Environmental Persistence, Safety, and Sustainability Considerations of Nonionic Synthetic Stabilizers in Pharmaceutical Colloidal Drug Delivery Systems: A Review

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ABSTRACT

Nonionic synthetic stabilizers are important excipients in colloidal drug delivery systems because they help preserve formulation integrity, enhance the solubilization of poorly water-soluble drugs, and improve product stability during storage. Common examples include polysorbates, poloxamers, polyethylene glycol (PEG)-based materials, polyvinyl alcohol, polyvinylpyrrolidone, and chemically modified cellulose materials. Despite their established pharmaceutical utility, increasing attention is directed toward the environmental consequences associated with their manufacture, application, degradation, transformation, and disposal. This review examines the environmental fate and sustainability implications of nonionic synthetic stabilizers used in colloidal drug delivery systems. Relevant peer-reviewed literature published between 1992 and 2026 was identified through searches of Scopus, PubMed, Web of Science, Science Direct, and Google Scholar. The review considers major stabilizer classes and stabilization mechanisms, sources and pathways of environmental entry, degradation processes, persistence, safety and ecotoxicological concerns, regulatory considerations, and emerging sustainable alternatives. Evidence indicates that pharmaceutical stabilizers may enter aquatic and terrestrial environments through manufacturing discharges, wastewater systems, pharmaceutical use, and inappropriate disposal. Their environmental behaviour varies according to chemical structure and physicochemical characteristics, and some substances or degradation products may exhibit persistence or potential ecological effects. Important gaps remain in long-term toxicological evidence, environmental surveillance, ecotoxicity assessment, and harmonization of regulatory approaches for pharmaceutical excipients. Emerging approaches involving biodegradable and renewable stabilizers, green chemistry, life-cycle assessment, and environmentally informed formulation design offer opportunities for reducing the ecological footprint of colloidal drug delivery systems. Future development should balance pharmaceutical functionality, patient safety, product quality, manufacturing feasibility, and environmental sustainability.

Keywords: nonionic synthetic stabilizers, colloidal drug delivery, pharmaceutical excipients, environmental fate, sustainability.

INTRODUCTION

Colloidal drug delivery systems are important pharmaceutical platforms for improving the delivery of drugs whose use may be limited by poor aqueous solubility, inadequate dissolution, instability, or low bioavailability. Systems considered in the manuscript include emulsions, nanoemulsions, liposomes, nano

suspensions, polymeric nanoparticles, and micellar formulations. Their dispersed nature creates a need for stabilizers capable of controlling interfacial behaviour and preventing physical instability such as aggregation, flocculation, coalescence, sedimentation, and Ostwald ripening. Nonionic synthetic stabilizers are widely used because their physicochemical characteristics and formulation performance are relatively predictable. Their principal roles include reduction of interfacial tension, steric stabilization, improvement of dispersion, enhancement of solubilization, and maintenance of physical stability during manufacture and storage. However, the pharmaceutical value of an excipient must be considered alongside possible human-health and environmental consequences. The review identifies concerns about the environmental fate of some synthetic stabilizers and notes that pharmaceutical manufacturing, patient use, wastewater discharge, and disposal may contribute to environmental entry. It also discusses potential degradation, persistence, and transformation. Certain excipients, including polysorbates and polyoxyethylene castor-oil derivatives, have been associated with biological effects or hypersensitivity reactions under particular circumstances. These concerns do not imply that all synthetic stabilizers are unsafe; rather, they support a more systematic, compound-specific assessment. The review also considers natural, biodegradable, and renewable-source materials as possible alternatives. However, it emphasizes that natural origin does not automatically establish environmental superiority. Sustainability requires consideration of raw-material sourcing, processing, energy requirements, waste, performance, safety, environmental fate, and end-of-life behaviour. (Patra, 2018; Müller, 2001; Anton, 2011; Tadros, 2004; Cortes, 2021; McClements, 2012; Blanco, 2015; Danhier, 2012; Mitchell, 2021; Shi, 2017; International Council for Harmonisation. (2009). ICH harmonised guideline Q8(R2): Pharmaceutical development. ICH, 2009; Mahmoudi, 2012; Solans, 2005)

