribution, shape, surface charge, and porosity of nanoparticles. However, each technique presents inherent analytical limitations. This section provides a critical discussion of the primary disadvantages associated with the following techniques used to probe nanoparticle properties.

TEM is resource-intensive, requiring meticulous, uniform sample deposition, high vacuum and skilled operators [248]. Polydisperse or aggregated samples are hard to characterize [249,250]. and organic, polymeric or hybrid nanoparticles are prone to beam damage, partly mitigated by cryo-TEM or lower voltages [248]. As a 2D projection technique, it can misrepresent morphology depending on orientation [249], and poorly resolves organic shells and ligands [251].

DLS requires temperature control, sample transparency and known solvent viscosity, and has limited resolution for closely sized populations (*e.g.*, monomers *vs*. dimers). Because scattering scales with d^6, trace large aggregates dominate the signal and mask smaller nanoparticles [252]. For core–shell systems it reports the hydrodynamic diameter – inflated by the solvation layer relative to dry-state methods – and its algorithms assume spherical, homogeneous nanoparticles in stable Brownian motion [150,253].

NTA relates Brownian motion to particle size through single-particle tracking. However, intense scattering from larger nanoparticles can hinder the detection of smaller ones within the same field of view. NTA requires careful optimization of the concentration range (typically 10^7–10^9 nanoparticles/mL) and relies heavily on user-defined settings for video capture and thresholding, which can introduce operator bias [254,255]. Additionally, non-spherical aggregates exceeding 500 nm may exhibit oscillating scattering centers, leading to tracking errors and inaccurate size assignments [256].

Zeta potential, the standard proxy for colloidal stability, is highly sensitive to ionic strength, pH and surfactants.[248] High ionic strength causes electrode polarization/blackening [249], and concentration must be balanced to avoid fluctuations at high dilution or multiple scattering at high concentration [257]. For ionizable groups it is strictly pH-dependent, with massive aggregation near the point of zero charge [248].

In NMR analysis of nanoparticles, sample stability is paramount; insoluble nanoparticles that sediment during the experiment change the effective concentration of the analyte within the active volume [258]. A fundamental limitation is the low inherent sensitivity arising from the small energy differences in Zeeman splitting, often requiring high-field magnets or advanced techniques like Dynamic Nuclear Polarization to resolve signals [259]. Furthermore, the proximity to a metallic or paramagnetic core can cause severe line broadening and dramatic decreases in relaxation times (T_1, T_2), often rendering the spectra uninterpretable for ferromagnetic materials [150,260].

UV–Vis is useful for monitoring the LSPR of noble metal nanoparticles. However, it is sensitive to external interference and requires long-term colloid stability [261]. It lacks the resolution necessary for polydisperse samples and is generally considered a qualitative or screening tool rather than a primary method for quantitative size distribution, for which microscopy is preferred [262,263].

In sp-ICP-MS, calculating the core size assumes ideal geometry and known bulk density, which may deviate from the actual properties of the nanomaterial. Results are also prone to polyatomic interferences from the plasma matrix [229], or molecular MS, minimizing ligand fragmentation is essential, necessitating high-resolution instrumentation to distinguish between nearly isobaric permutations [264].

AFM limitations primarily involve tip-sample interactions. The measured lateral dimensions are a convolution of the actual nanoparticle geometry and the probe tip radius, leading to an overestimation of width, although height measurements (z-axis) remain highly accurate.[265] Additionally, AFM requires deposition on flat, rigid substrates and suffers from low throughput due to slow scanning speeds compared to SEM [150,248].

XPS provides essential elemental and oxidation state data but has limited lateral resolution (~10 μm) and cannot analyze individual nanoparticles [266]. The requirement for ultra-high vacuum and potential surface modification during ion sputtering are significant constraints. Furthermore, the complexity of data interpretation has contributed to a considerable body of unreliable data in existing

literature [150,267].

ITC is exquisitely sensitive to temperature fluctuations and baseline drift [217]. If reactant concentrations are too high, site saturation occurs too rapidly to extract binding constants; if too low, the heat of reaction may fall below the detection limit [244]. Moreover, ITC provides a global heat measurement, making it difficult to deconvolve simultaneous, overlapping processes [245].

TGA cannot identify the number or chemical identity of adsorbed molecules without hyphenation (*e.g.*, TGA-MS), struggles to resolve molecular-weight distributions or end-group differences, and needs milligram-scale samples that can be prohibitive for high-cost or low-yield materials [150,239].

DCS cannot resolve nanoparticle shape [150] and cannot size agglomerates without prior knowledge of their effective density, which can introduce spurious sub-populations [197]. Density or structural changes during sedimentation distort measurements [268], over-dilution lowers signal-to-noise, and precise temperature control in the spinning disc remains challenging for reproducibility [197].

Ellipsometry offers limited spatial resolution for ultra-thin (<10 nm) films, struggles with small absorption coefficients, and requires prior optical constants to model multilayers [246]. The field also lacks standardized protocols for absolute accuracy, so progress will rely on multi-diagnostic, hybrid platforms [247].

Until the community converges on standardized, multi-technique reporting – with explicit disclosure of each method's assumptions and detection limits – coating characterization will remain a source of irreproducibility rather than a safeguard against it. We regard agreed reference materials and minimum-information reporting standards, more than any new instrument, as the field's most urgent characterization need.

7. From interface to function: structure–property relationships

We now ask, property by property and material class by material class, what the molecular design, interfacial organization and self-assembly of Sections 2–5 are known to control, as distinct from merely correlated with.

The properties surveyed below are ordered from those for which the causal link from molecular structure to function is best established to those where it remains largely inferred (Fig. 5). In each case we ask not merely whether a surfactant influences the property, but whether that influence is understood well enough to be designed rather than discovered, and we treat contradictory outcomes – a coating that promotes one property while degrading another – as evidence of the multi-objective trade-offs that any genuinely rational design framework must confront.

7.1. Colloidal stability

Colloidal stability is the most universally invoked function of a surfactant coating and the one for which the structure–property relationship is best established. As developed in Sections 3 and 6, stability derives from the balance between attractive van der Waals forces and the electrostatic and steric repulsion imposed by the adsorbed layer; the molecular determinants – head-group charge, chain length, grafting density and denticity – map onto measurable colloidal descriptors (zeta potential, hydrodynamic size, aggregation onset) in a way that is, for a given material and medium, largely predictive. It is precisely because this one link in the causal chain is comparatively well understood that it is often over-generalized: a coating that confers stability in water at low ionic strength is routinely assumed to perform in biological or high-salt media, where charge screening and competitive adsorption (Section 9) can collapse the same repulsive barrier. Colloidal stability is therefore a necessary but insufficient proxy for the interfacial control on which the remaining properties in this section depend.

7.2. Surface charge and interfacial reactivity

Surface charge follows almost as directly from molecular structure: ionic head-groups set the sign and, together with grafting density, the magnitude of the interfacial potential, while the pH-dependence of the coating (Table 3) determines how that charge responds to the surrounding medium. Charge, in turn, governs interfacial reactivity by controlling the local concentration of ions and charged reactants at the surface, the accessibility of the underlying material, and the electrostatic contribution to the adsorption of biomolecules and analytes. Unlike colloidal stability, however, the link from charge to a specific downstream reactivity is rarely quantified: zeta potential is reported almost universally, yet its mechanistic consequence for a given reaction or binding event is usually inferred rather than measured. This asymmetry – a well-characterized cause paired with a poorly-quantified effect – recurs throughout the properties discussed below.

7.3. Optical properties

The optical response of plasmonic and semiconductor nanomaterials provides one of the clearest demonstrations that a surfactant shell is an optical component in its own right, rather than merely a stabilizing layer. For plasmonic metals, the localized surface plasmon resonance is sensitive to the local refractive index set by the adsorbed layer: systematic studies of gold colloids show that the resonance red-shifts with increasing ligand refractive index, and even with the addition of a single methylene unit to an alcohol-based capping molecule [269], while the choice of surfactant directs the anisotropic growth that produces the longitudinal plasmon bands of rods and wires in the first place [270]. The relationship is thus doubly causal: the surfactant sets both the shape that defines the optical modes and the dielectric environment that tunes them. For semiconductor nanocrystals the coupling is even more intimate: the

geometric fit of a zwitterionic phospholipid head-group into the surface lattice governs the photoluminescence quantum yield and single-particle emission stability of lead-halide perovskites, with rationally matched ligands pushing quantum yields above 96% [271]. Optical behavior is therefore among the most direct read-outs of interfacial organization, but also among the most sensitive to it, which makes reproducibility contingent on control over ligand coverage and packing that is seldom reported.

7.4. Catalytic activity

Catalysis exposes the central tension of surfactant engineering most sharply, because the same adsorbed layer that stabilizes a nanocatalyst also occupies the surface sites on which catalysis depends. The capping agent is neither simply a poison nor simply a promoter: it can block active sites and depress turnover, or it can create a metal–ligand interphase that improves selectivity and even rate, and which of these dominates is specific to the reaction and the ligand [102]. Recent work has moved from treating this as a nuisance to exploiting it deliberately. Surface ligands tune the local solvation, electric field and reactant access at the active site, in a manner explicitly analogous to an enzyme pocket, to steer electrocatalytic CO_2 reduction [272], while the steric and hydrophobic character of the surfactant shell around Pt nanoparticles creates hydrophobic nanopockets that bias selectivity toward C=O over C=C hydrogenation [273]. These examples are among the strongest evidence in this Review that a surfactant can be a designed functional element rather than a necessary evil, but they also show how far the field remains from being able to predict, rather than discover, which ligand will promote a given transformation.

7.5. Photocatalysis

Photocatalysis inverts the picture painted above: here the residual surfactant is far more often a liability than an asset. Because photocatalytic activity depends on charge-carrier transfer across the semiconductor surface to adsorbed reactants, a dense capping layer that blocks that surface generally suppresses activity. Comparative studies of ZnO nanoparticles capped with different agents show measurable reductions in photocatalytic dye degradation relative to less-capped controls [274], and the choice of organic capping agent modulates both the optical absorption and the resulting photocatalytic activity of mesoporous TiO_2 [275]. The surfactant beneficial role in photocatalysis is therefore largely indirect and confined to synthesis – controlling particle size, porosity and defect density – rather than being an active contributor at the working interface. The design implication is the mirror image of catalysis: for photocatalytic materials the goal is frequently a surfactant that directs structure and is then substantially removed, which returns the discussion to the under-measured problem of post-synthetic surfactant removal (Section 4.5).

7.6. Electronic and magnetic properties

The magnetic properties of nanoparticles reveal a subtler structure–property link, in which the surfactant acts not by blocking or exposing a surface but by chemically completing it. The uncoordinated surface atoms of a magnetic nanocrystal carry canted or disordered spins that reduce the saturation magnetization; an appropriately bound ligand can restore surface atomic coordination, repairing missing bonds and thereby modulating surface anisotropy and recovering saturation magnetization [276]. Whether surface- or volume-derived contributions dominate the magnetic response depends on the particle size and the specific coordination chemistry of the coating [277]. The relationship is genuine but delicate, and it sets up a direct conflict of objectives: the dense, strongly-bound shells that optimize colloidal stability do not necessarily optimize the magnetic surface, an instance of the multi-property trade-offs that arise whenever a single coating is asked to serve several functions at once.

7.7. Energy storage and conversion

In energy materials the surfactant most often exerts its influence one step upstream of function, as a structure-directing agent whose imprint on the electrode determines electrochemical performance. Acting as template, porogen, stabilizer and occasionally carbon source, surfactants control the nanoparticle size, crystallinity, porosity and morphology of battery and supercapacitor electrode materials, and these structural attributes translate into measurable differences in rate capability and cycling stability [278]. Surfactants also operate directly within the electrolyte as performance-enhancing additives that modify the electrode–electrolyte interface [279]. As in materials synthesis generally, the causal chain here runs from molecular structure through directed morphology to function; but the reported evidence is dominated by empirical performance comparisons between named surfactants rather than by mechanistic accounts of why a given amphiphile yields a given microstructure – a gap that predictive design (Section 11) would need to close.

7.8. Friction, lubrication and mechanical behavior

The tribological use of surfactant-stabilized nanoparticles as lubricant additives illustrates the design chain operating at the macroscopic scale. Here the surfactant plays two distinct roles: it maintains the dispersion stability of the nanoparticle additive in the base oil – without which the additive aggregates and sediments – and it participates, together with the nanoparticles, in forming the protective tribofilm and boundary layer that reduce friction and wear [280]. The proposed mechanisms (ball-bearing rolling, tribofilm formation, surface mending and polishing) all depend on the nanoparticles reaching and remaining at the contact interface, which the surfactant governs; yet the stabilizing layer is itself temperature-sensitive, with dispersion stability degrading above roughly 60 °C

[281]. Macroscopic mechanical function therefore inherits the same fragility as colloidal stability, and the optimization of a nanolubricant is in large part the optimization of its surfactant.

7.9. Surface permeability and molecular transport

Finally, the surfactant shell acts as a selectively permeable barrier that governs the transport of molecules to and from the underlying material. The same ligand layer that occupies catalytic sites can impart selective permeability, admitting some reactants while excluding others and thereby contributing to the selectivity discussed in 7.4 [272]. In delivery contexts, the permeability of the coating to the surrounding medium controls the release of an encapsulated cargo, linking molecular shell structure to release kinetics (Section 8.5). Compared with the other properties in this section, surface permeability is the least systematically characterized as a design variable in its own right: it is usually inferred from a functional outcome (a reaction selectivity, a release profile) rather than measured directly, and it represents a clear opportunity for the correlative interfacial characterization advocated in Section 6.

8. Surfactant-engineered materials in technology

The structure–property relationships established in Section 7 are only as valuable as the technologies they enable; here we examine how surfactant-controlled interfaces are exploited in practice, treating each application as an illustration of the underlying design principles rather than as an independent sub-field.

Application performance is the usual yardstick for a coating, but it is no longer a sufficient one. Many surfactant strategies that are effective in the biomedical, environmental and industrial settings reviewed here were optimized without reference to the toxicological and regulatory constraints now tightening around them, and a design that excels *in vitro* may already be a translational dead-end under incoming legislation. We therefore consider the applications literature against, rather than apart from, the regulatory and safety pressures developed later in the review, distinguishing coatings with a credible path to deployment from those whose success is confined to the conditions of their own demonstration.

8.1. Catalysis and photocatalysis

Catalysis is the application in which the surfactant dual character – stabilizer and site-blocker – is most consequential, and it illustrates directly the structure–activity relationship developed in Section 7.4. In thermal catalysis, the capping layer that enables size- and shape-controlled synthesis simultaneously governs access to the active sites, so that the same coating can poison or promote a reaction depending on the ligand and the transformation [102]; the deliberate use of the surfactant shell to define a catalytic microenvironment (e.g., tuning solvation, electric field and reactant access at the active site) has become a design strategy in its own right for reactions such as electrocatalytic CO_2 reduction and selective hydrogenation [272,273]. Photocatalysis inverts the balance (Section 7.5): here a residual coating that blocks charge transfer to adsorbed reactants generally depresses activity, so the surfactant's contribution is largely upstream, in directing the particle size, porosity and defect density that set photocatalytic performance [274,275]. Across both, the surfactant is not incidental to the catalytic material; it is a determinant of it, and the central practical challenge remains reconciling the coating needed for controlled synthesis with the exposed surface needed for turnover.

