International Journal of Global Science Research **ISSN: 2348-8344 (Online)**
Vol. 13, Issue. 1, April 2026, pp. 9018-9023 **DOI: https://doi.org/10.26540/ijgsr.v13.i1.2026.340**
***Available Online* at www.ijgsr.com**

Review

Nano-Encapsulation of Antibiotics for Controlled Drug Release and Enhanced Therapeutic Efficiency in Aquaculture Species: A Review

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Received: 24/02/2026
Revised: 01/03/2026
Accepted: 08/03/2026

Abstract: The expansion of aquaculture has intensified bacterial disease outbreaks, compromising fish health, productivity, and economic returns. Conventional antibiotics face challenges including low bioavailability, rapid environmental loss, and the emergence of antimicrobial resistance due to uncontrolled dosing. Nano-encapsulation strategies, which deliver antibiotics via nanoscale carriers, enable controlled and sustained release, improved pharmacokinetics, and targeted action with reduced environmental impact. This review evaluates nanocarrier types, drug release mechanisms, comparative performance, and experimental approaches for antibiotic delivery in aquaculture. Emerging evidence suggests that nanoscale delivery can enhance therapeutic efficacy, limit resistance development, and support sustainable aquaculture, while considerations of toxicity, regulatory compliance, and commercialization remain critical.

Keywords: Nanoparticles, Antibiotic Delivery, Aquaculture, Controlled Release, Therapeutic Efficacy, Nanocarriers

Introduction:

Aquaculture now accounts for over half of the global seafood supply, with production expanding to meet increasing protein demands (FAO, 2020). Intensive farming practices, including high stocking densities and reliance on formulated feeds, heighten susceptibility to disease, resulting in substantial economic losses. Common bacterial pathogens responsible for outbreaks include *Aeromonas hydrophila*, *Vibrio* spp., and *Streptococcus iniae* (Defoirdt et al., 2011; FAO, 2020).

Antibiotics such as oxytetracycline, florfenicol, sulfonamides, and enrofloxacin are frequently administered through feed or immersion. However, conventional delivery methods face several limitations: poor absorption due to leaching, uneven dosing among individuals, rapid metabolism with low retention, promotion of antimicrobial resistance, and accumulation in the environment leading to ecological disruption. Cabello et al. (2013) highlighted that residues of antibiotics in aquatic environments accelerate the spread of resistant bacteria in both farmed and natural waters.

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Nanotechnology, particularly nano-encapsulation, offers a promising solution by protecting active compounds, enabling controlled release, and enhancing uptake within the host. This approach has the potential to improve therapeutic efficacy while reducing both environmental contamination and the risk of antimicrobial resistance (Farokhzad & Langer, 2009).

Nanocarrier Systems for Antibiotic Delivery:

The design of nanocarriers emphasizes parameters such as particle size, composition, drug-loading efficiency, biocompatibility, and release kinetics. Frequently employed systems include polymeric nanoparticles, lipid-based carriers, and inorganic nanoparticles (Table 1).

Table 1: Comparative Performance of Different Nanocarrier Systems

Nanocarrier Type	Composition	Particle Size (nm)	Drug Loading (%)	Release Mechanism	Advantages	Limitations	Reference
Chitosan Nanoparticles	Chitosan polymer	50–200	60–85	Swelling + degradation	Biocompatible, mucoadhesive	Limited stability in saline	Agnihotri et al., 2004
PLGA Nanoparticles	Poly(lactic-co-glycolic acid)	100–300	50–80	Polymer degradation	Sustained release, predictable kinetics	Higher costs	Danhier et al., 2012
Liposomes	Phospholipids + cholesterol	50–200	40–70	Diffusion from core	Can encapsulate hydrophilic & lipophilic drugs	Instability in salts	Bozzuto & Molinari, 2015
Solid Lipid Nanoparticles	Solid lipid matrix	80–250	60–85	Diffusion through lipid	High physical stability	Lower hydrophilic drug loading	Mehnert & Mäder, 2012
Mesoporous Silica Nanoparticles	Silica, porous structure	50–150	70–90	Pore diffusion	High drug loading	Poor biodegradation	Vallet-Regí et al., 2007
Magnetic Nanoparticles	Iron oxide core	10–100	50–75	Functionalized diffusion	Targeted delivery	Bioaccumulation risk	Pankhurst et al., 2