REVIEW METHODOLOGY

A structured literature search was conducted using Scopus, PubMed/MEDLINE, Web of Science, ScienceDirect, and Google Scholar, supplemented by authoritative sources including PubChem, OECD resources, and published US/EU environmental risk assessments. Searches combined stabilizer names and synonyms with terms related to biodegradation, environmental fate, ecotoxicity, environmental concentration, and PEC/PNEC. Reference lists of relevant primary studies and reviews were also screened. Peer-reviewed studies, regulatory assessments, authoritative databases, and scientifically documented environmental-risk assessments addressing environmental fate, biodegradation, physicochemical properties, exposure, toxicity, or risk characterization were eligible. Priority was given to standardized OECD or equivalent tests, measured environmental concentrations, formal PEC/PNEC assessments, and recent primary studies. Evidence from non-pharmaceutical applications was included where environmentally relevant findings were transferable to pharmaceutical use. Data extracted included stabilizer class, molecular weight, water solubility, logKow, biodegradation percentage and test conditions, environmental half-life where available, measured environmental concentrations, predicted environmental concentrations (PEC), predicted no-effect concentrations (PNEC), PEC/PNEC ratios, and ecotoxicological endpoints such as EC50, LC50, NOEC, growth inhibition, immobilization, reproduction, and developmental effects. For polymers and heterogeneous mixtures, single molecular-weight and logKow values were reported as not reliably defined where appropriate. Biodegradation was interpreted according to test design and endpoint, distinguishing primary degradation, ultimate biodegradation/mineralization, and wastewater-treatment removal. OECD 301 results were therefore not considered equivalent to OECD 303A removal data. Environmental half-life was reported only where a reliable measured or modelled value was available. Measured environmental concentrations were distinguished from PECs, and PEC/PNEC ratios below 1 were considered indicative of exposure below the predicted no-effect level, whereas ratios ≥1 indicated potential environmental concern requiring further assessment. Where reliable PEC/PNEC data were unavailable, ratios were not derived from unrelated datasets. For PVOH 18-88, published local and regional freshwater PECs of 0.00389 and 0.000951 mg/L, respectively, compared with a PNEC of 1 mg/L, yielded PEC/PNEC ratios of approximately $3.89 \times 10{-}3$ and $9.51 \times 10{-}4$. Ecotoxicological evidence was assessed across relevant trophic levels, including algae, aquatic invertebrates, fish/fish embryos, microorganisms, and chronic or sublethal endpoints. Environmental concern was comparatively classified as lower, intermediate/uncertain, or greater by integrating biodegradability, persistence, environmental occurrence, ecotoxicological potency, exposure, and available risk characterization. This classification represents an evidence-based comparative assessment rather than a regulatory hazard classification. The principal limitations were heterogeneity among polymers, mixtures, and grades; differences in molecular

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weight and substitution; and variability in environmental concentrations arising from use patterns, wastewater-treatment efficiency, dilution, geographic setting, and analytical detectability. Consequently, quantitative comparisons were made only where data were sufficiently comparable, and the findings should be considered a screening-level environmental assessment rather than a substitute for substance-specific regulatory risk assessment.

Nonionic synthetic stabilizers in colloidal drug delivery

Nonionic synthetic stabilizers form an important group of excipients in colloidal drug delivery. Their lack of a permanent ionic charge can provide useful formulation characteristics and, for many materials, relatively good compatibility with pharmaceutical ingredients. They stabilize dispersed systems through several mechanisms, particularly steric stabilization and interfacial adsorption. In steric stabilization, polymeric or surfactant molecules associate with particle or droplet surfaces and form a hydrated layer that reduces close approach between dispersed entities. This decreases attractive interactions and helps prevent aggregation. In emulsions and nanoemulsions, surfactants also reduce interfacial tension and facilitate droplet formation. In nanosuspensions and polymeric nanoparticles, adsorbed polymers can provide a protective surface layer and limit particle growth or aggregation. This review emphasizes that stabilizer selection is formulation-dependent. Molecular weight, hydrophilic–lipophilic balance, concentration, temperature, ionic strength, pH, processing conditions, and interactions with the drug and other excipients may affect performance. Consequently, the choice of stabilizer should be based on both desired pharmaceutical function and compatibility with the formulation. (Alexandridis, 1995; Rosen, 2012; Israelachvili, 2011; Bhattacharjee, 2016; Wang, 2013; Aulton, 2018; Danaei, 2018; International Organization for Standardization. (2006). ISO 14040:2006 environmental management—Life cycle assessment—Principles and framework. ISO, 2006; Mason, 2006; Torchilin, 2005)

Polyoxyethylene-based surfactants and polysorbates

Polyoxyethylene surfactants contain hydrophilic and hydrophobic components that allow them to accumulate at interfaces and stabilize dispersed phases. Polysorbates are among the most widely used nonionic surfactants in pharmaceutical formulations. They can improve emulsification, solubilization, and colloidal stability and are also used in formulations containing biological molecules. This review notes that polysorbate behaviour is not completely static during storage. Degradation can occur through pathways such as hydrolysis and oxidation, and degradation products may alter formulation quality. This is particularly relevant to biopharmaceutical formulations, where surfactant degradation may influence protein stability and particle formation. Consequently, monitoring excipient integrity may be important during product development and stability assessment. From an environmental perspective, the manuscript highlights the need to understand the fate of polysorbates after use and disposal. Their environmental behaviour depends on chemical structure, concentration, environmental conditions, and biodegradation pathways. Their presence in environmental systems should therefore be evaluated using exposure and effect data rather than assumptions based solely on their widespread pharmaceutical use. (Kerwin, 2008; Kishore, 2011; Weber, 2023; Maher, 2023)