8.2. Energy materials

In energy conversion and storage, surfactants act predominantly as structure-directing agents whose morphological imprint on the electrode determines device performance; the mechanistic basis of this relationship, and the limits of the supporting evidence, are set out in Section 7.7 and are not repeated here. What distinguishes the applied setting is the additional constraint imposed by device integration: residual surfactant that is tolerable in a dispersion may be prohibitive in an electrode, so the removal and exchange strategies of Section 4.5 become part of the performance specification rather than a post-synthetic afterthought.

8.3. Sensors and biosensors

Sensing exploits the surfactant interface in two complementary ways. Optically, the sensitivity of the plasmon resonance to the local dielectric environment (Section 7.3) is the basis of refractometric and surface-enhanced Raman detection, where the surfactant or ligand shell both stabilizes the plasmonic transducer and defines the molecular pocket in which analytes are detected [187,188]. Electrochemically, surfactants adsorbed on the electrode – often together with nanoparticles or carbon nanomaterials – modify the interfacial charge, accumulate target analytes and enhance electron transfer, improving the sensitivity and selectivity of the resulting sensor [282]. In both modes the recurring design tension of this Review reappears in miniature: the coating that provides stability and analyte affinity must not so passivate the transducer that it suppresses the very signal it is meant to enable, making sensor performance a direct read-out of how well the interface has been balanced.

8.4. Environmental remediation

While the industrial applications described above highlight the functional versatility of surfactant-nanoparticle systems, the same colloidal and interfacial properties can be deliberately exploited for active environmental remediation. Beyond their well-documented

role in governing nanoparticle fate and transport in environmental matrices, the amphiphilic architecture of surfactant layers enables the sequestration of hydrophobic organic contaminants through a combination of hydrogen bonding, hydrophobic interactions, and – interactions between surfactant molecules and target pollutants [58,283]. By orienting hydrophobic chains toward organic contaminants while preserving hydrophilic interactions with the aqueous phase, these coatings promote favorable pollutant partitioning from solution and establish a stable interfacial environment that enhances sorptive capacity [284,285]. Furthermore, the molecular architecture and charge of the surfactant layer govern the thermodynamics of particle–pollutant interactions through electrostatic attraction and micellar assembly at the nanoparticle interface, parameters that can be rationally tuned to optimize both adsorption efficiency and catalytic performance [286,287].

Surfactant-modified metal-oxide nanoparticles (ZnO, TiO_2) are widely used for photocatalytic degradation of dyes and pharmaceutical residues in wastewater [288–290], with CTAB-assisted ZnO synthesis increasing surface area, catalytic activity and antimicrobial performance [291,292]. Surfactant coatings also improve the mobility of reactive species through porous media for in situ soil and aquifer remediation [293], and function as selective adsorbents for heavy metals and hydrophobic organics via the amphiphilic layer's dual affinity [294,295]. Reported removal efficiencies for phenolics, dyes and heavy metals show how the same interfacial tunability that complicates risk assessment can be redirected toward sustainable remediation [296,297].

8.5. Nanomedicine and drug delivery

In biomedicine, surfactant-coated nanoparticles serve as drug-delivery systems that improve solubility and stability and enable controlled release across the systemic, microenvironmental and cellular barriers that vary between patients and diseases [298,299]. Beyond stabilization, surfactants support targeted delivery and protect payloads from premature degradation: non-ionic coatings limit opsonization and prolong circulation [28], while amphiphilic layers ease membrane permeation and uptake. Tuning coating structure, thickness, charge and hydrophobicity controls surface potential and non-specific immune interactions, and biocompatible biosurfactants enable environment-responsive carriers (*e.g.*, acidic tumor microenvironments) with improved safety over synthetic stabilizers. The surfactant layer thus optimizes pharmacokinetics while allowing conjugation of targeting ligands [38,300–302].

Surfactant-coated nanoparticles enhance photodynamic (PDT) and photothermal (PTT) therapy of solid tumors [303,304]. In PDT, coatings disperse photosensitizer-bearing nanoparticles, improving uptake and reactive-oxygen-species generation on light activation; PEG, for instance, prolongs circulation and tumor accumulation [305]. In PTT, coatings raise photothermal conversion efficiency [306]: CTAB stabilizes gold nanoparticles and enables ligand functionalization for tumor targeting, though its cytotoxicity must be offset by biocompatible coatings [307–309]. Lipid coatings mimic membranes to improve biocompatibility and cargo encapsulation, while chitosan adds biodegradability and further functionalization [310,311].

Early detection and diagnosis of disease are crucial parts of clinical practice; current challenges remain in achieving fast, detailed imaging of tissue microstructures and lesion characterization, which could be addressed by developing nontoxic contrast agents with longer circulation times [312,313]. A good example is superparamagnetic iron oxide nanoparticles (SPIONs), which offer a safer, more effective, and more versatile alternative to gadolinium chelates for MRI, particularly for imaging atherosclerotic plaques. The surface coating of SPIONs, such as poly(maleic anhydride-*alt*-1-octadecene) (PMAO), imparts a negative surface charge and a hydrodynamic size that maximizes circulation time and evades rapid clearance via renal excretion or phagocytosis [314].

Fluorescent nanoparticles provide high-resolution, high-contrast images and, when conjugated with targeting molecules, can specifically bind to certain biomarkers, allowing precise localization and imaging of tumors. NIR-emitting nanoparticles minimize tissue absorption and scattering, leading to deeper tissue penetration and clearer images. They also enable real-time monitoring of biological processes and nanoparticle distribution within the body, which is valuable for both diagnostic and therapeutic purposes [315].

Coated nanoparticles functionalized with specific surfactants can be used in ultra-sensitive sensors for detecting pathogens (*e.g.*,

Table 7
Comparative overview of liposomes and lipid nanoparticles as surfactant-based self-assembled delivery systems.

Feature	Liposomes	Lipid Nanoparticles (LNPs)
Discovery era	1960 s	1990 s
Core structure	Hollow aqueous core enclosed by phospholipid bilayer(s)	Electron-dense, homogeneous lipid/cargo condensate
Primary surfactant component	Natural or synthetic phospholipids (*e.g.*, DPPC, DOPE)	pH-responsive ionizable lipids (*e.g.*, ALC-0315, SM-102, DLin-MC3-DMA)
Cholesterol role	Membrane fluidity modulator; seals packing defects	Structural integrity; phytosterol analogues tune internal mesophase
PEG-lipid role	Stealth coating; opsonization suppression	Stealth coating; critical CQA determinant (size, PDI, expression)
Preferred payloads	Small molecules (hydrophilic in core; hydrophobic in bilayer)	Nucleic acids (mRNA, siRNA, saRNA, ASOs, pDNA)
Internal mesophases	Predominantly lamellar	Lamellar, inverse hexagonal (HII), bicontinuous cubic (QII)
Endosomal escape mechanism	Membrane fusion or passive endocytosis	pH-triggered ionization → inverse mesophase transition → membrane disruption
Representative approved products	Doxil®, AmBisome®, Vyxeos®	Onpattro®, Comirnaty®, Spikevax®
Key regulatory precedent	Decades of clinical use; established safety data	Rapid authorization leveraged on prior liposome/lipid excipient knowledge

viruses, bacteria, and fungi) or toxic substances in real time [316]. The presence of surfactants on the nanoparticle surface plays a crucial role in stabilizing the colloidal system and in providing functional chemical groups that enable selective interactions with biological targets. Through appropriate surface engineering, these nanoparticles can be further conjugated with biomolecules such as antibodies, proteins, or nucleic acids, allowing highly specific recognition of target analytes [317].

In biosensing platforms, the interaction between the functionalized nanoparticles and the target pathogen can induce measurable changes in optical, electrical, or colorimetric signals. For instance, nanoparticle aggregation, plasmonic shifts, or fluorescence variations can be exploited to generate rapid and easily detectable responses. This capability enables the development of point-of-care diagnostic devices that provide fast results without the need for complex laboratory instrumentation [318,319].

However well engineered, the nanoparticle surface is dynamic once in biological fluids: competitive adsorption of biomolecules rapidly reshapes interfacial properties and downstream cellular interactions. This time-dependent evolution of the nano–biointerface critically affects circulation, recognition and targeting *in vivo*, and must therefore be considered in rational coating design.

8.6. Lipid nanoparticles and liposomes as paradigmatic self-assembled systems

Beyond stabilizing preformed nanoparticles, surfactants are building blocks for constructing delivery systems de novo through self-assembly in water. Their amphiphilic nature lowers interfacial free energy by organizing them into micelles, vesicles, bilayers, lamellar and liquid-crystalline mesophases, and hybrid lipid–polymer assemblies, whose geometry reflects a balance between headgroup hydration, tail packing and intermolecular interactions and can be tuned through molecular design and conditions (pH, ionic strength, temperature, concentration).

Pharmaceutically, this self-organization is a versatile delivery platform: assemblies encapsulate hydrophobic drugs in cores or bilayers and hydrophilic drugs or biomacromolecules in aqueous or condensed compartments, improving apparent solubility and protecting cargo from degradation. Crucially, tuning surfactant chemistry and architecture allows control of release kinetics and responsiveness to physiological cues (pH, temperature, redox, enzymes), turning passive repositories into intelligent, triggered carriers [320].

Importantly, the functional performance of these carriers is not solely determined by their chemical composition but emerges from their internal nanostructure. Parameters such as curvature elasticity, membrane fluidity, permeability, and defect density directly influence cargo retention and release kinetics, as well as interactions with biological membranes and serum proteins. This makes surfactant-based assemblies inherently "structure-active" systems, where small variations in molecular architecture can translate into large differences in biological behavior and release profiles [321].

Advances in lipid chemistry, polymeric-surfactant design and formulation have moved these self-assembled systems from solubilization tools to clinically relevant nanomedicines with tunable pharmacokinetics [322]. Among them, vesicular liposomes and lipid nanoparticles (LNPs) are the most clinically validated manifestations of amphiphile self-assembly [323].

8.6.1. Liposomes and lipid nanoparticles

Liposomes and lipid nanoparticles (LNPs) are the foremost clinical embodiment of surfactant-driven self-assembly, in which engineered amphiphiles spontaneously organise into stable carriers. Their approved products – from liposomal doxorubicin (Doxil®) to the COVID-19 mRNA vaccines Comirnaty® and Spikevax® – are the most significant demonstrations of surfactant science in modern nanomedicine [323–325]. Framing them as surfactant systems shows how changes in headgroup chemistry, ionization state, tail geometry and PEG grafting cascade into differences in morphology, mesophase, biological interaction and therapeutic outcome.

8.6.1.1. Liposomes: The first generation of vesicular surfactant carriers. First described by Bangham in the 1960 s, liposomes are hollow, membrane-bounded spheres formed by the spontaneous self-assembly of phospholipids (the archetypal biological surfactants) into one or more concentric bilayers enclosing an aqueous lumen. Their architecture faithfully mimics the plasma membrane, conferring intrinsic biocompatibility and enabling the simultaneous encapsulation of hydrophilic drugs in the aqueous core and hydrophobic agents intercalated within the lipid bilayer [324,326].

Liposomes are classified by size and lamellarity: small unilamellar vesicles (SUVs, 20–100 nm), large unilamellar vesicles (LUVs, 100–1000 nm), and giant unilamellar vesicles (GUVs, > 1 μm), as well as multilamellar vesicles (MLVs) and multivesicular liposomes. PEGylation (*e.g.*, by DSPE-PEG2000) confers a "stealth" hydration shell that suppresses protein opsonization and extends systemic circulation half-life, a concept directly drawn from the non-ionic surfactant steric stabilization mechanisms discussed in Section 2 [324,327]. Despite their remarkable versatility and the clinical success of Doxil® and AmBisome®, classical liposomes can suffer from limited drug-loading capacity for specific payloads and physicochemical instability leading to cargo leakage during storage.

8.6.1.2. Lipid nanoparticles: Compositional evolution and functional architecture. LNPs emerged in the 1990 s as a structurally distinct and functionally superior platform, engineered specifically for nucleic acid delivery. Unlike the hollow bilayer of liposomes, LNPs feature a dense, electron-rich lipid/cargo condensate core in which genetic material is electrostatically compacted and physically shielded from nuclease degradation. Clinical LNP formulations are four-component systems, each constituent serving a defined surfactant-derived role [323,328,329]:

Ionizable lipids are the primary functional architects. They carry a tertiary amine headgroup that remains neutral at physiological pH (pKa typically 6.2–6.8), thereby minimizing systemic toxicity and non-specific interactions, but acquires positive charge within the acidic endosomal compartment (pH $\sim$ 5.5). This pH-triggered ionization drives electrostatic destabilization of the endosomal

membrane, promoting inverse mesophase formation and nucleic acid release into the cytosol [328,330,331].

Helper phospholipids (*e.g.*, DSPC, DOPE) provide structural integrity to the nanoparticle shell and facilitate membrane fusion events during endosomal escape. DOPE, a cone-shaped lipid prone to form inverse hexagonal phases, has been deliberately exploited to enhance fusogenicity [323].

Cholesterol fills packing defects, modulates membrane fluidity, and enhances structural integrity. Critically, replacement of cholesterol with naturally occurring phytosterol analogues (β-sitosterol, campesterol, stigmasterol) induces polymorphic nanoparticle shapes – polyhedral or faceted rather than spherical – that lower the energy barrier for LNP-endosome fusion and significantly enhance intracellular mRNA delivery [332].

PEG-lipids function as stabilizing surfactants that reduce inter-particle aggregation during manufacture, suppress protein corona formation, and modulate tissue biodistribution. Their chemical identity – DSPE-PEG *vs*. DMG-PEG2000 (Spikevax®) *vs*. ALC-0159 (Comirnaty®) – markedly influences *in vivo* protein expression independently of LNP size or ζ-potential, because PEG-lipid dissociation kinetics from the nanoparticle surface govern the window of available ionizable lipid for endosomal engagement [327,333–335] (Table 7).

8.6.1.3. Self-assembly mechanisms and internal mesophase topology. LNP formation is typically achieved by rapid solvent mixing – most commonly through microfluidic or T-junction devices – whereby an ethanolic lipid solution is abruptly diluted into an acidic aqueous phase containing the nucleic acid payload. The resulting polarity gap triggers instantaneous electrostatic collapse of the ionizable lipid around the anionic nucleic acid, simultaneously driving hydrophobic condensation of the apolar tails to minimize solvent-exposed surface area [328,336]. The kinetics of this assembly step, controlled by flow rate ratio, total flow rate, and lipid-to-nucleic-acid charge ratio (N/P ratio), are primary determinants of nanoparticle size, polydispersity index (PDI), and encapsulation efficiency.