Nanoparticle Fabrication and Characteristics:

Polymeric Nanoparticles

Chitosan Nanoparticles

Chitosan, a naturally occurring polysaccharide obtained from crustacean shell chitin, is widely utilized for its biodegradability and mucoadhesive properties. Chitosan nanoparticles can interact with negatively charged mucosal surfaces, improving oral absorption (Agnihotri et al., 2004). These

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nanoparticles are capable of encapsulating antibiotics and providing sustained release through polymer swelling and gradual erosion, thereby prolonging therapeutic effects.

PLGA Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) is a synthetic, biodegradable polymer approved by regulatory authorities. Antibiotics can be incorporated within the PLGA matrix and gradually released as the polymer degrades into lactic and glycolic acids. This controlled degradation allows sustained drug release over prolonged periods, reducing the need for frequent dosing (Danhier et al., 2012).

Lipid-Based Nanocarriers

Liposomes

Liposomes consist of a phospholipid bilayer surrounding an aqueous core, allowing hydrophilic drugs to be encapsulated in the core while lipophilic drugs integrate into the lipid membrane. This structure protects antibiotics from degradation and can enhance systemic circulation, improving therapeutic efficacy (Bozzuto & Molinari, 2015).

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are composed of a solid lipid core stabilized by surfactants. They protect sensitive drugs from hydrolytic and oxidative degradation, offer high physical stability, and enable controlled drug release (Mehnert & Mäder, 2012).

Inorganic Nanoparticles

Mesoporous Silica Nanoparticles

These nanoparticles feature a highly ordered porous structure that enables high drug-loading capacity and controlled diffusion. Surface functionalization can further modulate release profiles; however, limited biodegradability remains a significant challenge (Vallet Regí et al., 2007).

Magnetic Nanoparticles

Magnetic nanoparticles enable targeted drug delivery through external magnetic guidance, potentially reducing off-target effects. Nevertheless, concerns regarding their long-term fate and bioaccumulation currently restrict widespread application (Pankhurst et al., 2003).

Mechanisms of Controlled Drug Release:

Nano-encapsulation achieves sustained drug delivery through multiple mechanisms:

Diffusion-Controlled Release

Drug release from nanoparticles typically occurs via diffusion, where molecules move from regions of higher concentration within the carrier matrix to lower concentrations in the surrounding medium. The kinetics of this process are often described using Fick's laws of diffusion, which mathematically relate the rate of drug transfer to concentration gradients and the physicochemical properties of both the drug and the carrier. Factors such as nanoparticle size, porosity, polymer composition, and degree of crosslinking influence the diffusion rate, allowing the design of systems with controlled and sustained release profiles. Modeling drug release using Fickian diffusion provides valuable insights for optimizing therapeutic efficacy and minimizing dosing frequency.

Degradation-Controlled Release

iodegradable polymeric carriers release drugs through gradual degradation of the polymer matrix under physiological conditions. As the polymer undergoes hydrolysis or enzymatic breakdown, the encapsulated drug is steadily liberated, providing sustained therapeutic levels over extended periods. The rate of drug release can be modulated by altering polymer composition, molecular weight, crystallinity, or the degree of crosslinking, allowing precise control over dosage and timing. This controlled degradation not only enhances treatment efficacy by maintaining consistent drug concentrations

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but also reduces the frequency of administration and minimizes systemic side effects. Such systems are particularly advantageous in aquaculture, where prolonged release can improve fish health while limiting environmental contamination.

Stimuli-Responsive Release

Advanced nanoparticle carriers can be engineered to release antibiotics selectively in response to specific physiological stimuli, such as pH variations, enzymatic activity, or other microenvironmental changes at infection sites. For instance, acidic conditions present in infected or inflamed tissues can trigger the breakdown or swelling of pH-sensitive polymers, promoting localized drug release. Similarly, enzyme-responsive carriers exploit elevated levels of bacterial or host enzymes to initiate polymer degradation or bond cleavage, ensuring that the antibiotic is released primarily at the site of infection. By restricting drug release to targeted regions, these stimuli-responsive systems enhance therapeutic efficacy, reduce systemic drug exposure, and minimize off-target side effects, representing a promising strategy for precision antimicrobial delivery in aquaculture and other biomedical applications (Farokhzad & Langer, 2009).