Polyoxyethylene castor-oil derivatives: cremophor EL and cremophor RH40

Polyoxyethylene castor-oil derivatives are nonionic surfactant systems used principally for solubilization and stabilization of poorly water-soluble substances. Cremophor EL is an important example and has been used in pharmaceutical formulations of poorly soluble drugs. This study highlights that Cremophor EL has also been associated with hypersensitivity and anaphylactoid reactions in some settings, making its safety profile relevant when considering formulation selection. Cremophor RH40 is another polyoxyethylene castor-oil derivative used in lipid-based and self-emulsifying formulations. It can facilitate solubilization and formation of dispersed systems. These materials are useful pharmaceutical excipients but differences in chemical composition and formulation context can affect their biological and physicochemi0063al behaviour.Environmental assessment should similarly be compound-specific. This review does not support assuming that one castor-oil-derived surfactant automatically has a superior environmental profile to another. Claims about degradation, persistence, toxicity, or sustainability should be based on comparative evidence. (Bu, 2016; Campos, 2014; Szebeni, 2005; Sarker, 2005)

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Poloxamers

Poloxamers are nonionic amphiphilic triblock copolymers composed of poly(ethylene oxide) and poly(propylene oxide) segments. Their amphiphilic architecture allows them to associate with hydrophobic surfaces while exposing hydrophilic segments to the aqueous phase. This makes them useful in micelles, emulsions, nanoparticles, and other colloidal systems. Poloxamers can stabilize colloidal systems through steric mechanisms. The hydrated poly(ethylene oxide) chains form a protective layer that limits particle–particle interactions. Poloxamer 407 is particularly notable because, in addition to its stabilizing function, it can form thermoreversible gels and therefore has applications in controlled and localized drug delivery. Different poloxamer grades are not interchangeable. Differences in molecular weight, hydrophilic–lipophilic balance, and block composition influence micellization, viscosity, gelation, solubilization, and stabilization. Selection therefore requires consideration of the intended dosage form and the desired physicochemical properties. (Alexandridis, 1995; Dumortier, 2006; Batrakova, 2008; Kabanov, 2002)

Polyethylene glycol (PEG) and PEG-containing materials

Polyethylene glycol and PEG-containing derivatives are important hydrophilic materials used in pharmaceutical formulation. PEG may improve aqueous compatibility, reduce nonspecific interactions, and provide steric stabilization. PEG molecular weight affects viscosity, solubility, hydration, and other formulation characteristics. PEG can also be incorporated into more complex delivery systems. PEG-containing phospholipid derivatives such as DSPE-PEG can associate with lipid-based particles while presenting hydrated PEG chains at the surface. This arrangement can reduce particle aggregation and influence interactions between colloidal carriers and biological systems. This review also discusses PEGylation as a strategy for modifying pharmacokinetic behaviour. Surface PEG layers can reduce recognition and clearance of some carriers and may contribute to prolonged circulation. However, PEG is not free from safety and environmental questions. Hypersensitivity reactions to PEG-containing materials have been reported, and environmental assessment should consider the chemical form, molecular size, exposure route, degradation, and transformation products rather than treating all PEG-containing materials as equivalent. (Harris, 2003; Knop, 2010; Veronese, 2005; Kolate, 2014; Nakamae, 2006; Reker, 2019)

Polyvinyl alcohol, polyvinylpyrrolidone and copovidone

Polyvinyl alcohol (PVA) is a water-soluble synthetic polymer used in pharmaceutical formulations, including polymeric nanoparticles and other dispersed systems. It can adsorb at particle surfaces and contribute to stabilization. Its degree of hydrolysis and molecular characteristics influence its physicochemical behaviour. Polyvinylpyrrolidone (PVP) is another important synthetic polymer. It can function as a stabilizer, solubilizer, and crystal-growth inhibitor and is frequently encountered in formulations involving poorly water-soluble drugs. PVP can influence amorphous solid dispersions and drug dissolution by interacting with drug molecules and limiting crystallization.Copovidone is a copolymer containing vinylpyrrolidone and vinyl acetate. It is used for binding, film formation, solubilization, and stabilization. PVA, PVP, and copovidone have different chemical structures and should not be assumed to have identical pharmaceutical or environmental behaviour. Their biodegradation and environmental fate require individual assessment. (Chiellini, 2003; Serajuddin, 1999; Vasconcelos, 2007; Rolsky, 2021; Pockle, 2023)

Cellulose derivatives

Cellulose derivatives are chemically modified forms of naturally occurring cellulose and occupy an important position among pharmaceutical excipients. Their chemical modification gives them properties useful for viscosity control, stabilization, film formation, controlled release, and other formulation functions. Their origin from a renewable natural polymer may appear advantageous, but this does not automatically demonstrate a lower environmental burden. Chemical modification, manufacturing processes, solvents, energy use, impurities, and disposal may all influence the final environmental profile. An important conclusion is that evidence remains insufficient to make broad comparative claims about environmental persistence, biodegradability, toxicity, or sustainability advantages for all cellulose derivatives. Compound-specific and process-specific evidence is required. (Luo, 2026; Sun, 2019; Liu, 2008)

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Lipid-based stabilizers

Lipid-based materials considered in this review include emulsifying wax, cetostearyl alcohol, and glyceryl monostearate. These materials may contribute to the formation and stabilization of pharmaceutical emulsions, creams, dispersions, and related dosage forms. Their hydrophobic and amphiphilic characteristics allow them to influence interfacial structure and the physical properties of formulations. However, evidence supporting detailed comparative claims about environmental superiority of these materials remains limited. Their use should therefore be considered in the context of pharmaceutical function, safety, manufacturing requirements, sourcing, biodegradation, and environmental fate rather than through a simple natural-versus-synthetic classification. (Jannin, 2014; Allen, 2013; McClements, 2015; Rowe, 2009; Ansel, 2011; Makadia, 2011)