The internal organization of the resulting LNP is not amorphous but comprises well-defined inverse mesophases whose topology is governed by the molecular geometry of the ionizable lipid. Three principal phases have been characterized by small-angle X-ray scattering (SAXS) and cryo-electron microscopy (cryo-EM): (1) lamellar (L) phases, with alternating lipid bilayers and nucleic acid sheets; (2) inverse hexagonal (HII) phases, comprising cylindrical water channels coated with ionizable lipid and surrounded by a continuous hydrophobic matrix; and (3) bicontinuous cubic (QII) phases, with saddle-shaped, triply periodic minimal surfaces that maximize membrane curvature and, critically, membrane fusion propensity [328,337].

These topologies carry direct functional consequences. LNPs with HII or QII internal structure – cuboplexes in the case of cubic phases – exhibit substantially higher endosomal escape rates than their lamellar counterparts, because the intrinsically high membrane curvature lowers the activation energy for stalk-pore fusion intermediates with the endosomal bilayer. Zheng et al. demonstrated that LNP topology is a stronger determinant of cytosolic RNA delivery than encapsulation efficiency alone, establishing internal mesophase engineering as a rational design axis orthogonal to lipid pKa optimization [337].

8.6.1.4. Structure-activity relationships of ionizable lipids. The evolution of ionizable lipid design – from permanently cationic lipids (DOTAP, DOTMA) through first-generation ionizable lipids (DLinDMA) to optimized clinical structures (DLin-MC3-DMA, ALC-0315, SM-102) – exemplifies an iterative, mechanism-guided structure–activity relationship (SAR) campaign [325,330,331]:

pKa engineering. The apparent pKa of the lipid nanoparticle (measured by TNS fluorescence) is the single most predictive parameter of *in vivo* hepatic transfection efficiency, with an optimal window of approximately 6.2–6.8. Lipids with pKa values outside this range show markedly reduced performance: too high a pKa increases systemic toxicity; too low reduces endosomal escape efficiency [328,330].

Tail geometry and mesophase propensity. Lipids bearing branched, unsaturated, or cyclopropyl tails form inverse cone-shaped molecular geometries that favor non-lamellar mesophases under acidic conditions. The landmark DLin-MC3-DMA → ALC-0315 progression illustrates how alkyl tail branching at the α-carbon reduces lamellar propensity and promotes HII formation at endosomal pH, boosting mRNA transfection by an order of magnitude relative to linear equivalents [328,331].

Biodegradable linker introduction. Incorporation of ester or acetal linkages between headgroup and tails enables enzymatic degradation after endosomal escape, reducing lipid accumulation and hepatotoxicity, a critical safety advance for repeat-dosing chronic disease applications [331,338].

8.6.1.5. Formulation strategies for diverse nucleic acid payloads. LNPs and liposomes can be engineered for a spectrum of nucleic acid cargo: siRNA, mRNA, self-amplifying RNA (saRNA), microRNA (miRNA), antisense oligonucleotides (ASOs), and plasmid DNA [323–325,330,338]. Formulation requirements differ substantially across payload types:

saRNA LNPs demand especially precise compositional optimization because the large saRNA molecule (~9–12 kb) is more

Table 8
Selected clinically approved lipid-based nanocarrier products: composition and indication.

Product	Cargo	Ionizable lipid + PEG-lipid	Indication	References
Doxil®	Doxorubicin (small molecule)	DPPC/Chol + DSPE-PEG2000 (liposome)	Kaposi sarcoma, ovarian cancer	[324,325]
AmBisome®	Amphotericin B	DPPC/DSPG/Chol (liposome)	Fungal infections	[324]
Onpattro®	siRNA	DLin-MC3-DMA + PEG2000-C-DMG	Hereditary transthyretin amyloidosis	[323,328,338]
Comirnaty®	mRNA	ALC-0315 + ALC-0159	COVID-19 (SARS-CoV-2)	[323,325,328]
Spikevax®	mRNA	SM-102 + DMG-PEG2000	COVID-19 (SARS-CoV-2)	[323,328,335]

susceptible to shear degradation during microfluidic assembly, and the extended replication phase amplifies even small differences in encapsulation and endosomal escape efficiency. Design-of-experiment (DoE) approaches have demonstrated that PEG-lipid identity and molar fraction are the dominant critical quality attributes (CQAs) governing nanoparticle size, PDI, and *in vivo* immunogenicity of saRNA-LNPs [329].

Co-encapsulation of siRNA and mRNA within a single LNP can synergistically enhance gene silencing and protein expression simultaneously, enabling combined therapeutic and vaccine strategies in a single nanoparticle. Incorporation of anionic "helper" polymers into the formulation further enables dose-sparing of the RNA payload [339].

Characterization accuracy is non-trivial: a careful re-evaluation by Schober et al. of benchmark LNP formulations revealed that actual encapsulation efficiencies – measured by asymmetric flow field-flow fractionation coupled to multi-angle light scattering (AF4-MALS) – are substantially lower than values obtained by standard RiboGreen assays, because the assay does not distinguish between intra-particle and surface-adsorbed RNA. LNP size is remarkably insensitive to nucleic acid length (from short ASOs to long mRNA strands), but encapsulation fidelity demands rigorous, orthogonal characterization [340] (Table 8).

8.6.1.6. Regulatory landscape and clinical translation. Among all nanocarrier classes, lipid-based systems have achieved the most extensive regulatory approvals, from Doxil® (1995) and AmBisome® through to the landmark authorization of Onpattro® (2018) – the first siRNA drug – and the COVID-19 mRNA vaccines (2020–2021) [323–325,338]. This translational success reflects two convergent advantages: the constituent lipid excipients (phospholipids, cholesterol, PEG-lipids) carry decades of regulatory familiarity and established safety data; and the self-assembled architecture provides a scalable, manufacturing-friendly platform compatible with microfluidic, membrane extrusion, or high-pressure homogenization processes.

Nevertheless, the structural and compositional complexity of these multicomponent systems keeps regulatory scrutiny high, particularly regarding: immunogenicity of ionizable lipids and PEG-lipids (including anti-PEG IgM responses that can accelerate LNP clearance upon repeat dosing); batch-to-batch variability in internal mesophase composition; and long-term storage stability of mRNA integrity [325,333,336,338]. Quality-by-Design (QbD) frameworks that link CQAs, including particle size, PDI, encapsulation efficiency, pKa, mesophase index, to critical process parameters (CPPs) are now a regulatory expectation for LNP-based INDs and BLAs.

8.6.1.7. Future frontiers: Beyond the four-component LNP. The next generation of self-assembled lipid carriers is moving toward programmable complexity along several axes:

Selective Organ Targeting (SORT). Addition of a fifth charged lipid component to conventional four-component LNPs systematically redirects biodistribution from the liver toward the lungs (cationic additives) or spleen (anionic additives) by modulating the composition of the adsorbed protein corona, which represents a paradigm-shifting demonstration that surfactant identity controls biological identity via corona programming, directly connecting the themes of Sections 5.1 and 5.3 [325,334].

Phytosterol-induced polymorphic shaping. Replacement of cholesterol with naturally occurring plant sterols (β-sitosterol, campesterol) induces non-spherical, polyhedral LNP geometries that enhance endosomal membrane disruption and cytosolic RNA delivery without altering nanoparticle size. This is an elegant example of lipid tail packing geometry controlling biological performance at the nano-bio interface [332].

Ionizable lipid screening and machine learning. High-throughput combinatorial synthesis coupled to *in vivo* barcoding screens has dramatically accelerated ionizable lipid discovery; machine learning models trained on pKa, logP, and tail geometry descriptors now enable predictive SAR navigation, compressing the optimization cycle from years to months [328,331].

Functionalized PEG-lipids for active targeting. Engineering of tumor microenvironment-responsive PEG-lipids – designed to shed their steric shield upon matrix metalloproteinase (MMP) or pH stimulus – enables conversion of "stealth" systemic circulation into active retention within the tumor interstitia, a strategy that has shown enhanced intratumoral accumulation in murine models [334].

8.6.2. Stimuli-responsive surfactant-coated nanoparticles for triggered drug release

Surfactant coatings also enable stimuli-responsive nanoparticles that release cargo in response to disease-specific cues. pH-responsive surfactants with ionizable groups (carboxylic acids, amines) protonate in acidic tumor or endosomal environments, destabilizing membranes and triggering release [13]; thermo-responsive polymers such as PNIPAM undergo sharp transitions near body temperature for localized release under mild hyperthermia [341]; and redox-responsive thiolated surfactants exploit the glutathione-rich intracellular environment for cancer-specific release [342]. Embedding responsiveness in surfactant architecture thus converts passive carriers into adaptive, environment-sensing platforms that enhance efficacy and reduce off-target toxicity [320].

Judged against deployment rather than demonstration, the applications reviewed here separate sharply: strategies compatible with the toxicological and regulatory constraints developed below retain a translational path, whereas several high-performing but non-compliant chemistries do not. Reporting application performance without this compliance lens increasingly overstates real-world readiness.

8.7. Industrial processes and advanced manufacturing

Surfactant-coated nanoparticles are increasingly employed across multiple industrial sectors because surfactants provide critical control over nanoparticle dispersion, stability, and interfacial activity within complex processing environments [343]. In industrial formulations, surfactants act as stabilizing and structuring agents that prevent nanoparticle aggregation while enabling homogeneous dispersion in liquids, polymers, or lubricants, and other multiphase systems. By preserving colloidal stability during large-scale

processing and operation, surfactants ensure that nanoparticles retain their functional properties and deliver consistent performance under demanding industrial conditions [344,345].

One of the most established industrial applications of surfactant-coated nanoparticles is found in tribological systems and nanolubricants used in mechanical and automotive technologies. In these formulations, surfactants maintain the stable dispersion of nanoparticles such as Fe_3O_4, CuO, and MoS_2 within base oils or aqueous lubricating media, preventing sedimentation and agglomeration during operation. The resulting stability facilitates the formation of protective tribofilms at sliding interfaces, which reduce friction and wear at the asperity level, improve energy efficiency, and prolong the service life of mechanical components. For example, surfactant-assisted Fe_3O_4 nanolubricants have demonstrated significant improvements in metal rolling processes owing to enhanced nanoparticle dispersion and lubrication stability [346,347].

The ability of surfactants to tailor nanoparticle interfacial properties is equally important in the energy sector, particularly in nanofluid technologies developed for enhanced oil recovery (EOR) [348–350]. In these applications, surfactant coatings modify nanoparticle surface characteristics, lower oil–water interfacial tension and regulate wettability and transport through porous geological formations. These combined effects improve oil displacement efficiency and facilitate the mobilization of hydrocarbons trapped within reservoir rocks. Furthermore, carefully designed surfactant layers can maintain nanofluid stability under harsh reservoir conditions characterized by elevated salinity and temperature. Such stabilization has been demonstrated for CuO nanofluids and silica nanoparticle dispersions using ionic surfactants, enabling prolonged operation in hypersaline environments and highlighting the importance of surface engineering for energy-related applications [351,352].

Beyond lubrication and energy technologies, surfactant-functionalized nanoparticles are increasingly incorporated into advanced coatings and polymer-based composite materials. In these systems, surfactants improve compatibility between inorganic nanomaterials and organic matrices while promoting uniform nanoparticle dispersion throughout the material. This enhanced dispersion contributes to improved mechanical performance, thermal stability, and barrier properties of the resulting composites. In anticorrosive coatings, for instance, surfactant-functionalized mesoporous silica nanoparticles can act as nanocarriers for corrosion inhibitors, where the surfactant layer stabilizes the nanoparticles and enables controlled release of active compounds, thereby extending the durability

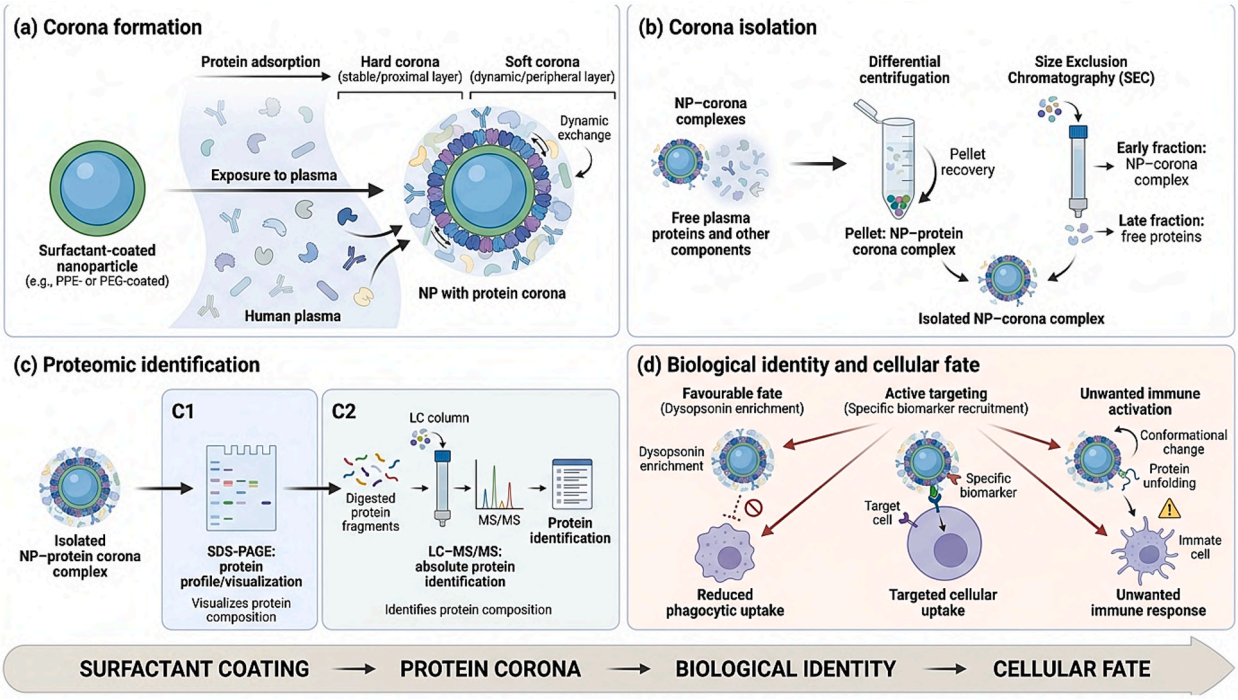

Fig. 6. From synthetic nanoparticle to biological identity: protein corona formation, characterization and cellular fate. The figure illustrates how a surfactant-coated nanoparticle (e.g., PPE- or PEG-coated) acquires a new biological identity upon exposure to biological fluids. **(a)** Incubation in human plasma results in the rapid adsorption of plasma proteins and the formation of dynamic hard and soft corona layers. **(b)** The nanoparticle–protein corona complex is isolated from unbound plasma proteins using approaches such as differential centrifugation or size-exclusion chromatography. **(c)** The composition of the protein corona is characterized by complementary proteomic approaches, including SDS-PAGE for protein-profile visualization and LC–MS/MS for protein identification and characterization. **(d)** The acquired biological identity can ultimately determine cellular fate: enrichment in dysopsonins may reduce phagocytic uptake, whereas the recruitment of specific proteins or biomarkers can promote receptor-mediated targeting and cellular uptake. Conversely, protein conformational changes or unfolding at the nanoparticle interface may expose altered biological signatures and trigger unwanted immune recognition. Together, the workflow highlights the transition from the engineered physicochemical identity of the nanoparticle to its acquired biological identity, which ultimately governs its interactions with cells and biological systems.

of metallic substrates exposed to aggressive industrial environments. Similarly, surface-modified silica nanoparticles dispersed within polymer matrices have been shown to enhance both mechanical strength and thermal barrier performance, demonstrating the versatility of surfactant-mediated interfacial engineering in materials design [353,354].

