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RECENT ADVANCES IN THE FORMULATION AND IN-VITRO EVALUATION OF N-ACETYLCYSTEINE DRUG DELIVERY SYSTEMS

Syed Gousefiroz*, B. Hepsibha[1], Ch. Venkata Durga Bhavani[2], A. Durga Prasad[3], K. John Raju[4]

[1]*Associate Professor, Department of Pharmaceutics, A.M. Reddy Memorial College of Pharmacy, Petlurivaripalem, Narasaraopet, Palnadu district, Andhra Pradesh.
[2,3,4,5]Research Scholors, A.M. Reddy Memorial College of Pharmacy, Petlurivaripalem, Narasaraopet, Palnadu District, Andhra Pradesh.

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***Corresponding Author: Dr. Syed Gousefiroz**

Associate Professor, Department of Pharmaceutics, A.M. Reddy Memorial College of Pharmacy, Petlurivaripalem, Narasaraopet, Palnadu district, Andhra Pradesh.

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ABSTRACT
N-acetylcysteine (NAC) is a cysteine-derived compound with antioxidant, mucolytic and anti-inflammatory properties and established clinical use in selected toxicological and respiratory settings. Its broad biological activity has encouraged investigation of NAC in localized and advanced drug-delivery systems intended to improve stability, residence time, release control and delivery to difficult biological targets. This review summarizes formulation and in-vitro evaluation approaches described in the supplied literature, with emphasis on polymeric and lipid nanoparticles, magnetic nanoparticles, conventional hydrogels, thermo-responsive hydrogels and multifunctional NAC systems. NAC-loaded lipid nanoparticles functionalized with D-amino acids were reported to have a mean hydrodynamic size of approximately 200 nm and demonstrated activity against Pseudomonas aeruginosa biofilms with low cytotoxicity and low hemolytic activity in the reported models. NAC-loaded sodium alginate–guar gum hydrogel showed an optimized formulation with a pH of 6.2 ± 0.168 and density of 1.026 ± 0.21, together with antimicrobial, antioxidant and cell-supporting potential. A methylcellulose-based thermo-responsive hydrogel demonstrated temperature-dependent gel formation and favorable fibroblast responses at lower tested NAC concentrations. The NAC–resveratrol–cyclodextrin multicomposite NACESOL™ showed greater reported biofilm reduction than free NAC at selected concentrations. Polymeric PLGA nanoparticles have additionally been investigated for pulmonary delivery, while poly-L-lysine-coated magnetic nanoparticles provide a route for MRI-assisted monitoring of NAC distribution and release. Across these systems, evaluation commonly includes particle size, polydispersity, zeta potential, drug content, encapsulation efficiency, spectroscopic and thermal characterization, morphology, release testing, stability, antioxidant activity, antimicrobial or antibiofilm assays and cell-compatibility studies. Because experimental conditions vary substantially between studies, release percentages and biological outcomes should not be compared without considering the formulation and assay conditions. Overall, the reviewed evidence supports continued development of NAC delivery platforms, while standardized testing and further in-vivo validation remain important.

KEYWORDS: N-acetylcysteine; drug delivery; nanoparticles; lipid nanoparticles; PLGA; hydrogels; thermo-responsive hydrogel; antibiofilm; antioxidant; MRI.

INTRODUCTION

N-acetylcysteine (NAC) is a derivative of the amino acid cysteine and is widely recognized for its ability to participate in thiol-based redox chemistry. The compound has antioxidant activity and is also used as a mucolytic agent. Its established medical use, together

with its biological effects in oxidative-stress and inflammatory models, has made NAC an attractive candidate for investigation in a variety of delivery strategies. The chemistry and biological actions of NAC have been reviewed extensively, including its role as a precursor for glutathione and its ability to influence redox-sensitive processes.[1]

Although NAC is pharmacologically useful, the performance of a formulation depends on the route of administration, the biological environment, the concentration delivered and the time for which an effective concentration can be maintained at the target site. In respiratory applications, for example, mucus forms a protective barrier that can influence the movement and retention of inhaled or locally administered materials.[3–5] Consequently, delivery systems designed to control particle characteristics, improve mucus interaction, or prolong local residence may be relevant to pulmonary NAC delivery.