Sources, manufacturing and sustainability of synthetic stabilizers

Many synthetic stabilizers are manufactured from petrochemical-derived feedstock. Their environmental footprint therefore begins before their use as pharmaceutical excipients. Manufacturing may involve chemical reactions, catalysts, solvents, purification, energy consumption, water use, and waste generation. This review applies green-chemistry and sustainability concepts to this issue. Replacement of fossil-derived raw materials with renewable resources may reduce dependence on non-renewable feed stocks, but renewable origin alone does not prove that a material has a lower overall environmental impact. A meaningful sustainability assessment should consider the entire production chain and compare resource use, energy, emissions, waste, toxicity, performance, and end-of-life behaviour. Life-cycle assessment is presented as a useful framework for evaluating environmental impacts from raw-material acquisition through production, distribution, use, and disposal. Such assessments are particularly relevant where alternative stabilizers have different manufacturing processes or different requirements for purification and formulation. (Anastas, 1998; Sheldon, 2007; Jiménez-González, 2011; Aulton, 2018)

Mechanisms of colloidal stabilizations

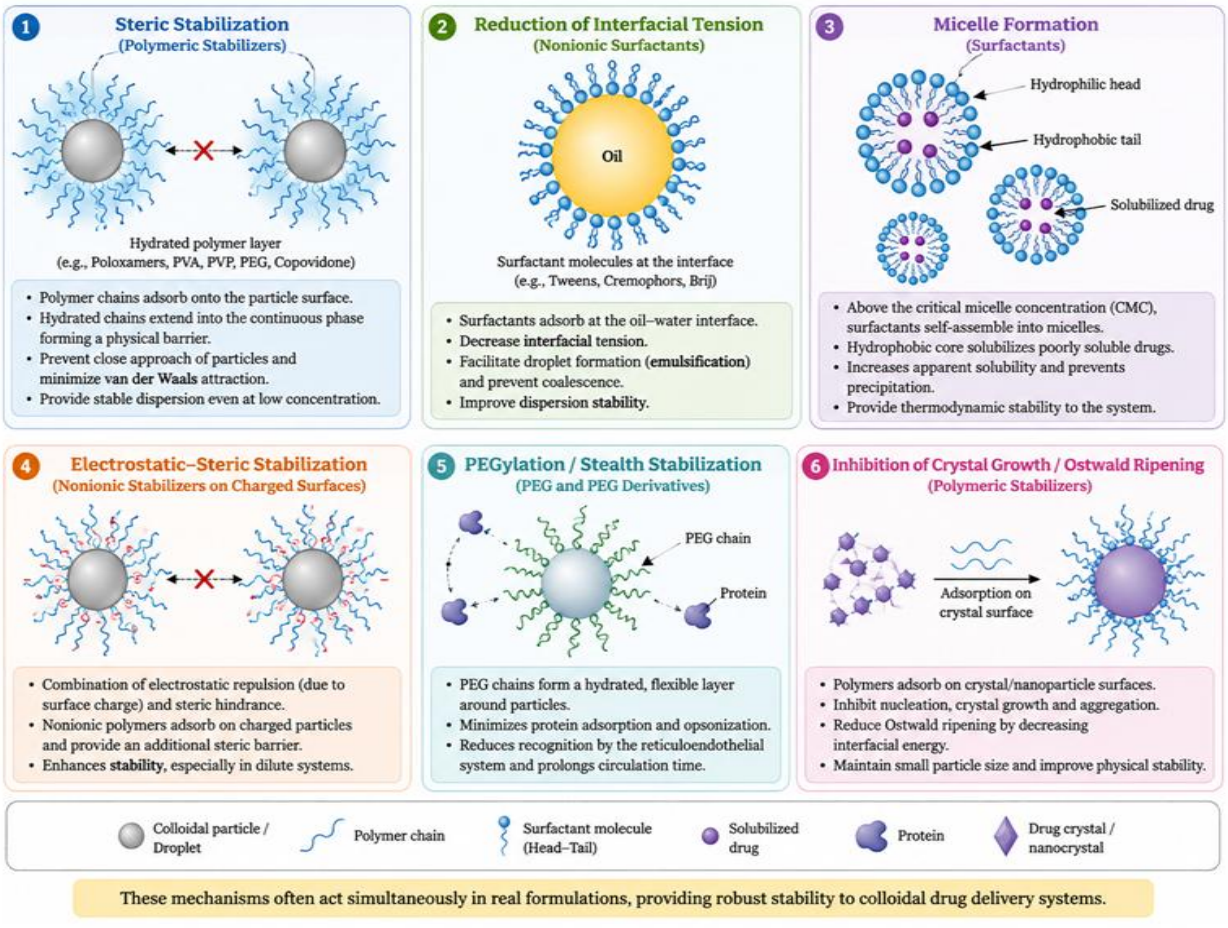

Fig. I: Mechanisms of Colloidal Stabilization

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Environmental persistence and environmental fate