The industrial relevance of surfactant-coated nanoparticles extends further to biocatalytic processes, where surfactant-functionalized nanostructures serve as platforms for enzyme immobilization. By providing a favorable microenvironment around the enzyme, the surfactant layer helps preserve catalytic activity, enhances resistance to denaturation, and improves operational stability under challenging process conditions. These advantages can significantly extend biocatalyst lifetime and increase process efficiency in applications ranging from industrial wastewater treatment to chemical manufacturing [355,356].

Together, these examples show surfactant coatings acting as multifunctional interfaces that govern nanoparticle stability, transport and interactions across lubrication, energy recovery, protective coatings, composites and biocatalysis [286,357]. Their expanding industrial deployment also underscores the need to understand the environmental fate and long-term sustainability of surfactant-coated nanoparticles after release, addressed in the following sections.

9. The biological and environmental fate of surfactant-engineered materials

A surfactant-engineered interface does not stop evolving once a material leaves the laboratory: the same dynamic, structure-dependent organization that governs synthesis and function in earlier sections continues to determine how these materials behave once released into biological and environmental systems.

9.1. Protein corona and dynamic biological identity

In biological fluids, surfactant-coated nanoparticles meet an excess of biomolecules that rapidly and spontaneously adsorb to form a dynamic protein corona, redefining the nanoparticle physicochemical identity [358–362]. Because cells, receptors and immune effectors engage the corona rather than the engineered surface, this acquired biological identity supersedes the synthetic one and governs biodistribution, uptake, immune engagement and efficacy [363–366]. Surfactant chemistry, charge, grafting density and hydration determine which proteins are recruited, in what orientation and with what affinity, making corona control a central design imperative for translational nanomedicine.

9.1.1. Thermodynamics, kinetics, and the Vroman effect

Protein corona formation is driven by a hierarchy of non-covalent forces, including electrostatic interactions, van der Waals forces, hydrogen bonding, and hydrophobic effects, whose relative contributions depend critically on the surfactant chemistry decorating the nanoparticle surface [367,368]. Temporal evolution follows the Vroman effect: abundant but weakly binding proteins (*e.g.*, albumin, fibrinogen) adsorb rapidly in the first seconds to minutes, and are subsequently displaced by progressively less abundant, higher-affinity species [358,359,369]. This competitive exchange governed by diffusion coefficients, local protein concentration, and binding kinetics, eventually yields a corona whose composition is thermodynamically favored but kinetically trapped, exhibiting memory effects and glassy, crowding-controlled dynamics that depend on the adsorption pathway as much as on equilibrium affinity [358,370].

The resulting corona is conceptually and operationally divided into two concentric layers. The hard corona (*i.e.*, the inner shell) consists of proteins that bind quasi-irreversibly and interact directly with the nanoparticle or surfactant surface, forming a relatively stable entity detectable by proteomic analysis after extensive washing. The soft corona (the outer shell) comprises loosely associated proteins in rapid dynamic exchange with the surrounding medium, reflecting the instantaneous biological environment [364,367–370]. Surfactant-regulated surface hydration, steric repulsion, and electrostatics dictate whether proteins form a thin, stable hard layer or a thick multilayer assembly, and whether conformational changes upon adsorption expose cryptic epitopes with

Table 9
Effect of surfactant type on protein corona formation, composition, and biological fate.

Surfactant Type	Representative Example	Effect on Protein Corona	Biological Consequence	Key References
Non-ionic / PEG brushes	PEG, polyphosphoesters (PPEs)	Steric (entropic) repulsion reduces total protein mass; alters corona composition toward albumin-rich profile	"Stealth" behavior; extended circulation; tunable organ targeting	[360,362,371,373]
Zwitterionic	Sulfobetaine (SB), protein corona, carboxybetaine (CB)	Strong hydration shells virtually abolish both hard and soft corona	Minimal immune recognition; unhindered intracellular Brownian diffusion	[364,371,374]
Cationic	CTAB, PEI	Preferential adsorption of negatively charged proteins (pI < 5.5); multilayer formation	High cellular uptake; potential cytotoxicity; opsonization	[361,366]
Ionic / anionic	SDS, Tween (mixed systems)	Charge-dependent adsorption; more negative ζ-potential increases protein loading and multilayer depth	Modified release kinetics; modestly reduced antibacterial or therapeutic efficacy	[372,373]
Biodegradable block copolymers	PPE-based amphiphiles	Selective enrichment of dysopsonins (clusterin, ApoA-I)	Prevention of macrophage-mediated clearance; corona-guided targeting	[371,375]

immunological consequences [361,365–367,371,372] (Fig. 6).

9.1.2. Surfactant architecture as the master regulator of corona composition

The ability of a surfactant coating to modulate protein adsorption hinges on two tangled parameters: surface chemistry (charge, polarity, functional groups) and grafting density (the spatial frequency of surfactant chains, which controls steric exclusion volume and hydration layer thickness).

Non-ionic polymeric surfactants and PEG brushes. Dense poly(ethylene glycol) (PEG) or poly(phosphoester) (PPE) shells generate a hydrophilic, mobile layer that repels incoming proteins via an entropic cushion mechanism, markedly reducing total protein mass adsorbed and biasing corona composition toward albumin-rich, low-opsonin profile [360,362,364,371,373]. Grafting density is critical: sub-dense PEG mushroom regimes afford only partial shielding, whereas brush regimes approaching full surface coverage can suppress hard corona formation to near-detectable levels and reproducibly redirect biodistribution [362,373].

Zwitterionic surfactants. Surfaces functionalized with zwitterionic betaines, including sulfobetaine (SB), phosphorylcholine (PC), or carboxybetaine (CB), form exceptionally strong hydration shells through electrostatically induced water structuring. This effect can virtually abolish both hard and soft corona formation in human serum, offering stealth performance that surpasses conventional PEG coatings while also enabling unhindered Brownian motion even within the cytoplasm [364,371,374].

Cationic and anionic surfactants. Ionic surfactants promote stronger, charge-mediated protein adsorption. Cationic coatings (*e.g.*, CTAB, PEI) preferentially recruit negatively charged proteins (pI < 5.5), while more negative zeta potentials correlate with higher total protein loading, multilayer formation, and measurable perturbations of drug release kinetics and antibacterial or therapeutic bioactivity [361,366,372,373].

Biodegradable and functional block copolymers. Beyond simple suppression, amphiphilic PPE-based block copolymers can program corona composition by selectively enriching dysopsonins, such as clusterin, apolipoprotein A-I, that actively inhibit macrophage uptake and extend circulation, illustrating a paradigm shift from corona avoidance toward corona engineering [371,375] (Table 9).

9.1.3. Biological identity: Opsonization, targeting, and conformational consequences

The biological identity conferred by the protein corona operates at multiple levels. First, opsonization: adsorption of immunoglobulins, complement proteins (C3b, C4b), and fibronectin flags nanoparticles for recognition by Fc and complement receptors on macrophages and dendritic cells, triggering rapid reticuloendothelial system (RES) clearance that is the principal barrier to long systemic circulation [363,365,366]. Surfactant stealth coatings specifically aim to suppress this opsonin layer.

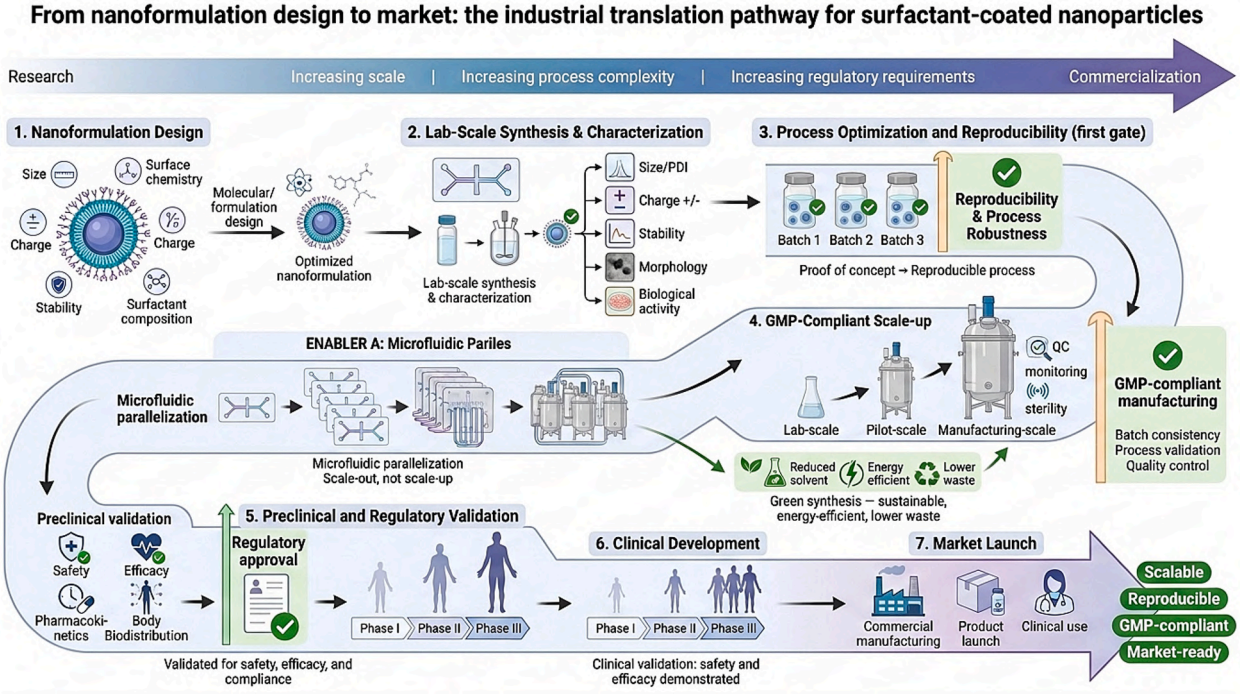

Fig. 7. The pathway to industrial translation of surfactant-coated nanoparticles. A conceptual roadmap linking rational nanoformulation design with process development, reproducible manufacturing and clinical translation. The pathway progresses from lab-scale synthesis and multidimensional characterization through process optimization and GMP-compliant manufacturing to preclinical and regulatory validation, clinical development and market launch. Microfluidic parallelization and green synthesis are highlighted as enabling strategies to achieve scalable, reproducible and sustainable production, underscoring that successful translation requires the integration of nanoparticle design, process engineering, product quality, safety, efficacy and regulatory compliance.

Second, the protein corona can mask or expose targeting ligands. Antibodies, peptides, or small molecules grafted onto nanoparticle surfaces to confer active targeting are frequently buried within the corona in a non-accessible orientation, abrogating receptor binding and causing the nanoparticle to behave as a passive, non-targeted carrier *in vivo* despite perfect *in vitro* functionality [360,365]. Conversely, "natural" targeting can emerge when corona proteins guide nanoparticles toward specific receptors – for instance, apolipoprotein E (ApoE) in the corona of PEGylated nanoparticles facilitates LDL-receptor-mediated endocytosis in hepatocytes and blood–brain barrier cells.

Third, protein conformational changes upon adsorption can have profound immunological consequences. The forced unfolding of fibrinogen or adsorption-induced exposure of cryptic epitopes on plasma proteins can trigger platelet aggregation or inflammatory cascades. Similarly, denaturation of enzymatic proteins may alter lysosomal processing of corona-coated nanoparticles [360,365–367].

9.1.4. Minimizing or exploiting the corona: Rational design strategies

Recently, surfactant-based nanoparticle engineering has converged on two complementary philosophies: corona suppression and corona programming.

Suppression strategies exploit high-density PEG brushes, zwitterionic coatings, and biomimetic membrane wraps to minimize non-specific adsorption. Dense PEG and PPE shells reliably reduce total corona mass and extend circulation half-lives, though complete elimination of the corona remains elusive under true physiological protein concentrations [362,364,371,373]. Zwitterionic sulfobetaine ligands come closest to total suppression, having demonstrated absence of detectable hard and soft corona in human serum, with consequent unhindered intracellular diffusion [364,374]. Cell membrane-derived coatings (erythrocyte, platelet, or leukocyte membranes) further push biological identity toward self-recognition, although the precise interplay between membrane lipids, embedded proteins, and the residual corona requires more systematic quantification [360,361,365,375].

Programming strategies harness the selectivity of specific polymer chemistries or pre-adsorbed protein layers to encode a desired corona fingerprint prior to *in vivo* administration. Deliberate pre-coating with albumin has been used to reduce inflammatory signaling; enrichment with ApoE guides nanoparticles across the blood–brain barrier; and selective dysopsonin loading prevents macrophage recognition in tumor microenvironments [361,371,375]. Controlled burst release profiles can also be modulated through corona engineering, adding a further pharmacokinetic lever [360,365].

9.1.5. In vitro/in vivo correlation and the standardization challenge

Translating protein corona data from bench to clinic hinges on the fidelity of *in vitro* models. Corona composition depends sensitively on fluid type (whole blood *vs*. plasma *vs*. serum), processing history, protein concentration relative to nanoparticle surface area, temperature, and incubation time, such that nominally identical nanoparticle cores can acquire vastly different coronas depending on the experimental protocol [359,361,369]. Serum-based models enrich apolipoproteins; plasma retains coagulation factors; whole blood adds erythrocyte and platelet-derived proteins absent from both [369].

In vivo analyses consistently reveal that coronas assembled under true physiological conditions – with continuous flow, competing cell surfaces, and dynamic protein pools – differ compositionally from those assembled ex vivo, and these differences critically control absorption, circulation time, organ distribution, and toxicity profiles [360,361,369]. An instructive recent example from Lynn et al. demonstrated that increased PEG surface density on polymeric nanoparticles not only reduced total protein adsorption but reshaped the corona from a fibrinogen-rich to an albumin-rich composition *in vitro*, directly correlating with preferential fetal organ targeting *in vivo* following intra-amniotic administration – a rare, mechanistically grounded *in vitro/in vivo* correlation (IVIVC) for surfactant-coated nanoparticles [362].

Despite such advances, the lack of standardized protocols for corona isolation (differential centrifugation *vs*. size-exclusion chromatography *vs*. magnetic separation), characterization (DLS, NTA, TEM for morphology; SDS-PAGE for band visualization; LC-MS/MS for quantitative proteomics), and reporting impedes cross-study comparison and quantitative IVIVC [359–361]. Emerging consensus advocates for absolute protein quantification (iBAQ or TOP3 methods) combined with surface chemistry dominating corona architecture over charge alone [361,368,373].