Modern formulation research has therefore moved beyond simple solutions toward systems capable of changing the spatial and temporal profile of NAC exposure. Polymeric nanoparticles can provide a carrier for sustained release, lipid nanoparticles can be surface-functionalized for interaction with biofilms, hydrogels can maintain a drug-containing matrix at a local site, and thermo-responsive systems can be administered in a fluid state before forming a gel under physiological conditions. Magnetic nanoparticles add a further function by coupling drug loading with an imaging-capable carrier.[12]

NAC has also been explored in antimicrobial and antibiofilm contexts. Biofilms are structured microbial communities embedded in an extracellular matrix, and Pseudomonas aeruginosa biofilms are particularly relevant to chronic respiratory disease.[2] The supplied literature describes both free NAC and the multicomposite NACESOL™, which combines NAC with resveratrol and cyclodextrin components. The reported results suggest that formulation can influence antibiofilm activity and the concentration at which an observable effect occurs.

Hydrogel research represents another important branch of NAC delivery. A sodium alginate–guar gum formulation was investigated for diabetic wound management, while a methylcellulose-based thermo-responsive formulation was studied for wound and oral-ulcer applications. These systems illustrate two different formulation objectives: maintaining NAC within a hydrated local matrix and creating a formulation that changes physical state in response to temperature.

In addition to biological performance, advanced formulations require systematic pharmaceutical characterization. Particle size, polydispersity index, zeta potential, drug content and encapsulation efficiency provide information about nanoparticle quality. FTIR, DSC and XRPD can help assess chemical interactions and solid-state characteristics, while SEM or TEM provides morphological information. Drug-release testing, stability studies, antioxidant assays, antimicrobial testing and cell-viability experiments provide complementary information about formulation behavior [source material].

The purpose of this review is to organize the supplied literature into a coherent overview of NAC delivery approaches and their in-vitro evaluation. The emphasis is on reported formulation methods and results rather than on introducing unsupported experimental claims. Particular attention is given to how carrier selection changes the intended function of NAC and to the need for standardized comparisons among different delivery systems.

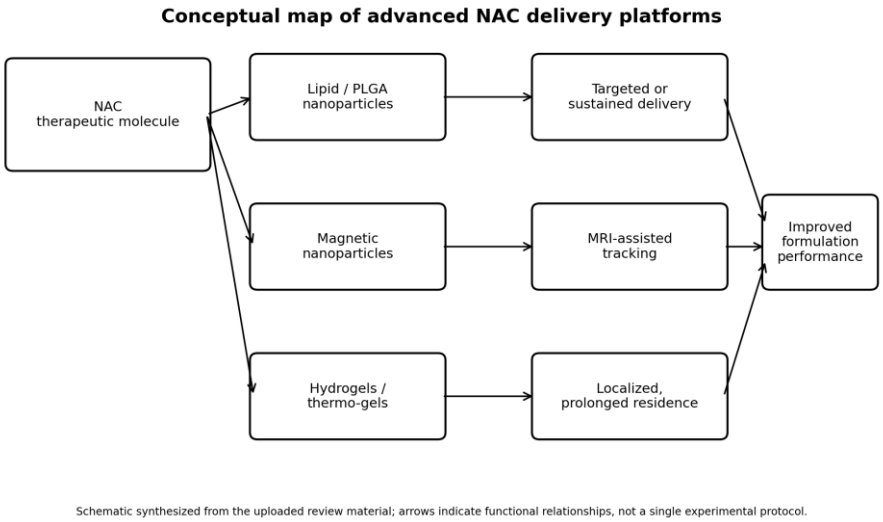

Figure 1: Conceptual relationship between NAC and major advanced delivery platforms described in the supplied literature.

METHOD

Literature-review approach

This article was prepared as a narrative review based primarily on the uploaded source document, which compiles literature concerning NAC formulation, advanced delivery systems and in-vitro evaluation. The source material was examined for information concerning formulation type, preparation approach, characterization methods, biological models, reported quantitative findings and conclusions. Where the source provided numerical results, those values were retained and presented as reported rather than recalculated into unsupported comparative claims.

The reviewed systems were grouped into five broad categories: (1) polymeric nanoparticles, particularly PLGA systems; (2) lipid nanoparticles and surface-functionalized lipid systems; (3) magnetic nanoparticles designed for imaging-assisted drug monitoring; (4) conventional and thermo-responsive hydrogels; and (5) multifunctional combination systems such as NACESOL™. Additional evidence concerning NAC stability and refrigerated platelet storage was considered as supporting material for the broader formulation context.