Pharmaceutical stabilizers may enter environmental systems through manufacturing effluents, wastewater, patient excretion, disposal of unused medicines, and other pathways. Wastewater treatment plants are important interfaces between pharmaceutical use and the environment. Depending on their physicochemical characteristics, stabilizers may remain in treated effluent, undergo degradation or transformation, or associate with sludge and sediments. Environmental persistence depends on chemical structure, molecular weight, solubility, sorption, microbial activity, temperature, pH, oxygen availability, and other environmental conditions. Applying a single degradation rate or persistence classification to an entire chemical class should be guarded against. Environmental transformation may involve biodegradation, hydrolysis, oxidation, photodegradation, or adsorption. Transformation products may have different properties from the parent substance and may require separate assessment. There's need for better information on the fate of pharmaceutical excipients compared with the much larger body of information available for many active pharmaceutical ingredients. (Daughton, 1999; Kümmerer, 2001; Kümmerer, 2004; aus der Beek, 2016; Heberer, 2002; Uluseker, 2025; Leal-Calderon, 2008; McClements, 2011; U.S. Food and Drug Administration. (2019). Using the inactive ingredient database: Guidance for industry. U.S. Department of Health and Human Services., 2019)

Human safety and toxicological considerations

Safety assessment of pharmaceutical stabilizers should consider chemical structure, concentration, route of administration, duration of exposure, formulation composition, and patient characteristics. An excipient that is well tolerated in one formulation or route may have different effects under another exposure condition. This review identifies polysorbates, Cremophor EL, PEG-containing materials, and other excipients as examples where safety considerations deserve attention. Polysorbates can undergo degradation during storage, and degradation products may influence formulation quality. Cremophor EL has been associated with hypersensitivity or anaphylactoid reactions. PEG-containing materials have also been associated with hypersensitivity in susceptible individuals. Stabilizers may also influence drug solubility, physical and chemical stability, dissolution, bioavailability, encapsulation, and release. Consequently, excipient safety cannot be considered separately from formulation performance. The preferred stabilizer should provide the required pharmaceutical function while remaining appropriate for the intended dose, route, patient population, and duration of use. (Pifferi, 2003; Maher, 2023; Reker, 2019; Szebeni, 2005; Campos, 2014)

Environmental degradation and transformation

Environmental degradation is influenced by the molecular structure of the stabilizer and the environmental compartment in which it occurs. Microbial degradation may convert susceptible substances into simpler products, while oxidation, hydrolysis, photolysis, and sorption can also influence environmental fate. PVA can undergo biodegradation under appropriate conditions, whereas PVP and other polymers may demonstrate different degradation patterns. It is therefore inappropriate to assume that all water-soluble polymers are rapidly biodegradable or that all polymers are persistent. Evidence should be evaluated for individual materials and realistic environmental conditions. Transformation products are another important consideration. Degradation does not necessarily mean complete mineralization or disappearance of environmental risk. Intermediate products may persist or possess biological properties different from those of the parent compound. Environmental assessment should therefore examine both disappearance of the original compound and the fate and effects of transformation products where evidence permits. (Scott, 2000; Ying, 2006; Chiellini, 2003; Rolsky, 2021; Weber, 2023)

Comparative environmental fate, exposure, and ecotoxicological profile of major stabilizers

The quantitative evidence identified in the literature is summarized in Table 1. "NR" denotes not reported/not identified in the reviewed evidence, while "NRD" denotes not reliably defined for a polymer or heterogeneous mixture. Environmental half-life was not substituted with human pharmacokinetic half-life because these are different concepts.

Stabilizer	MW	Water solubility	logKow	Biodegradation removal	Environmental concentration / PEC	PNEC	PEC/PNEC	Ecotoxicological endpoints / interpretation
PVA/PVOH 18-88	Polymer; grade-dependent	Water-soluble	NRD	OECD 301F: 91.2 ± 8.0%; OECD 303A: 97.4 ± 7.1% removal	EU local PEC 0.00389 mg/L; regional PEC 0.000951 mg/L	1 mg/L	0.00389 local; 0.000951 regional	Algae, invertebrate and fish-embryo L/EC50 >1000 mg/L; chronic COC 10 mg/L; low aquatic toxicity in assessed scenario.
PEG	Grade-dependent; PEG 300 ≈300; PEG 400 ≈400	Very soluble/water-miscible for low-MW grades	NRD/grade-dependent	OECD 301F: 73.0 ± 3.3%; test-system dependent	No robust pharmaceutical-specific PEC or measured environmental concentration identified	NR	NR	Readily biodegradable under higher-diversity OECD 301F conditions; direct quantitative risk characterization remains limited.
PVP	Grade-dependent; commonly tens–hundreds kDa	Highly water-soluble	NRD	<10% in tiered OECD 301 assessment; no increase after 42 days	Receiving freshwater ≈0.1 mg/L; WWTP effluent up to 7 mg/L	NR	NR	Sublethal effects reported; 2025 Daphnia work indicates molecular-weight-dependent toxicity.
Copovidone	Copolymer; grade-dependent	Water-soluble	NRD	<10% in tiered OECD 301 assessment; no meaningful increase after 42 days	NR	NR	NR	Persistence signal is stronger than for readily biodegradable polymers; quantitative aquatic risk data remain limited.
Poloxamer 188	Average ≈8400	Soluble in cold water	NRD	No measurable biodegradation in the reported tiered assessment	NR	NR	NR	Poor biodegradation increases persistence concern; chronic aquatic data are limited.
Poloxamer 407	Approx. 10–15 kDa; grade-dependent	Water-soluble/highly hydrophilic	NRD	No robust quantitative environmental percentage identified in reviewed evidence	NR	NR	NR	Environmental concern remains uncertain because direct exposure-effect data are sparse; water solubility alone does not establish low risk.
Polysorbate 20	Average ≈1228; heterogeneous mixture	Very soluble/dispersible	NRD for mixture	Comparable standardized environmental biodegradation data insufficient	NR	NR	NR	Recent freshwater-snail evidence supports further acute, chronic and life-stage-specific ecotoxicity assessment.
Polysorbate 80	Average ≈1310; heterogeneous mixture	Very soluble/dispersible	NRD for mixture	Comparable standardized environmental biodegradation	NR	NR	NR	Hydrolysis/oxidation can occur; environmental risk should be