9.1.6. Implications for nanomedicine applications

Protein corona formation is an inescapable but controllable consequence of deploying surfactant-coated nanoparticles *in vivo*, and a principal lever for translational control. Current strategies suppress the corona (PEG, zwitterionic coatings) or program it (pre-adsorbed proteins), yet its dynamic remodeling under flow and competing cell surfaces differs fundamentally from static *in vitro* models, constraining predictable design until *in vitro/in vivo* correlations are established. Rational tuning of shell chemistry, grafting density, charge and hydration offers a toolkit to suppress non-specific adsorption and immune clearance, encode dysopsonin-rich or ligand-presenting coronas, exploit corona fingerprints as diagnostics, and align *in vitro* models with *in vivo* outcomes [361,362,364,371,373–375]. Treating the corona as an early design variable, not an afterthought, is essential to advance clinically programmable nanomedicines.

9.2. Surfactant exchange in biological fluids

The protein corona (Section 9.1) is only one half of a two-way exchange at the biological interface: while biomolecules adsorb onto the nanoparticle, the original surfactant coating is itself subject to competitive displacement and desorption. The susceptibility follows directly from the binding mechanism catalogued in Section 3.9: covalently and multivalently anchored ligands largely persist, whereas

electrostatically or hydrophobically bound surfactants can be partially stripped by the abundant proteins, lipids and small molecules of serum [11,206]. This exchange is dynamic and time-dependent rather than a single event: the coating that leaves the laboratory is not necessarily the coating that reaches the target, and quantitative studies of ligand shells and of corona kinetics show the composition of the interface evolving over minutes to hours in biological media [251,358,359]. The consequence for design is significant and frequently overlooked – a surface engineered and characterized in buffer may present a materially different, partially exchanged interface *in vivo*, so that the biological identity the coating was meant to confer is set as much by what desorbs as by what was originally deposited.

9.3. Cellular interactions and intracellular trafficking

Whatever interface survives the exchange above is what cells encounter, and it is the surfactant coating – through the size, surface charge and chemistry it imposes – that governs how a nanoparticle is recognized, taken up and trafficked. Systematic studies establish that surface properties, more than core composition, determine the endocytic pathway and the efficiency of cellular uptake [33,34]. Uptake, however, is only the first step: most internalized nanoparticles are routed into the *endo*-lysosomal system, where acidification and degradation can trap or destroy a cargo before it reaches its site of action, making endosomal escape the decisive bottleneck for intracellular delivery [13]. The coating is central at both stages, providing the charge and ligand presentation that drive uptake and, in the most advanced systems, the pH-responsive or membrane-active chemistry that enables escape – the mechanism exploited most consequentially by the ionizable lipids of lipid nanoparticles (Section 8.6). Tracking this intracellular fate reliably remains difficult, and quantitative, correlative imaging of where nanoparticles actually go inside the cell is still a methodological frontier [106].

9.4. Toxicological mechanisms

The primary mechanism underlying surfactant-nanoparticle toxicity is membrane disruption. Amphiphilic surfactants adsorb onto lipid bilayers through electrostatic attraction and hydrophobic insertion, perturbing membrane packing, fluidity, permeability, and curvature. At sufficiently high local concentration, this process induces membrane thinning, pore formation, cytoplasmic leakage, ionic imbalance, and eventually cell death (Fig. 7).

The severity and kinetics of membrane damage strongly depend on surfactant class. Cationic surfactants are most cytotoxic, exploiting electrostatic attraction to negatively charged membranes. Cationic additives incorporated into lipid and polymeric nanoparticles triggered membrane disruption, intracellular Ca^{2+} influx, neutrophil degranulation, superoxide production, and inflammatory activation leading to apoptosis and necrosis [376]. Similarly, membrane-lytic studies on sulfonated methyl ester surfactants revealed that both anionic and cationic surfactants can destabilize model membranes near or below the critical micellar concentration (CMC), with quaternary ammonium surfactants such as CTAB exhibiting particularly aggressive lytic behavior.

Non-ionic surfactants are often considered milder alternatives. However, recent mechanistic studies reveal that they can induce complex stress responses that extend beyond simple membrane permeabilization. Exposure of intestinal epithelial cells to the pharmaceutical excipient Solutol® HS15 (Kolliphor HS15) produced rapid membrane fluidization, mitochondrial hyperpolarization followed by depolarization, reactive oxygen species (ROS) generation, and apoptosis through a cellular response resembling heat-shock-induced stress signaling [377]. These findings challenge the historical assumption that non-ionic excipients are intrinsically biologically inert.

Surfactant structure–activity relationships further demonstrate that cytotoxicity depends critically on amphiphilic balance. Non-ionic alkyl ethoxylates with intermediate hydrophilic/lipophilic balance (HLB) exhibit the highest membrane lytic activity because they efficiently partition into lipid bilayers while maintaining sufficient aqueous dispersibility to solubilize membrane fragments. In contrast, highly hydrophilic surfactants generally exhibit weaker partitioning into lipid membranes, whereas increasing hydrophobicity favors membrane association and can alter the kinetics and extent of membrane perturbation and solubilization [378]. Alkyl chain length also modulates toxicity: shorter chains often produce rapid membrane permeabilization, while longer hydrophobic tails can reduce acute lytic potency despite enhancing membrane association.

Notably, membrane disruption is not the only mechanism of surfactant-mediated toxicity. Several nanoparticle systems induce mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum (ER) stress independently of overt membrane perforation.

Table 10
Representative toxicological and ecotoxicological outcomes associated with surfactant-nanoparticle systems.

System	Principal Effect	Mechanistic Interpretation	References
AuNPs + non-ionic surfactants (*e.g.*, polysorbates)	Strong synergistic embryonic zebrafish toxicity	Surfactant corona formation enhances nanoparticle uptake and tissue burden	[382]
SiO_2 nanoparticles + anionic/non-ionic surfactants	Reduced acute toxicity but lower biodegradability	Surfactant adsorption onto nanoparticles surface decreases membrane interaction but limits microbial degradation	[351,384]
TiO_2 nanoparticles + SDS or NP-9	Reduced aggregation and sedimentation; increased persistence and transport	Electrostatic and steric stabilization enhance colloidal stability in environmental waters	[385]
Cationic lipid/polymeric nanoparticles	Neutrophil activation, oxidative burst, inflammatory signaling	Membrane disruption and intracellular Ca^{2+} mobilization	[376]
SiO_2 nanoparticles in lung epithelial cells	ROS generation, mitochondrial dysfunction, ER stress, apoptosis	Oxidative stress-mediated intracellular signaling perturbation	[376,379]

Silica nanoparticles, for example, trigger ROS production, glutathione depletion, perturbation of CoA metabolism, mitochondrial dysfunction, ER stress signaling, and apoptosis in lung epithelial cells [379,380]. Likewise, multifunctional cationic surfactants containing labile amide linkers were shown to induce oxidative and mitochondrial stress without major membrane rupture, illustrating that subtle surfactant structural modifications can profoundly alter cellular response pathways [381].

Collectively, these findings establish that surfactant-mediated nanotoxicity emerges from a multiscale interplay between membrane biophysics, amphiphilic molecular geometry, colloidal organization, and intracellular stress signaling.

One of the most important developments in nanotoxicology is the recognition that nanoparticle-surfactant mixtures frequently display synergistic rather than additive toxicity. In these systems, surfactants not only stabilize nanoparticles but also modify cellular uptake, protein corona formation, biodistribution, membrane interaction, and intracellular trafficking.

A landmark example was reported by Ginzburg et al., who demonstrated that mixtures of biocompatible gold nanoparticles (AuNPs) and widely used non-ionic surfactants such as polysorbates produced unexpectedly high embryonic zebrafish mortality despite minimal toxicity of the individual components alone [382]. Mechanistically, surfactant adsorption onto the AuNP surface enhanced nanoparticle bioavailability and tissue uptake, illustrating how surfactant coronas can transform biologically benign nanoparticles into highly toxic assemblies [383].

Surfactant polydispersity can further amplify these effects. Binary non-ionic surfactant mixtures composed of molecules with different chain lengths display synergistic membrane-disruptive activity exceeding that of monodisperse analogues possessing similar average composition [384]. Such findings are highly relevant because industrial and pharmaceutical surfactants are rarely chemically homogeneous [351].

Cationic surfactant-containing nanoparticles also exhibit potent immunotoxic and inflammatory activity. In human neutrophils, cationic LNPs induce intracellular Ca^{2+} mobilization, oxidative burst activation, and inflammatory signaling pathways that may contribute to systemic immune responses and infusion-related toxicity [376]. In pulmonary systems, surfactant-coated silica nanoparticles can intensify oxidative stress and mitochondrial dysfunction by perturbing redox homeostasis and intracellular metabolic pathways [379,380].

As highlighted in Par. 5.1 related to nanoparticle protein corona, also nanotoxicology reflects the fundamental principle that surfactants do not merely stabilize nanoparticles physically but actively define their biological identity.

9.5. Environmental transformation and persistence

Surfactants profoundly influence nanoparticle behavior in environmental matrices by altering colloidal stability, aggregation kinetics, sedimentation, dissolution, and interactions with natural organic matter (Table 10). Because environmental mobility determines bioavailability and exposure, surfactant-mediated changes in nanoparticle transport are central determinants of ecological risk.

In natural waters, elevated ionic strength typically promotes nanoparticle aggregation and sedimentation. However, adsorbed surfactants can reverse this process by introducing electrostatic or steric stabilization. Li et al. demonstrated that both ionic and non-ionic surfactants adsorbed onto TiO_2 nanoparticles significantly reduced aggregation and sedimentation in aquatic environments, thereby increasing nanoparticle persistence and transport potential [385]. While such stabilization is advantageous during formulation and manufacturing, it may simultaneously increase environmental mobility and organismal exposure.

Surface coatings also regulate interactions with naturally occurring eco-coronas composed of proteins, humic substances, polysaccharides, and extracellular biomolecules. These coronas alter nanoparticle surface charge, dissolution, aggregation state, and biological interaction. Studies on cerium oxide nanoparticles showed that polysaccharide coatings substantially modified nanoparticle colloidal behavior and ecotoxicological responses in Daphnia magna and marine mussels [386,387]. More broadly, reviews on environmental nanotoxicology consistently identify surface functionalization as one of the dominant determinants of nanoparticle fate across aquatic and terrestrial ecosystems [388,389].

Nanoplastics and surfactant-coated nanoparticles further complicate this scenario because they can adsorb hydrophobic pollutants, metals, and organic contaminants, effectively functioning as transport vectors within ecosystems. Dang et al. emphasized that aggregation dynamics, eco-corona formation, and contaminant co-transport represent critical knowledge gaps requiring integration into a One Health framework for environmental risk assessment [390].

Importantly, surface stabilization can produce opposite toxicological outcomes depending on context. While certain coatings mitigate toxicity by reducing ion dissolution or suppressing direct membrane interaction, others increase environmental persistence and biological uptake. Consequently, eco-sustainability assessment requires simultaneous consideration of acute toxicity, chronic exposure, mobility, persistence, and transformation pathways.

9.6. Aquatic and terrestrial fate

Extending the environmental transformations of Section 9.5 to specific compartments, the surfactant coating is again the variable that determines fate. In aquatic systems, whether a nanoparticle remains suspended and mobile or aggregates and sediments is set by the balance between the coating's stabilizing repulsion and the aggregating effect of natural ionic strength and organic matter, so that surface chemistry directly controls transport, bioavailability and exposure [343,391]. Surfactant coatings can shift this balance in either direction – stabilizing dispersions that persist and travel, as shown for surfactant-treated oxide nanoparticles in natural waters [387], or being overprinted by natural molecular coatings that redirect the nanoparticle fate [389]. In terrestrial systems the same principles govern mobility through soil and porous media, where retention versus transport to groundwater depends on the interaction

between the coated surface and mineral and organic phases [287,343]. Across both compartments, the coating engineered for performance in application is rarely the coating assessed for environmental fate, and this disconnect – designing for function in one medium while the material persistence and mobility are decided in another – is the environmental counterpart of the design-versus-reality gap that recurs throughout this Review.

9.7. One Health perspective

The convergence of nanotoxicology, ecotoxicology and sustainable materials engineering has encouraged the adoption of Safe-by-Design (SbD) principles for nanoparticle development, in which hazard is anticipated and reduced during material design rather than assessed retrospectively after commercialization. We use the narrower SbD term deliberately here: the surfactant literature supplies hazard-relevant evidence, but not the comparative life-cycle and techno-economic data that the formal Safe and Sustainable by Design framework requires (Section 10.7).

A One Health perspective is particularly relevant because surfactant-coated nanoparticles simultaneously impact human health, environmental systems, microbial communities, food webs, and water quality. Nanoparticles released into ecosystems can undergo transformation, aggregation, eco-corona formation, and contaminant adsorption, generating interconnected exposure pathways that bridge environmental and biomedical domains [392,393].

From an SbD standpoint, surfactant selection becomes a critical design parameter. Replacing persistent petrochemical surfactants with biodegradable biosurfactants, engineering biodegradable linkers, reducing ROS-generating photoactivity, minimizing immunotoxicity, and optimizing colloidal stability to avoid unnecessary environmental persistence are all emerging strategies aligned with European REACH and sustainability-oriented regulatory frameworks.

Importantly, the future of sustainable nanotechnology will likely depend not only on reducing toxicity but also on designing adaptive and environmentally responsive nanomaterials whose degradation, transport, and biological interactions are predictable across their entire life cycle. Achieving this objective will require integration of colloid science, mechanistic toxicology, environmental chemistry, systems biology, and regulatory science into unified predictive frameworks, taking advantage of modern tools offered by AI and machine learning.

10. Sustainable surfactants and Safe-by-Design materials

Sustainability is treated here not as an add-on to the design chain but as a further constraint on it: the same molecular and interfacial parameters that determine performance in Sections 2–8 also determine biodegradability, toxicity and the feasibility of safer substitutes.

Sustainability has become the field's most confident claim and its least tested. Biosurfactants and green-synthesis routes are routinely presented as drop-in, safer replacements for conventional surfactants, yet the cost, scalability, batch consistency, ecotoxicological and comparative-toxicity data needed to substantiate substitution at industrial scale are frequently absent. Within a Safe-by-Design and One Health framing, we weigh what is known about the molecular cytotoxicity, environmental fate and biodegradability of surfactant-coated nanoparticles against what is merely asserted and ask directly whether biosurfactant substitution is ready or

Table 11
Reported tendencies and evidence gaps in the comparison between conventional synthetic surfactants and biosurfactants in nanoparticle systems. Entries describe the current state of the evidence rather than established class-level properties; all comparisons remain structure-, formulation- and test-dependent.