Formulation and characterization parameters

The source material describes a common set of evaluation parameters across different NAC formulations. Physical appearance and pH provide initial information about suitability and formulation consistency. For nanoparticle systems, particle size and PDI describe the size distribution, while zeta potential provides information related to surface charge and colloidal behavior. Drug content and encapsulation efficiency determine how much NAC is present and how successfully it has been incorporated into a carrier.

FTIR may be used to investigate characteristic functional groups and possible interactions between NAC and excipients. DSC provides information on thermal transitions, while XRPD can help distinguish crystalline and amorphous states. SEM and TEM provide morphological information. In-vitro release experiments are used to establish the temporal pattern of NAC liberation from the formulation. Biological testing can include antioxidant assays, antimicrobial or antibiofilm tests, cell-viability assays and other model-specific endpoints.

Biological and statistical evaluation

The supplied material describes the use of microbial biofilm models, mammalian cell models and, where relevant, pharmacokinetic measurements. In the antibiofilm work, P. aeruginosa biofilms were grown on stainless-steel discs and evaluated using viable bacterial counts and SEM–EDS. Cell studies included fibroblast or HepG2 models depending on the formulation and research question. The source also describes HPLC-based plasma drug measurement for pharmacokinetic analysis. Statistical procedures included ANOVA, t-tests, correlation analysis and dose-response analysis, with $p < 0.05$ used as a significance criterion in the reported work.

An important methodological limitation is that drug-release results from different studies cannot be interpreted solely from the final percentage released. Release medium, membrane type, sampling interval, test duration, temperature and sink conditions can differ substantially. Accordingly, this review reports formulation-specific observations and avoids treating heterogeneous release experiments as a single directly comparable dataset.

RESULT

1. Overview of advanced NAC delivery

The reviewed literature demonstrates that formulation technology can be used to alter the practical performance of NAC. Conventional NAC may be administered as a solution, but advanced systems attempt to address particular formulation or biological challenges: maintaining NAC at a target site, extending exposure, improving interaction with a microbial biofilm, reducing premature loss, or enabling monitoring of distribution. The resulting platforms are not interchangeable because each has been developed for a different delivery objective.

Nanoparticles are particularly useful when control over particle size, surface characteristics and release kinetics is desired. Hydrogels are suited to local administration because the polymer network can retain drug and water at the site of application. Magnetic systems add imaging functionality. Combination systems such as NACESOL™ illustrate an alternative strategy in which NAC is placed in a multicomponent environment intended to modify stability and biological activity.

2. Lipid nanoparticles for antibiofilm delivery

The supplied literature describes NAC-loaded lipid nanoparticles functionalized with D-amino acids for delivery toward mature biofilms. The optimized systems had a mean hydrodynamic diameter of approximately 200 nm, low polydispersity and high loading capacity. Storage stability was reported for up to six months in the study summarized by the source. In-vitro testing showed low cytotoxicity toward fibroblasts and low hemolytic activity.

Biological evaluation showed a reduction in P. aeruginosa biofilm biomass and bacterial viability. The effect was not reproduced to the same extent against Staphylococcus epidermidis, demonstrating that the observed activity was dependent on the microbial model rather than being universally transferable to all bacterial biofilms. The source also reports additional antibiofilm effects when NAC-loaded nanoparticles were combined with moxifloxacin. These observations support the concept of using a carrier to modify local exposure of NAC within a biofilm environment.

The formulation principle is important: D-amino-acid functionalization is intended to influence interaction with mature biofilm structures, while the lipid carrier provides the physical platform for NAC incorporation. In practice, the performance of such systems depends on particle size, surface composition, drug loading, colloidal stability and the biological characteristics of the target biofilm.

3. NAC-loaded PLGA nanoparticles for pulmonary delivery

PLGA is a biodegradable polymer commonly used as a carrier in controlled drug delivery. The supplied material describes NAC-loaded PLGA nanoparticles prepared using a double-emulsion approach and coated with lactose. Pluronic F127 was used in the described system to improve interaction with mucus and support pulmonary delivery. Characterization included particle size, PDI, zeta potential, encapsulation efficiency, morphology, drug release and lung deposition.

The formulation was designed for sustained pulmonary delivery, and the source reports a release period extending to approximately 48 hours. The use of lactose coating and mucus-related surface modification reflects an effort to improve the suitability of the particles for inhaled delivery. The source also discusses the possibility that mucus-penetrating NAC-PLGA particles could improve lung retention and potentially reduce reliance on repeated systemic administration, although this concept requires further validation.