				data insufficient				based on exposure-effect evidence rather than widespread use.
Cremophor EL/RH40	Complex polyethoxylated castor-oil mixtures	Water-dispersible/solubilizing systems	NRD for mixture	NR	NR	NR	NR	Direct environmental fate and chronic ecotoxicity evidence are sparse; best categorized as intermediate/uncertain.
Cellulose derivatives (e.g., HPMC/CMC)	Polymer; substitution/ grade dependent	Usually water-soluble/dispersible	NRD	Variable; derivatization can reduce microbial accessibility	NR	NR	NR	Often expected to have lower intrinsic hazard than persistent synthetic polymers, but environmental superiority cannot be assumed without grade-specific evidence.
Glyceryl monostearate/cetostearyl alcohol	GMS ≈358.6; cetostearyl alcohol is a mixture	GMS practically insoluble; formulation-dispersible	NR/compound-dependent	Likely susceptible to biological transformation, but directly comparable pharmaceutical-excipient data are limited	NR	NR	NR	Potentially lower persistence concern than non-biodegradable water-soluble polymers, but quantitative PEC/PNEC evidence is insufficient for definitive ranking.

Interpretation of the comparative evidence. PVA/PVOH 18-88 currently has the strongest quantitative evidence for comparatively low environmental concern among the reviewed polymeric stabilizers. It showed extensive wastewater-treatment biodegradation and very low predicted freshwater exposure relative to a PNEC of 1 mg/L; the local and regional PEC/PNEC ratios were approximately 3.89×10^{-3} and 9.51×10^{-4}, respectively. Acute aquatic effect concentrations were >1000 mg/L, supporting a wide margin of safety in the assessed scenario (McDonough et al., 2024). PEG also appears comparatively favourable when tested under conditions supporting diverse microbial communities, with 73.0 ± 3.3% biodegradation in an OECD 301F assessment. However, results varied with test conditions and inoculum, so PEG should not be described as universally rapidly biodegradable in every environmental compartment (Bading et al., 2024). PVP represents the clearest greater-concern stabilizer in the present evidence map. It was categorized as non-biodegradable (<10% degradation) in the tiered OECD 301 assessment, has been detected in wastewater at concentrations up to approximately 7 mg/L and in receiving freshwater at approximately 0.1 mg/L, and recent work indicates that molecular weight can modify Daphnia toxicity. These findings support prioritizing PVP for environmental monitoring, transformation-product assessment, and development of more biodegradable alternatives (Bading et al., 2024; Tarring et al., 2025; Julinová et al., 2018). Poloxamer 188 and copovidone also warrant elevated attention because of poor biodegradation in the available standardized testing. Nevertheless, poor biodegradation alone does not demonstrate ecological risk because reliable PEC/PNEC data are not yet available. Polysorbates, Cremophor derivatives, and many cellulose derivatives should presently be considered intermediate/uncertain categories because their environmental fate is compound-and grade-specific and the evidence does not justify a universal low- or high-risk designation.

Overall ranking for formulation decision-making. On the current evidence, the stabilizers may be grouped as follows: (1) comparatively lower environmental concern: well-characterized PVA/PVOH 18-88 and PEG

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under favourable biodegradation conditions; (2) intermediate/uncertain concern: polysorbates, polyoxyethylene castor-oil derivatives, cellulose derivatives, lipid-based stabilizers, and poloxamer 407 because of insufficient comparable PEC/PNEC and chronic ecotoxicity data; and (3) greater concern requiring priority assessment: PVP, copovidone, and poloxamer 188 because of poor biodegradation/persistence signals. This ranking is not a regulatory classification and should be revised when substance-specific PEC/PNEC, chronic toxicity, transformation-product, and life-cycle data become available.

Abbreviations: MW, molecular weight; NR, not reported/not identified; NRD, not reliably defined; PEC, predicted environmental concentration; PNEC, predicted no-effect concentration; EC50/LC50, median effect/lethal concentration; COC, concentration of concern; OECD, Organisation for Economic Co-operation and Development.