Property	Conventional synthetic surfactants	Biosurfactants	Sustainability implication
Acute ecotoxicity	Reported values span a wide range; moderate-to-high for several long-chain cationic and some anionic compounds	Lower in several reported comparisons, but strongly compound- and test-dependent; head-to-head data generated to common protocols remain scarce	Hazard reduction plausible for specific compounds; not established at class level
Biodegradability	Variable: readily biodegradable for linear alkyl chains, slower for branched and highly ethoxylated homologues	Readily biodegradable for some compounds and formulations; strongly structure- and test-dependent	Environmental compatibility must be assessed per compound and test protocol
Source	Petrochemical or bio-based feedstock; chemically synthesised	Renewable microbial or plant-derived feedstocks	Lower fossil-resource dependence where renewable feedstocks are used
Effect on nanoparticle stabilization	Efficient colloidal stabilization	Efficient stabilization reported for several systems; biocompatibility is compound- and context-specific	Enables synthesis from renewable feedstocks
Environmental persistence	Accumulation in aquatic systems reported for some compounds	Potential for lower persistence, requiring compound- and formulation-specific verification	Comparative long-term ecological burden not yet quantified
Role in remediation	Comparative sustainability data limited	Enhance biodegradation and pollutant bioavailability in selected reported systems	Supports nanobioremediation strategies in specific applications
Alignment with Safe-by-Design principles	Often requires mitigation strategies	Aligned with Safe-by-Design principles in intent, though supporting comparative data remain limited	Supports hazard-oriented design; formal SSbD assessment requires life-cycle and techno-economic data not yet available

aspirational.

The success of surfactant-engineered nanomaterials across nanomedicine, cosmetics, agriculture and environmental technologies has intensified concern over their toxicological and ecological footprint. The same amphiphilic properties that control nucleation, morphology, stability and biological interaction also govern membrane integrity, oxidative stress, corona formation, environmental transport, persistence and biodegradability. Nanoparticle safety therefore cannot be inferred from the core alone, because surfactants redefine the nano–bio and nano–eco interface [394], and surfactant–nanoparticle systems behave as integrated entities whose activity often differs from the sum of their parts.

This concept has become particularly relevant as engineered nanomaterials transition from controlled laboratory environments into complex real-world ecosystems. In environmental matrices, surfactant-coated nanoparticles undergo aggregation, corona evolution, dissolution, adsorption of organic contaminants, and interactions with organisms across trophic levels [391]. Consequently, toxicology, ecotoxicology and sustainability assessment are converging within Safe-by-Design and One Health framings that link molecular-scale interactions to ecosystem-level outcomes.

10.1. Biosurfactants

Biosurfactants are among the most actively pursued strategies for improving the sustainability profile of nanoparticle systems. Produced by microorganisms, plants, or renewable feedstocks, biosurfactants are being investigated as potential means of combining amphiphilic functionality with favourable biodegradation and ecotoxicity profiles while reducing reliance on petrochemical feedstocks, although these advantages remain compound- and formulation-specific.

Microbial surfactants such as rhamnolipids, sophorolipids, and lipopeptides are increasingly used as capping agents, stabilizers, emulsifiers, and templating agents during nanoparticle synthesis [395,396]. Their incorporation into metallic and inorganic nanoparticles is widely proposed as a greener alternative to conventional surfactants, on the grounds that they stabilize colloids while potentially reducing environmental burden [58].

Nevertheless, direct ecotoxicological evidence for biosurfactant-coated nanoparticles remains comparatively limited. Most available data derive from broader studies on surfactant-nanoparticle systems or from bioremediation applications rather than systematic nanoparticle ecotoxicity testing. Despite this limitation, several studies strongly support the sustainability potential of biosurfactants. For example, lipopeptide-functionalized TiO_2 nanoparticles developed within an SbD framework displayed substantially reduced *in vitro* cytotoxicity and ecotoxicity while simultaneously improving UV photoprotective performance [397]. The biosurfactant coating reduced ROS generation and mitigated photoinduced oxidative damage, demonstrating how molecular-level surface engineering can simultaneously improve functionality and safety.

Biosurfactants also play an increasingly important role in nanobioremediation. Rhamnolipids have been used as green stabilizers for nanoscale zero-valent iron (nZVI), improving nitrate removal efficiency in groundwater remediation systems [398]. Similarly, combinations of biosurfactants with iron oxide or silver nanoparticles enhance biodegradation of petroleum hydrocarbons and polyaromatic hydrocarbons by increasing pollutant bioavailability and stimulating microbial activity [399–401]. Importantly, formulated biosurfactants have demonstrated relatively low toxicity toward aquatic organisms, plants, and bivalves while maintaining effective pollutant dispersion and biodegradation capacity in oil-spill remediation context [402]. These studies demonstrate the potential utility of biosurfactants in selected remediation applications, but they do not yet establish a generally improved environmental profile for the resulting nano-enabled systems.

Despite these advances, major knowledge gaps remain. Chronic low-dose exposure studies, realistic environmental transformation experiments, trophic transfer analyses, and direct comparisons between biosurfactant-coated and synthetic-surfactant-coated nanoparticles remain scarce. Establishing robust comparative datasets will be essential for translating the conceptual promise of biosurfactants into validated sustainability metrics (Table 11).

The pharmaceutical and materials industries are under increasing pressure to reduce the environmental footprint of nanoparticle manufacturing. Biosurfactant-stabilized nanoparticles produced using microbial sophorolipids, rhamnolipids or saponins have been proposed as alternatives to synthetic poloxamers and Tweens, with individual studies reporting comparable colloidal stabilization capacity together with favourable degradation and toxicity profiles. These reports concern specific compound–formulation combinations, and the comparative data needed to establish a general advantage over the incumbent surfactants are not yet available [18,403].

Self-surfactant polymer systems represent a further advance. Amphiphilic polyhydroxyalkanoates (PHAs) such as PHBHHx possess intrinsic surfactant activity that eliminates the need for added synthetic surfactants. PHBHHx nanoparticles loaded with the antimicrobial agent usnic acid were produced using only non-toxic solvents (ethanol, ethyl acetate), demonstrating that self-surfactant green chemistry is compatible with pharmaceutical-grade solvent constraints; scalability beyond laboratory preparation has not yet been demonstrated for this system [404]. For green synthesis routes based on plant extracts or agricultural by-products, reductions of up to 30% in energy consumption and up to 40% in production cost relative to conventional chemical synthesis have been reported for particular systems. These figures should not be read as general advantages of green synthesis: they derive from individual case comparisons rather than from a broad comparative analysis, and systematic lifecycle analyses for pharmaceutical-grade nanomedicines remain limited and are an active research priority [403].

10.2. Biodegradable amphiphiles

Biodegradability represents a central criterion for evaluating the sustainability of surfactant-based nanomaterials. Conventional

petrochemical surfactants often display limited biodegradability and can accumulate in aquatic systems, whereas biosurfactants are generally promoted as biodegradable and environmentally compatible alternatives.

However, recent evidence demonstrates that nanoparticle incorporation can substantially alter surfactant biodegradation profiles. Lechuga et al. showed that mixtures of anionic and non-ionic surfactants with silica nanoparticles exhibited reduced primary and ultimate biodegradation compared with surfactant-only systems [351,384]. Increasing nanoparticle concentration reduced mineralization efficiency and, in some cases, shifted formulations below the threshold required for classification as readily biodegradable. The proposed mechanism involves surfactant adsorption onto nanoparticle surfaces, which decreases surfactant bioavailability to degrading microorganisms. Interestingly, these same formulations sometimes exhibited lower acute ecotoxicity because adsorption onto silica surfaces reduced direct membrane interaction with aquatic organisms [384]. This apparent paradox highlights the complexity of sustainability assessment: mitigation of short-term toxicity may occur simultaneously with increased environmental persistence.

The influence of nanoparticle physicochemical properties on biodegradability is similarly complex. Larger silica nanoparticles can enhance suppression of biodegradation, while surfactant class influences the CMC behavior differently in the presence of nanoparticles. Silica nanoparticles increase the CMC of certain non-ionic surfactants but decrease it for some anionic surfactants due to electrostatic interactions, thereby altering both colloidal organization and biodegradation pathways.

These findings underscore that surfactant-nanoparticle systems cannot be evaluated solely using conventional surfactant ecotoxicology frameworks. Instead, they require integrated assessment of colloidal chemistry, biodegradation kinetics, microbial accessibility, and environmental transformation.

10.3. Bio-based and renewable feedstocks

Beyond the microbial biosurfactants of Section 10.1, a broader shift is underway from petrochemical to renewable feedstocks for surfactant production. Sugar-derived amphiphiles such as alkyl polyglucosides, agricultural and industrial by-products, and waste-derived routes to glycolipids exemplify a supply chain that decouples surfactant manufacture from fossil resources [4,5,84]. Feedstock choice is itself a design variable: renewable sources such as cashew nutshell liquid yield surfactants with distinctive molecular architectures, and waste-derived production of sophorolipids couples sustainability to circular-economy principles [26,65,87]. The critical qualification, consistent with the skeptical stance of this section, is that a renewable origin is a claim about the feedstock, not about the finished material's performance, safety or biodegradability: bio-based provenance does not by itself guarantee a lower environmental burden, and the techno-economic viability of these routes at the scale required for materials applications remains, in most cases, to be demonstrated [4].

10.4. Polymer–surfactant hybrids

Combining surfactants with polymers, introduced as a self-assembly strategy in Section 5.4, is also a route to more sustainable coatings. Two design logics are being pursued. In the first, a polymer is co-assembled with a surfactant to add mechanical robustness, responsiveness and multivalency to the intrinsic organizing tendency of the amphiphile [123]. In the second, the distinction between polymer and surfactant is collapsed altogether: amphiphilic biodegradable polymers – polyhydroxyalkanoates and related self-surfactant systems (Section 10.1), or sustainable graft copolymers such as inulin-based amphiphiles – act as their own surface-active agents while carrying an inherently degradable backbone [226]. The appeal of hybrids is that they can, in principle, reconcile the durability that a coating needs in application with the degradability it needs afterwards; whether a given hybrid actually achieves both, rather than compromising each, is a question that returns directly to the performance-versus-biodegradability trade-off of Section 10.6.

10.5. Life-cycle considerations

Judging sustainability by the coating alone, or by a single endpoint such as biodegradability, is inadequate: the environmental burden of a surfactant-engineered material accrues across its entire life cycle, from feedstock extraction and synthesis through use to end-of-life fate. A life-cycle perspective reframes several of the trade-offs already noted — the energy and solvent cost of a synthesis, the techno-economic viability of a renewable feedstock (Section 10.3), and the toxicity and persistence of degradation products, not merely of the parent surfactant [4,385,386]. Systematic optimization studies show that toxicity, biodegradability and performance can be co-considered rather than traded blindly, but such assessments remain the exception; the field still overwhelmingly reports performance in isolation. Until life-cycle thinking is built into surfactant selection from the outset, sustainability claims will continue to rest on the properties of the molecule rather than on the full footprint of the material it produces.

10.6. Balancing performance, stability and biodegradability

The preceding subsections converge on a single, unresolved tension: the same molecular features that make a coating perform (strong, durable, multivalent attachment and colloidal stability under demanding conditions) are frequently the features that make it persist, while the labile, readily degraded architectures favored for end-of-life are often those least able to survive an application. This conflict is not merely conceptual. The incorporation of a surfactant onto a nanoparticle can itself alter its biodegradability, so that neither performance nor degradability can be predicted from the free surfactant alone (Section 10.2) [385]. A genuinely sustainable

design is therefore not one that maximizes any single property but one that resolves this trade-off deliberately: engineering coatings that are stable on the timescale and in the medium of use, yet degrade cleanly and non-toxically thereafter. Achieving such tunable, context-dependent stability is, in our view, the central materials-design challenge of sustainable surfactant science, and the clearest illustration of why sustainability belongs inside the design chain (Section 1) rather than appended to it as a separate objective.

10.7. Regulatory drivers and Safe-by-Design principles

Two terms are used in this area and are not interchangeable. Safe-by-Design (SbD) denotes the anticipation and reduction of human and environmental hazard during the design of a material or process, and is the concept engaged by most of the evidence discussed in this Review. Safe and Sustainable by Design (SSbD) is the broader framework formalised by the European Commission, which couples that safety dimension to a full life-cycle assessment of environmental, social and economic sustainability, applied through defined criteria at each design stage. The surfactant literature to date supplies substantial SbD-relevant evidence but very little of the comparative life-cycle and techno-economic data that an SSbD assessment requires. We therefore use SbD when describing what is currently demonstrable, and refer to SSbD only where the full framework is at issue.

Because surfactants are used at large scale, their environmental fate matters: their persistence and distribution depend on adsorption, photodegradation and conditions such as pH, temperature and salinity, and they rank among the more problematic aquatic and terrestrial pollutants [405]. They accumulate in waters, sediments, sludge and soils, can foam in rivers and treatment plants, enter soils via agrochemicals and sludge (a route to groundwater), and can increase the solubility of persistent organic pollutants [406].

These impacts have driven successive regulation, largely originating in the detergent sector. In Europe, Regulation 73/404/EEC (1973) banned surfactants below 90% biodegradability across the four main classes, with accompanying biodegradability-testing directives for anionic and non-ionic surfactants (73/405/EEC; 82/243/EEC; 82/242/EEC) and mandatory labelling (89/542/EEC) [407–411]. Regulation 648/2004/EC then defined surfactants and set ultimate-biodegradability requirements, later amended with waivers (2009) and standardized phosphorus limits (2012) [412–415]. The voluntary EU Ecolabel further certifies lifecycle safety and biodegradability [416]. A 2023 proposal and amendment require full biodegradability and update labelling and market rules [417,418]. In the USA, the EPA has regulated surfactant tolerances and manufacturing (Rule 1141.2, 1984/2002) and issued environmental-fate and aquatic-toxicity guidance (2009, revised 2015 and 2024) [419–421]. Most significantly, the EU Council approved a new Detergents and Surfactants Regulation on 8 December 2025, adopted by the European Parliament in February 2026; replacing the 2004 framework, it introduces clearer labelling, phosphate limits, reduction of animal testing, and coverage of new categories such as microorganism-containing detergents (permitted only if proven safe and non-GMO) [422–424].

On present evidence, biosurfactant substitution is promising but not yet demonstrably ready: the sustainability case is strong in principle and thin in comparative, quantitative data. A credible Safe and Sustainable by Design transition, in the formal sense defined above, would require head-to-head toxicological, ecotoxicological and techno-economic comparison against the incumbent surfactants it aims to replace, generated to common standards rather than asserted case by case.

11. Ai-enabled and predictive surfactant design

If molecular structure determines interfacial organization and, through it, material function, that relationship should in principle be predictable. This section examines how far computational and data-driven methods have gone toward making it that way.

Data-driven design is the newest and most heavily promoted route to rational surfactant engineering, and the one most in need of critical calibration. Graph-neural-network prediction of critical micelle concentration, QSPR models and generative approaches to molecular design report impressive in-domain accuracy, but their training data are narrow, their extrapolation to unseen chemistries and to the nanoparticle interface is rarely validated, and predictions are seldom checked against mechanistic or toxicological ground truth. We distinguish demonstrated predictive capability from extrapolated promise and identify the data and validation standards that would let these tools contribute to design rather than to expectation.

The enormous chemical space associated with surfactants, which consists of practically unlimited combinations of hydrophilic head groups and hydrophobic tail structures, poses a substantial challenge for conventional empirical optimization. The critical limitation of trial-and-error approaches – their inability to navigate this vast combinatorial landscape efficiently – has driven a fundamental shift toward machine learning (ML) and artificial intelligence (AI)-based design. This shift from empirical optimization toward computational screening is a significant methodological development, but it is at present a change in how candidates are generated and prioritized rather than a demonstrated improvement in the materials that reach the bench. Its current standing is best judged against three criteria that we apply throughout this section: whether models have been validated outside their training chemistries, whether the predicted property is the one that governs performance at a nanoparticle interface, and whether predictions have been tested prospectively rather than retrospectively.