Pharmacokinetic Advantages of Nano-Encapsulation:

Nano-encapsulation can significantly improve the pharmacokinetic properties of antibiotics. By enhancing absorption efficiency, promoting broader tissue distribution, protecting the drug from enzymatic degradation, and prolonging systemic retention, nanoscale carriers optimize therapeutic performance. For example, Mohan et al. (2015) reported that oxytetracycline delivered via nanoparticles resulted in higher survival rates and lower bacterial loads in tilapia compared with conventional dosing, highlighting the potential of nano-encapsulation to improve treatment outcomes in aquaculture.

***In Vivo* Efficacy and Therapeutic Outcomes:**

In vivo trials with fish models (e.g., Nile tilapia) have shown:

- Higher survival post-challenge with pathogenic bacteria
- Reduced antibiotic dosage requirements
- Improved feed conversion and growth performance
- Enhanced immune responses (lysozyme, complement activity)

Zhang et al. (2016) showed that nano-carried antibiotics improved therapeutic outcomes relative to free antibiotic treatment.

Environmental and Resistance Considerations:

Routine antibiotic use has led to accumulation of residues in sediments and water bodies, promoting resistant bacterial strains. Nano-encapsulation reduces the amount of antibiotic released into the environment and raises the local therapeutic concentration within fish tissues, decreasing selection pressure for resistance (Cabello et al., 2013; Kümmerer, 2009).

Toxicity and Safety Assessment:

Although nano-encapsulation improves drug performance, nanomaterials may pose:

- Oxidative stress
- Tissue inflammation
- Bioaccumulation
- Effects on non-target organisms

Researchers evaluate histopathology, oxidative stress biomarkers (MDA, SOD, CAT), and acute/chronic toxicity to ensure safety (Handy et al., 2011).

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Detailed Experimental Methodology:
Nanoparticle Preparation
Chitosan Nanoparticle Synthesis (Ionic Gelation)
1. Dissolve 1% chitosan in 1% acetic acid.
2. Add TPP solution dropwise under stirring.
3. Add antibiotic during formation.
4. Sonicate 5 minutes.
5. Centrifuge at 15,000 rpm, wash and freeze-dry.
(Agnihotri et al., 2004)

PLGA Nanoparticle Synthesis (Emulsion-Solvent Evaporation)
1. Dissolve PLGA and antibiotic in acetone.
2. Add to aqueous PVA under magnetic stirring.
3. Evaporate solvent; centrifuge and wash nanoparticles.
4. Freeze-dry for storage.
(Danhier et al., 2012)

Characterization Techniques

S.No.	Parameter	Tool
01	Particle size	DLS
02	Morphology	TEM/SEM
03	Charge	Zeta sizer
04	Encapsulation efficiency	UV-Vis/HPLC
05	Release profile	Dialysis method

***In Vivo* Treatment and Challenge**
1. Fish grouped (Control, Free antibiotic, Nano-encapsulated).
2. Administer antibiotic orally for 7–14 days.
3. Challenge with *A. hydrophila*.
4. Monitor survival, growth, immune function.
5. Tissue drug concentration measured by HPLC.
(Mohan et al., 2015; Zhang et al., 2016)

Statistical Analysis:
Triplicate experiments
Mean ± SD
One-way ANOVA ($p < 0.05$)
Software: SPSS or GraphPad Prism

Conclusion:
Nano-encapsulation offers a promising strategy to enhance antibiotic therapy in aquaculture by improving drug delivery, enabling controlled release, and minimizing environmental contamination. Although challenges such as toxicity, regulatory approval, and large-scale implementation remain, growing evidence indicates that nanocarrier systems have the potential to become effective tools for sustainable disease management in aquaculture.

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