Ecotoxicological considerations

Environmental occurrence does not automatically establish ecological toxicity. Ecotoxicological assessment requires information about exposure concentration, duration, bioavailability, environmental compartment, species sensitivity, and relevant biological endpoints. The review emphasizes this distinction throughout its environmental discussion.Surfactant-based materials may affect organisms by altering cellular membranes and other biological processes. Potentially affected organisms include microorganisms, algae, aquatic invertebrates, and other aquatic species. However, effects observed at high experimental concentrations should not automatically be interpreted as evidence of significant environmental effects at concentrations encountered in real-world settings.This review identifies chronic exposure and environmentally relevant concentrations as important knowledge gaps. Long-term exposure may produce effects that differ from those observed during short-term studies, and additional work is needed to determine whether concentrations measured in environmental compartments approach levels associated with adverse biological effects. (Fent, 2006; Santos, 2010; Wang, 2021; Schultz, 2010; Ogunbanwo, 2022; Mura, 2012; Zhang, 2010)

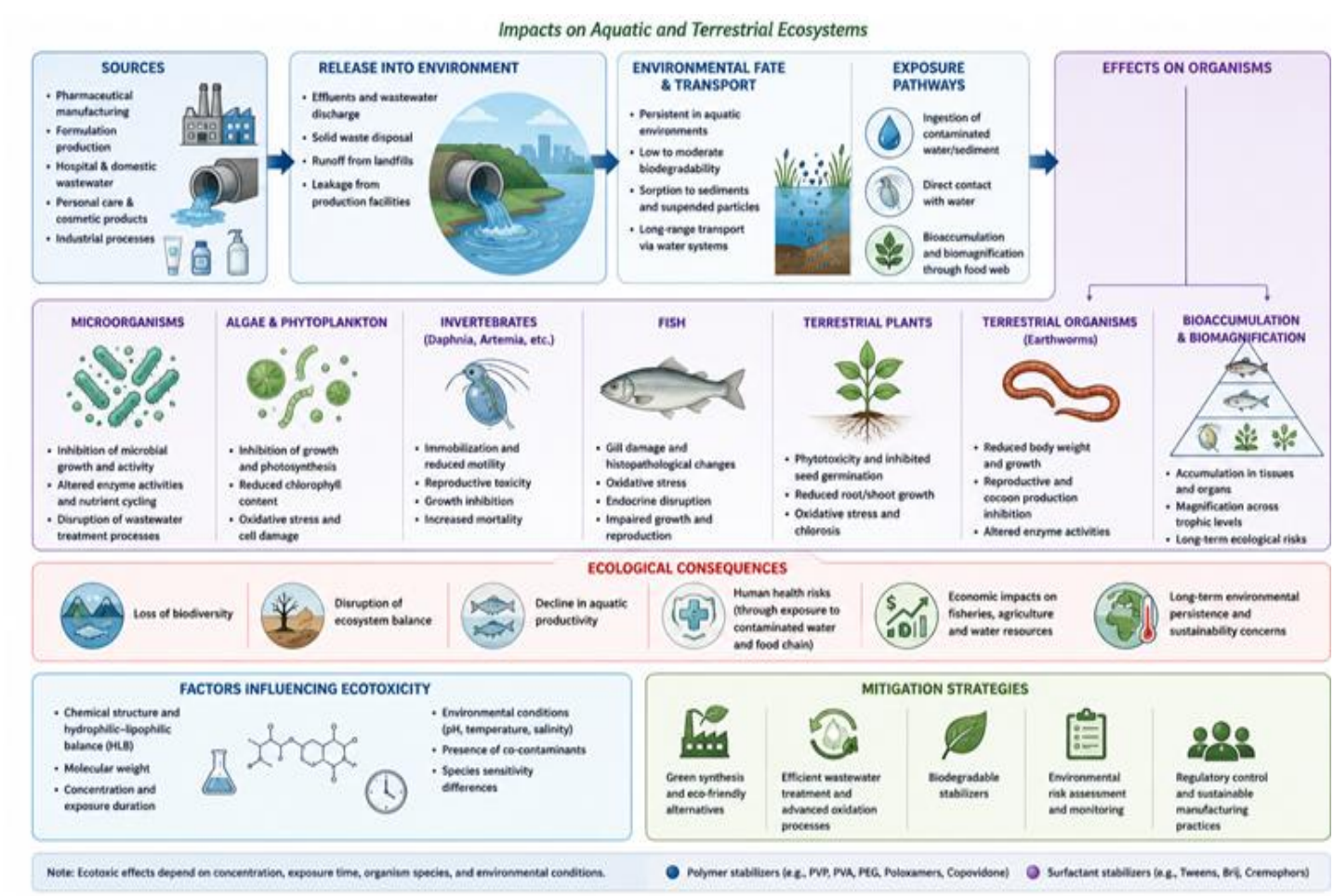

Fig. II: Ecotoxicological Effects of Nonionic Surfactants

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Regulatory perspectives

Regulatory evaluation of pharmaceutical stabilizers involves both pharmaceutical quality and safety considerations. The importance of science-based formulation development and the role of regulatory frameworks such as ICH guidance in understanding formulation components and their effects on product quality cannot be overemphasized. The FDA Inactive Ingredient Database provides information about inactive ingredients used in approved pharmaceutical products and can support formulation development. Regulatory documentation concerning excipient identity, quality, concentration, and intended use is also important. For the Nigerian setting, recognition is given to the relevance of the National Agency for Food and Drug Administration and Control (NAFDAC). However, detailed claims concerning current Nigerian regulatory requirements should be supported by the specific current NAFDAC documents applicable to the product and dosage form. The review emphasizes that regulatory systems should increasingly consider environmental as well as human-health dimensions where evidence and policy frameworks support such evaluation. (Pockle, 2023; Pifferi, 2003; Rowe, 2009)

Current challenges and research gaps

Several challenges are identified. First, environmental information for pharmaceutical excipients is less developed than the evidence base for many active pharmaceutical ingredients. Second, long-term human safety and chronic ecotoxicological data are limited for some stabilizers. Third, environmental degradation and transformation products are not adequately characterized for many materials. Another challenge is the absence of sufficiently harmonized approaches to environmental assessment of excipients. Differences in chemical structure, molecular weight, formulation concentration, exposure route, manufacturing method, and environmental compartment make generalized classifications difficult. The manuscript therefore calls for standardized testing, compound-specific environmental fate studies, chronic ecotoxicological investigations, improved monitoring, and better integration of environmental data into pharmaceutical development. Such approaches should avoid assuming that environmental presence equals toxicity while also avoiding the opposite assumption that widespread pharmaceutical use guarantees environmental safety. (Bading, 2025; Virtanen, 2026; Uluseker, 2025; Zakar-Jiya, 2022; Olarinoye, 2016; Ajibola, 2021)

Sustainable alternatives and green pharmaceutical development