11.1. Molecular descriptors and QSPR

QSPR models, increasingly powered by deep learning architectures, allow libraries of thousands of bio-based and synthetic surfactants to be ranked. It should be emphasized that such screening prioritizes candidates for experimental testing; it does not establish either stabilization capacity or ecotoxicological safety, both of which remain to be measured. Ecotoxicity endpoints in particular are predicted from sparse and heterogeneous training data, and reported accuracies are typically in-domain. Used with these limits in mind, the approach supports the hazard-anticipation step of a Safe-by-Design workflow. It is important, especially for such areas as

heritage protection, where sustainable surfactants such as rhamnolipids and alkyl polyglucosides are currently under investigation [425].

11.2. Machine-learning prediction of surfactant properties

Whereas the best surfactant for a given core was traditionally found by trial and error or HLB scales, data-driven approaches allow large candidate libraries to be ranked in silico before synthesis. Machine-learning models – notably Graph Neural Networks (GNNs) – predict the critical micelle concentration (CMC), limiting surface tension and packing density with good accuracy within the chemical classes represented in their training sets, with performance degrading on scaffolds outside that domain [424,426,427]. The CMC is the threshold for micelle formation and therefore for maintaining sufficient free stabilizer to prevent aggregation. Dedicated models exist for bio-based (*e.g.*, sugar) surfactants [428], and GNNs have been used to estimate the binding affinity between surfactant headgroups and specific crystallographic facets, although these estimates are benchmarked almost exclusively against computed rather than measured affinities [429].

11.3. Graph neural networks

Graph neural networks, which represent a surfactant as a molecular graph, are the architecture underlying most of the property

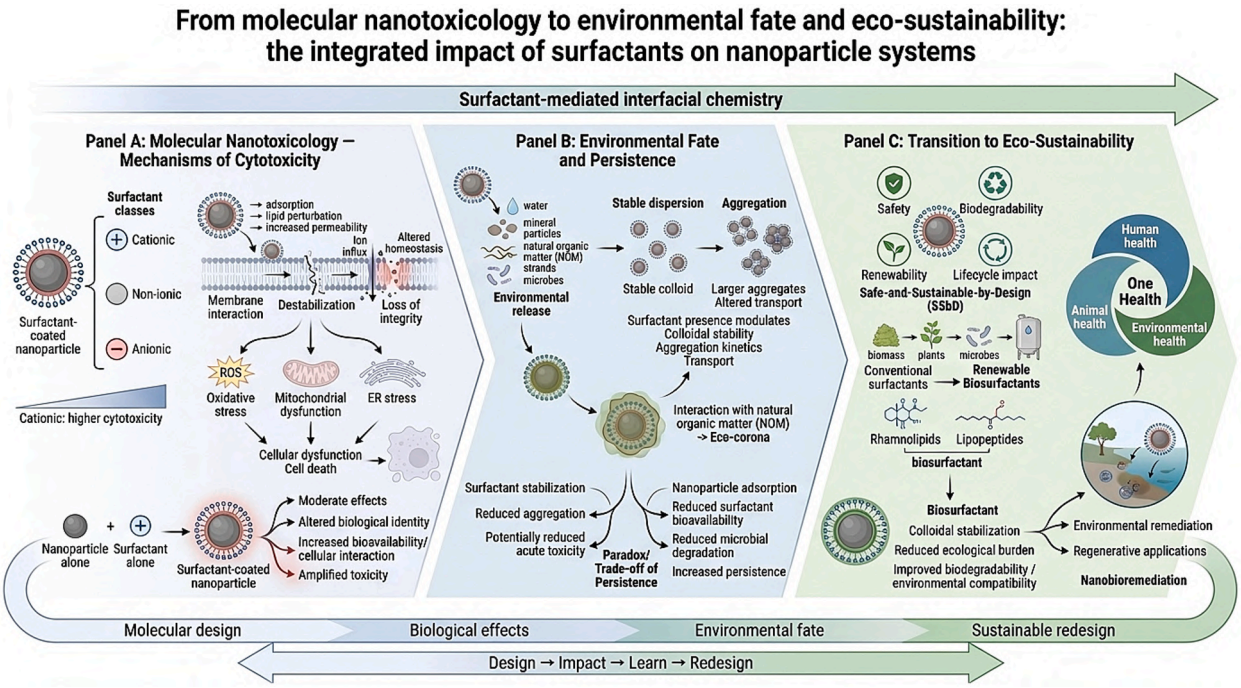

Fig. 8. Integrated impact of surfactants on nanoparticle systems: from molecular nanotoxicology to environmental fate and eco-sustainability. Surfactant-mediated interfacial chemistry can simultaneously determine the biological effects, environmental behavior and sustainability profile of nanoparticle systems. **(A) Molecular nanotoxicology.** Surfactants can induce cytotoxicity by perturbing and destabilizing biological membranes, with the magnitude of the response depending on surfactant chemistry and, generally, cationic surfactants showing greater membrane-disruptive activity. Downstream effects can include reactive oxygen species (ROS) generation, mitochondrial dysfunction and endoplasmic reticulum stress. Importantly, surfactant adsorption can reshape the biological identity and cellular interactions of nanoparticles, potentially leading to enhanced or non-additive toxicity relative to the individual components. **(B) Environmental fate and persistence.** In environmental compartments, surfactant coatings can modulate nanoparticle colloidal stability, aggregation kinetics, transport and interactions with natural organic matter, contributing to the formation of an eco-corona. Although enhanced colloidal stability may reduce acute toxicity in some contexts, adsorption of nanoparticles can also alter the environmental availability and biodegradation of surfactants, potentially increasing their persistence. These opposing effects highlight the context-dependent trade-offs associated with surfactant-mediated stabilization. **(C) Transition to eco-sustainability.** Safe-by-Design and One Health framings provide a basis for integrating safety, biodegradability and resource renewability into nanoparticle design; extending this to a full Safe and Sustainable by Design assessment would additionally require life-cycle and techno-economic data that are not yet available for most surfactant-stabilized systems. Biosurfactants derived from renewable feedstocks, including rhamnolipids and lipopeptides, offer promising alternatives for colloidal stabilization and may reduce the environmental burden of nanoparticle systems while enabling regenerative applications such as nanobioremediation. Together, the three panels illustrate how surfactant choice can propagate across biological, environmental and lifecycle scales, motivating a shift from performance-driven formulation toward integrated safe-and-sustainable design.

predictions described in 11.2 – most prominently for the critical micelle concentration and for head-group/facet binding affinity – and are discussed there rather than repeated here.

11.4. Molecular simulation and multiscale modelling

Machine-learning methods are also being used to address the sampling problem in colloidal simulation: in particular implementations, learned coarse-grained models and simulation-derived descriptors reduce the computational cost of modelling the surfactant–corona interface, resolving ligand orientation and packing on highly curved surfaces [429,430], and predicting properties elusive to standard spectroscopy and scattering [431]. By relating binding affinity to surface curvature, these methods point toward predictive, multi-scale design, and in the longer term toward integration with self-driving laboratories; both remain prospective rather than established for surfactant-stabilized systems [432].

11.5. Generative molecular design

An emerging development in this area is the use of Generative Adversarial Networks (GANs) and other generative AI frameworks, often integrated with Reinforcement Learning (RL) and SELFIES representations, to propose entirely new surfactant structures with tailored HLB values and biodegradable motifs that do not yet exist in chemical catalogues [433].

The ability to propose surfactants that have never been synthesized is a genuine advance in candidate generation. Its practical value, however, is still to be established: generated structures are optimized against predicted descriptors such as HLB or biodegradability proxies rather than against measured interfacial or biological performance, synthetic accessibility is rarely assessed, and prospective experimental validation of a generatively designed surfactant at a nanoparticle interface has not yet been reported.

Taken together, the constraints on data-driven surfactant design are consistent across the methods surveyed above. Training sets are small by the standards of chemical machine learning and are dominated by a few well-studied families, so reported accuracies reflect interpolation rather than discovery. Interfacial descriptors are not standardized: surface coverage, grafting density and conformational state are reported in incommensurable ways between laboratories, which limits data pooling. Labels are frequently uncertain, since CMC and ecotoxicity values vary between protocols by amounts comparable to the differences the models are asked to resolve. Transferability from bulk solution behaviour to a curved, heterogeneous nanoparticle surface is assumed more often than demonstrated. And prospective validation, in which a model prediction is made before the experiment and then tested, remains rare. These are tractable problems, and Section 13 identifies the specific developments that would address them; but until they are addressed, computational design should be regarded as a means of narrowing experimental search space rather than of replacing it.

11.6. Predicting adsorption and interfacial organization

The application of these simulation and machine-learning methods specifically to predict surfactant adsorption, ligand orientation and packing on highly curved nanoparticle surfaces is the pivot on which predictive interfacial design turns; it is treated together with the coarse-grained modelling of the surfactant–corona interface in 11.4.

11.7. From trial-and-error formulation to inverse materials design

For now, machine learning augments rather than replaces surfactant design intuition: its predictions are most trustworthy inside the chemistries on which it was trained and least tested precisely where design most needs them – at the nanoparticle interface and against biological endpoints. Coupling model development to standardized, interface-relevant experimental validation is the prerequisite for AI to move from promise to practice.

12. Manufacturing, scale-up and translation

A design principle that only holds at milligram, laboratory scale is not yet a design principle for materials science; here we examine whether the molecular-to-functional relationships established throughout this Review survive the transition to reproducible, industrial-scale manufacture.

The gap between a coating that works at the bench and one that can be manufactured reproducibly, at scale, and under regulatory

Table 12
Comparative overview of batch and continuous nanoparticle manufacturing.

Parameter	Batch	Continuous/Microfluidic
Scale-up control	Empirical, trial-and-error	Systematic, flow/geometry-driven
Batch reproducibility	High variability at large scale	High, under stable operation
Throughput	Vessel-volume limited	Parallelization / run-time limited
GMP readiness	Established (many approved products)	Rapidly advancing (LNP vaccines)
Capital cost	Lower initial investment	Higher for chip fabrication

Key differences between batch and continuous microfluidic production relevant to GMP scale-up [442,443,445–448].

scrutiny is where much of the field's rational-design rhetoric meets reality. Batch-to-continuous transitions, Quality-by-Design control of critical quality attributes, GMP-compatible surface chemistry, and post-production stabilization each impose constraints that are rarely considered at the point of surfactant selection. Here we examine where scale-up genuinely preserves the designed interface and where it silently alters coating structure, heterogeneity and performance.

Translating surfactant-coated nanoparticles from milligram synthesis to kilogram-scale GMP manufacture requires coordinated advances in process engineering, quality assurance, sustainability and regulatory science. This section addresses the key scalability drivers: manufacturing platform selection, Quality by Design (QbD), surface coatings as Critical Quality Attributes (CQAs), biosurfactant/green-synthesis strategies, and post-production stabilization (Fig. 8).

12.1. Reproducibility of surfactant-mediated material synthesis

Regulatory agencies (FDA, EMA) strongly advocate the QbD paradigm for nanomedicines, which demands the a priori identification of CQAs and systematic linkage of Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) to product performance [434,435]. For surfactant-coated nanoparticles, the primary CQAs cluster around five interrelated parameters:

Particle size and polydispersity index (PDI): universally set as primary CQAs; surfactant type and concentration strongly modulate size and PDI [436,437]. Acceptance criteria such as diameter < 200 nm and PDI < 0.2 are commonly embedded in QbD design spaces for injectable formulations.

Zeta potential: a direct proxy for electrostatic coating coverage and colloidal stability; thresholds such as $|\zeta| > 30$ mV (or near neutral for PEGylated stealth carriers) are commonly adopted as in-house CQA limits in particular formulation contexts. Such values are working rules of thumb rather than regulatory acceptance criteria: authorities require CQAs and their limits to be justified for the specific product and process, not drawn from generic thresholds [436,437].

Surface chemistry and coating efficiency: quantified by XPS, FTIR, phospholipid assays, or fluorescent ligand titration. Heterogeneity in PEG density, ligand number, and patchy coverage is now recognized as an emerging structural CQA because subpopulations of under-coated nanoparticles can drive aberrant biodistribution and immunogenicity [438,439].

Drug loading and encapsulation efficiency (EE%): governed by interfacial partitioning between the surfactant shell and the core and must be tightly linked to process parameters via Design of Experiments (DoE) [436].

Morphology and batch-to-batch reproducibility: cryo-TEM and NTA provide orthogonal particle-level data; batch-to-batch variation in PEGylation density on gold nanoparticles has been shown to alter *in vivo* outcomes, reinforcing reproducible coating levels as a de facto CQA.

Analytical characterization of these CQAs for GMP purposes requires orthogonal and complementary methods: DLS and NTA for size/concentration, microelectrophoresis for charge, ToF-SIMS for surface PEG density quantification, and LC-MS or ELISA for ligand quantification [440,441]. The persistent challenge is measuring surface modification and heterogeneity at the single-particle level; population-average methods can conceal coated/uncoated subpopulations that critically affect therapeutic outcome [439].

12.2. Scale-dependent effects

The reason a bench protocol cannot simply be magnified is physical. Surfactant-mediated synthesis and coating depend on local conditions – the rate of mixing, the steepness of concentration and temperature gradients, and the resulting local supersaturation – that do not scale linearly with reactor volume. In a small vessel, reagents mix and equilibrate quickly relative to nucleation and adsorption; in a larger one, mixing and mass transfer slow, so that different regions of the same batch experience different histories and produce nanoparticles with different sizes, morphologies and coating densities [442,443]. Because the surfactant adsorbs during, not after, this heterogeneous process, scale-up alters the very interface that was optimized at small scale, degrading the batch-to-batch reproducibility that Sections 12.1 and 12.4 identify as critical. This scale-dependence is the principal technical argument for continuous and microfluidic manufacturing (Section 12.3), which controls the local environment directly and decouples production rate from reactor geometry, and it is a recurring obstacle in documented scale-up and cGMP campaigns [444].

12.3. Continuous-flow manufacturing

Two broad paradigms dominate nanoparticle manufacturing: conventional batch processes and emerging continuous or microfluidic approaches. Batch methods – including thin-film hydration, high-pressure homogenization (HPH), nanoprecipitation, and solvent injection – offer flexibility but suffer from scalability limitations: poor mixing homogeneity, wide size distributions, and batch-to-batch variability that escalates during scale-up [442,445]. Scale-up of batch processes is largely empirical, requiring extensive re-optimization whenever reactor volume increases.

Continuous and microfluidic platforms decouple production rate from reactor geometry, enabling scalable and reproducible assembly. Devices such as the NanoAssemblr™ and parallelized staggered herringbone micromixers enable precise, reproducible control over nanoparticle self-assembly through well-defined flow rate ratios (FRR) and total flow rates (TFR) [443,446]. Reproducible surfactant-based niosomes and PLGA nanoparticles have been produced without post-processing steps, greatly simplifying industrial workflows [447]. A landmark advance is the SCALAR-AF platform, which incorporates an immobilized perfluorodecalin lubricant layer to create antifouling microfluidic channels; this innovation enables hours-long, liter-per-hour production of RNA- LNPs with preserved size, encapsulation efficiency, and transfection activity, directly addressing the commercial-scale bottleneck for mRNA therapeutics [448] (Table 12).

12.4. Surface reproducibility and batch-to-batch variability

Variability in coating density or structural integrity is not merely a quality-control metric, but it has direct therapeutic consequences. Surface chemistry heterogeneity (patchy PEG, subpopulations of uncoated nanoparticles, variable ligand density) is now recognized as an emerging structural parameter that modulates *in vivo* biodistribution, drives unexpected immunogenic responses, and can produce nonlinear dose–response relationships [439,449]. Specific mechanistic consequences include:

Endocytic pathway switching: albumin-coated iron oxide nanoparticles are internalized predominantly via clathrin-mediated endocytosis, whereas PEG-coated counterparts shift to caveolin/lipid raft pathways – an effect of coating chemistry rather than nanoparticle core [450].

Cooperative aggregation: cell-membrane-coated silica nanoparticles with $< 50\%$ surface coverage must pre-aggregate before endocytosis, while highly coated ($\geq 50\%$) nanoparticles internalize individually, leading to distinct endosomal loading kinetics [451].

PEG density and lymphatic transport: dense PEG brush coatings maximize lymph node accumulation; low-density PEG provides substantially poorer transport, implying that an optimal density window must be defined and controlled as a CQA [452].

Release kinetics: chitosan outer coatings on PLGA nanoparticles attenuate the initial burst without altering later diffusion-controlled release, demonstrating that the surfactant/polymer shell acts as a gating membrane whose integrity must be preserved through scale-up and storage [453].

These observations converge on a single manufacturing imperative: coating homogeneity must be treated as a critical structural parameter throughout the production workflow, not merely assessed retrospectively. Achieving this requires closed-loop process control – integrating in-line nanoparticle size monitoring, real-time spectroscopic surface analysis where feasible, and rigorous statistical process control (SPC) – from laboratory scale through GMP manufacture.

Scale-up is not a neutral magnification of a bench protocol; it reshapes the very interface that was designed. The manufacturing literature makes clear that coating identity, uniformity and stability must be defined as critical quality attributes and controlled in-process – otherwise "rational" bench-scale design is silently undone at the point of production.

12.5. Stability, storage and lyophilization

Long-term physical and chemical stability is a pivotal commercial requirement. Nanoparticle dispersions are thermodynamically metastable; indeed, Ostwald ripening, aggregation, and surfactant desorption can all degrade CQAs during storage. Lyophilization (freeze-drying) is the gold standard for extending shelf-life, but it introduces new challenges: ice crystal formation during freezing can disrupt the lipid or surfactant shell unless appropriate lyoprotectants (trehalose, sucrose, mannitol) are incorporated and freeze-drying cycle parameters (primary and secondary drying temperatures, shelf ramp rates) are systematically optimized [454]. Reconstitution behavior, such as nanoparticle size recovery and resuspendability, must itself be specified as a CQA for lyophilized products.

Scalable downstream purification via tangential flow filtration (TFF) replaces laboratory dialysis for removal of unencapsulated drug, organic solvents, and excess surfactant; TFF retentate concentration simultaneously enables adjustment of final nanoparticle concentration. Sterility assurance for parenteral nanoformulations typically relies on aseptic processing rather than terminal steam sterilization, since heat or radiation can compromise the surfactant coating; this places additional demands on cleanroom design and process validation [454,455].

12.6. Industrial scalability and cost

Technical feasibility is necessary but not sufficient for translation: a coating strategy must also be economically viable at industrial scale. Cost enters at several points, including the purity and price of the surfactant itself, the number and complexity of synthetic and purification steps, and the overhead of GMP-compliant manufacturing and analytical control [442,444]. A strategy that performs excellently at the bench can be disqualified at scale if it depends on a specialty amphiphile, a multi-step ligand exchange (Section 4.5), or characterization that cannot be implemented as an in-line quality control. The techno-economic viability of renewable and bio-based feedstocks (Section 10.3) is part of the same calculation, since a sustainable coating that cannot be produced affordably will not displace an incumbent [4]. Cost and scalability are therefore not downstream afterthoughts but design constraints that, like sustainability, belong in the surfactant selection from the outset; the coatings most likely to translate are those engineered with manufacturability in view, not merely with performance.

12.7. Translational barriers

Surfactant-coated nanomedicines are regulated under current GMP frameworks (cGMP, a recent benchmark): 21 CFR Parts 210–211 in the United States, and EU GMP Annex 1 and clinical trial guidelines in Europe [455]. Importantly, regulatory agencies treat surface coatings, namely PEGylation, lipid shells, targeting ligands, as integral components of the drug product rather than excipient adjuncts. Consequently:

1) Incomplete or variable coatings are identified as potential causes of altered biodistribution, complement activation (accelerated blood clearance, ABC phenomenon), and batch-to-batch immunogenicity that must be mitigated by validated manufacturing [456].

2) Non-standard dosage forms (*e.g.*, liposomes, polymeric micelles, and nanoparticulate complexes) require validated production-scale data in marketing applications, reflecting the non-biological complex drug (NBCD) concept that acknowledges the difficulty of full molecular characterization [455,457].

3) GMP for nanomedicines stresses: well-defined raw material specifications (surfactant purity, lipid composition), scalable processes with bridging studies across scales, in-process controls, and retained samples. Scale-up of saponin/MPLA nanoparticle adjuvants to cGMP manufacture illustrated how QbD-guided process development, combined with orthogonal analytics for surface attributes, can satisfy regulatory expectations [444].

13. Unresolved priorities for surfactant-engineered materials

We close not by projecting where the field is heading, but by specifying what it would need to resolve in order to get there.

Taken together, the preceding sections describe a field rich in chemical options and application successes but still short of the mechanistic, analytical, regulatory and computational foundations that "rational design" presupposes. In closing, we do not restate these achievements but specify what remains unresolved: the predictive gaps in classification, the interfacial mechanisms still assumed rather than measured, the characterization standards not yet agreed, and the sustainability and safety claims not yet substantiated. A genuinely rational, regulation-aware framework for surfactant engineering of nanoparticles is achievable, but only once these specific gaps are closed – and we outline the priorities by which the field can close them.

13.1. Quantitative and transferable interfacial descriptors

The most consequential gap identified in this Review is descriptive rather than synthetic: the field lacks agreed quantitative descriptors of the interface itself. Surface coverage, grafting density, ligand conformation and the fraction of accessible surface are reported in units and by methods that differ between laboratories, are often inferred from bulk composition rather than measured, and are seldom reported alongside the uncertainty of the determination. The consequence is that data cannot be pooled, structure–property correlations cannot be tested across studies, and the same nominal coating can denote materially different interfaces. A minimum reporting set – coverage per unit area with its method of determination, ligand conformational regime, accessible-surface fraction, and the dispersion medium in which each was measured – would do more to enable predictive design than any single new technique.

13.2. Dynamic and in situ characterization of the working interface

Almost everything known about surfactant layers has been measured on dried, diluted or otherwise non-native samples, whereas the interface that governs function is hydrated, crowded and continuously exchanging with its medium. Closing this gap requires methods that report on the interface in situ and in real time – liquid-cell and cryogenic electron microscopy, in situ small-angle scattering, high-speed atomic force microscopy, and single-particle rather than population-averaged optical and spectroscopic methods. Two questions in particular remain effectively unaddressed: the residence time and exchange rate of individual ligands under application-relevant conditions, and the distribution of coverage across a particle population rather than its mean. Both are experimentally accessible and both would immediately constrain the structure–property relationships discussed in Section 7.

13.3. Transferable structure–function models across material families

Multivalency and cooperative binding illustrate both the promise and the limits of current understanding. Multidentate polymeric anchors demonstrably outperform monodentate ligands in colloidal and chemical stability, yet the quantitative relationship between denticity, binding free energy and service lifetime has been established for few systems and transfers poorly between material families. More generally, the structure–function relationships summarized in Fig. 5 are largely material-specific: a coverage–activity relationship established for a noble-metal catalyst does not predict the corresponding relationship for an oxide photocatalyst or a semiconductor quantum dot. Identifying which relationships are governed by generic interfacial physics and which by the specific chemistry of the underlying solid is a prerequisite for design rules that transfer beyond the system in which they were derived.

13.4. Prospective and multiscale validation of predictive models

Predictive approaches span molecular simulation, coarse-grained modelling and machine learning, but they are validated almost exclusively against the data on which they were trained. What is missing is validation across scales and in prospect: a model that predicts head-group binding affinity should be tested against measured adsorption isotherms, the resulting interfacial organization against in situ structural data, and the predicted material property against an independently measured endpoint – with the prediction registered before the experiment. Community benchmark sets containing interface-relevant, consistently measured properties, and the routine reporting of negative and out-of-domain results, are the practical mechanisms by which this would be achieved.

13.5. Standardized safety and sustainability assessment

Safety and sustainability claims are currently the least standardized element of the field. Toxicological and ecotoxicological data for surfactant-stabilized materials are generated under protocols that differ in medium, exposure duration, dispersion state and endpoint, so that values cannot be compared between studies and dose–response relationships cannot be aggregated. Biodegradation is frequently asserted from the behaviour of the free surfactant rather than measured for the surfactant–material combination actually released. The specific requirement is a minimum harmonized dataset – free surfactant and coated material tested in parallel, dispersion

state characterized and reported, ecotoxicity determined against a common species set, and degradation assessed on the released form – applied consistently enough that substitution claims can be evaluated rather than assumed. It is worth noting that this requirement applies symmetrically: bio-based and biosurfactant alternatives should be held to the same evidentiary standard as the incumbents they are proposed to replace.

13.6. Multi-objective optimization and adaptive interfaces

The final priority follows from a recurring finding of this Review: interfacial properties trade off against one another. Increasing coverage improves colloidal and chemical stability while reducing catalytic accessibility, charge transport, optical coupling and magnetic interaction; increasing biodegradability generally reduces shelf-life; increasing binding strength impedes the post-synthetic ligand exchange on which downstream function often depends. Design is therefore intrinsically multi-objective, yet it is still usually reported as the optimization of a single property. Two developments would change this. The first is the routine reporting of trade-off surfaces rather than single optima, so that the cost of an improvement is visible. The second is the use of interfaces that are adaptive rather than fixed – coatings whose coverage or conformation changes with the environment, and which can therefore satisfy conflicting requirements at different points in the material's life. Stimuli-responsive and dynamically exchanging ligand shells are the most developed examples, and their extension beyond biomedical release to catalysis, sensing and energy materials is among the more tractable opportunities in the field. Environmental responsibility is a further constraint of the same kind: cationic agents with long alkyl chains such as CTAB and oleylamine perform well as structure-directing agents while carrying well-documented aquatic toxicity, and substitution must be assessed against both objectives rather than either alone.

Regulatory drivers: New legislative frameworks (*e.g.*, Regulation (EC) No 1907/2006 and the restriction on intentionally added synthetic polymer microparticles) are shaping how polymeric interfacial agents are selected and documented. The restriction applies to solid polymer particles meeting defined size and insolubility criteria, with derogations for polymers that are soluble or that satisfy the degradability tests it sets out. Whether a given polymeric coating falls within scope therefore depends on its physical form, solubility, degradability, intended use and release pathway, and cannot be inferred from polymer class alone: PVP and most PEG grafts are water-soluble and are not, as such, in scope. The practical consequence is a stronger requirement to characterise and document degradability and release behavior, rather than a general obligation to replace these materials.

Bio-based Alternatives: Microbially derived biosurfactants are the most frequently proposed substitution route, and several combine high emulsifying ability with favourable degradation profiles; as noted in Sections 2.6 and 10, however, these advantages are compound-specific and the comparative datasets needed to support substitution at scale are still largely absent.

13.7. From priorities to practice

These six priorities are not independent. Quantitative descriptors (13.1) are what in situ methods (13.2) must deliver; transferable models (13.3) cannot be built or tested (13.4) without them; and neither safety assessment (13.5) nor multi-objective design (13.6) can be placed on a quantitative footing until the interface itself is reported reproducibly. The practical implication for the field is therefore narrower than the breadth of this Review might suggest: progress depends less on new chemistries than on measuring, reporting and validating the interfaces we already make. Three near-term steps follow directly:

I. *Standardization* of interfacial reporting: adopting a minimum descriptor set (coverage, conformational regime, accessible fraction, medium, method and uncertainty) as a condition of publication, so that results become comparable across laboratories.
II. *Correlative characterization*: moving from parallel to genuinely correlative measurement on the same specimen – for example scattering, cryogenic microscopy and spectroscopy on a single sample in its native, hydrated state – so that structural and compositional information refer to the same interface.
III. *Harmonized safety testing*: embedding toxicological and ecotoxicological assessment into surfactant development under common protocols (*e.g.*, EC50 and IC50 determined on both the free surfactant and the coated material, with dispersion state reported), so that hazard can be compared rather than asserted.

These three steps (*i.e.* descriptor standardization, correlative in situ measurement and harmonized safety testing) are unglamorous by comparison with the chemistries they would serve, but they are what would convert surfactant engineering from a practice guided by empirical analogy into one guided by measurement. They are also, unlike most of the advances surveyed in this Review, achievable with existing instrumentation and without new chemistry.

14. Conclusions and outlook

This Review has argued that surfactants are best understood not as passive formulation additives but as molecular architects of materials: their structure determines how they adsorb and organize at an interface (Sections 2–3), how that organization directs the nucleation, growth and self-assembly of the surrounding material (Sections 4–5), how reliably that organization can be characterized (Section 6), and ultimately what structural, functional, technological, biological, environmental and economic consequences follow from it (Sections 7–12). Where this causal chain has been demonstrated with mechanistic, quantitative evidence, it constitutes genuine design knowledge; establishing the extent to which such knowledge transfers across material classes remains an important challenge, and, as Section 13.3 argues, is a separate property that requires its own validation. Where the chain has instead been assumed by

analogy to prior empirical success, it does not constitute design knowledge at all, regardless of how often it is repeated in the literature. Closing this gap – extending predictive, structure-based design from the handful of systems where it has been rigorously established to the full breadth of surfactant-engineered materials – is, in our view, the central task facing the field in the years ahead.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used generative-AI tools to assist with figure preparation (*FigureLabs*, licensed version) and with language editing, formatting and reference checking (*Claude* – Anthropic, licensed version). All outputs were reviewed, edited and verified by the authors, who conceived the scientific content and take full responsibility for the accuracy and integrity of the published article.

CRediT authorship contribution statement

Marco Davide Giustra: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Brian Novati:** Writing – original draft, Investigation. **Alessandro Colombo:** Writing – original draft, Investigation. **Giulia Sinesi:** Writing – original draft, Investigation, Formal analysis. **Lucia Morelli:** Writing – review & editing, Investigation, Formal analysis. **Stefania Garbujo:** Writing – review & editing, Investigation, Formal analysis. **Miriam Colombo:** Resources, Investigation, Funding acquisition, Conceptualization. **Davide Prosperi:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review. All data mentioned in this study are contained within the text, figures, and cited references.

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