Potential alternatives include biodegradable and renewable-source materials such as chitosan, alginate, cellulose derivatives, starch-based materials, pectin, xanthan gum, and gelatin. These materials may provide useful pharmaceutical functions and can sometimes be sourced from renewable biological resources. Nevertheless, the manuscript explicitly cautions against assuming that natural materials are inherently more sustainable. Agricultural production, extraction, purification, chemical modification, transport, energy consumption, waste, microbial contamination, batch variability, and end-of-life behaviour can all influence sustainability. Green chemistry provides a framework for designing safer chemicals and processes while minimizing waste and environmental burden. Life-cycle assessment can complement green-chemistry principles by evaluating environmental effects across the full life cycle. Sustainable pharmaceutical development should therefore integrate therapeutic performance, patient safety, manufacturing feasibility, economic considerations, resource efficiency, and environmental responsibility. (George, 2019; Anastas, 1998; Bading, 2025; Virtanen, 2026; Jiménez-González, 2004; Organisation for Economic Co-operation and Development. (1992). OECD guideline for testing of chemicals 301: Ready biodegradability. OECD Publishing., 1992)

Overall synthesis

The central message of the manuscript is that nonionic synthetic stabilizers remain indispensable to many colloidal pharmaceutical systems because they provide reliable and technically useful stabilization, solubilization, dispersion, and interfacial control. Their pharmaceutical advantages, however, should be considered alongside potential human-health, environmental, and sustainability implications. The environmental profile of a stabilizer is determined by more than whether it is synthetic or natural. Molecular structure, production route, dose, formulation, environmental release, degradation, transformation, and

ecological effects all contribute to the overall assessment. Similarly, detection in environmental systems should not be interpreted as proof of ecological harm without appropriate exposure and effect evidence.Future pharmaceutical development should move toward evidence-based selection of stabilizers that balance performance with safety and environmental responsibility. Better environmental monitoring, standardized testing, life-cycle assessment, and evaluation of transformation products are needed. Renewable and biodegradable materials are promising, but they should be compared with synthetic materials using rigorous, quantitative and life-cycle-based approaches. (Bading, 2025; Kümmerer, 2009; aus der Beek, 2016; Patra, 2018; George, 2019; Tadros, 2013)

CONCLUSION

Nonionic synthetic stabilizers are fundamental components of modern colloidal drug delivery and contribute substantially to the stability, performance, solubilization, and manufacturability of pharmaceutical formulations. Polysorbates, polyoxyethylene castor-oil derivatives, poloxamers, PEG-containing materials, PVA, PVP, copovidone, cellulose derivatives, and lipid-based materials each possess distinct physicochemical characteristics and formulation roles.At the same time, pharmaceutical development increasingly requires consideration of environmental persistence, degradation, ecotoxicity, human safety, manufacturing burden, and sustainability. Existing evidence is uneven, and important uncertainties remain regarding chronic exposure, transformation products, environmental occurrence, and the comparative environmental performance of alternative excipients.The review therefore supports an integrated approach in which stabilizer selection is guided by pharmaceutical performance, patient safety, environmental fate, ecological evidence, regulatory requirements, green chemistry, and life-cycle considerations. Sustainable alternatives should be investigated, but claims of environmental superiority should be based on rigorous comparative evidence rather than on natural origin alone.

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