The methodological importance of this system lies in the combination of pharmaceutical characterization with deposition and biological testing. A formulation intended for pulmonary administration cannot be evaluated only by particle size; deposition behavior, interaction with mucus, release kinetics and cellular responses all contribute to its performance.

4. Magnetic nanoparticle-assisted NAC delivery

A distinct approach involved adsorption of NAC onto poly-L-lysine-coated iron oxide magnetic nanoparticles. The objective was not only to carry NAC but also to investigate whether magnetic resonance imaging could be used to monitor the distribution and release behavior of the drug. In the optimized sample described in the supplied source, the hydrodynamic particle size was 154 nm, PDI was 0.22 and zeta potential was approximately +32 mV. The reported system showed good stability under the tested physiological conditions and no cytotoxicity in the investigated cellular model.

MRI relaxometry demonstrated that adsorption of NAC altered the relaxation properties of the magnetic nanoparticles. This creates the possibility of distinguishing particles with and without adsorbed NAC and therefore using imaging measurements as an indirect tool for monitoring drug distribution. The source identifies this as a foundation for further studies of spatial NAC distribution in the lungs.

This system illustrates a multifunctional formulation concept: the carrier contributes both a delivery function and an imaging function. Such systems are scientifically useful because drug localization can become an experimentally measurable property rather than an assumption. Nevertheless, imaging performance, drug loading, biological compatibility and the behavior of the carrier after administration all require independent validation.

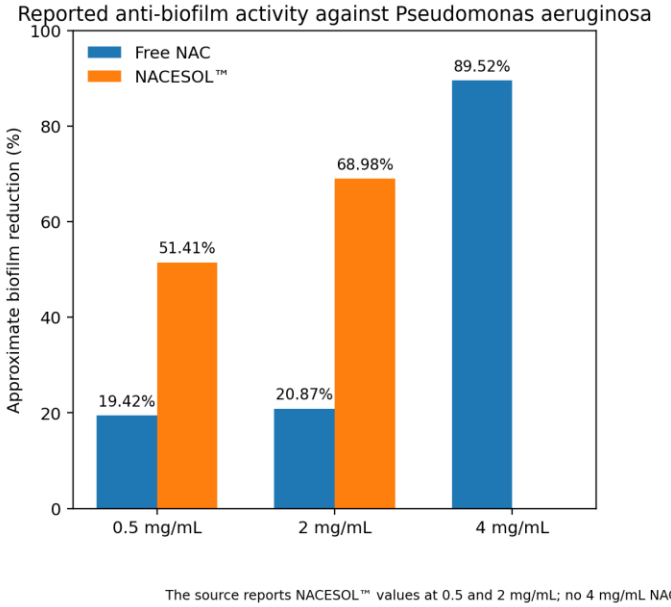

Figure 2: Approximate P. aeruginosa biofilm reduction reported for free NAC and NACESOL™ at the concentrations specified in the supplied material.

5. NAC-loaded sodium alginate–guar gum hydrogel

Hydrogels provide a hydrated polymeric environment that can retain a drug at a local application site. The supplied material describes a NAC-loaded sodium alginate–guar gum hydrogel developed for diabetic wound management. Four polymer ratios—1:1, 1:2, 1:3 and 2:1—were investigated. The F3 formulation was identified as the optimized formulation, with a reported pH of 6.2 ± 0.168 and density of 1.026 ± 0.21.

The optimized hydrogel was assessed for in-vitro drug release and antimicrobial activity against P. aeruginosa, Escherichia coli, Staphylococcus aureus and Candida albicans. The source further reports potential to support cell adhesion and proliferation and describes antioxidant and antimicrobial activity. These endpoints are relevant to wound-care formulation because the desired system must provide more than drug release alone; it should also remain compatible with tissue and provide a local environment appropriate for the intended application.

The use of two polymers provides an opportunity to modify gel structure and handling characteristics by changing the polymer ratio. However, the optimum ratio in one formulation cannot automatically be transferred to another formulation because polymer grade, concentration, crosslinking, drug concentration and testing conditions may change the final properties.

6. Thermo-responsive methylcellulose NAC hydrogel

A thermo-responsive methylcellulose-based NAC hydrogel was investigated for wound and oral-ulcer applications. The major formulation concept is that the material can be administered in a relatively fluid state and subsequently undergo temperature-dependent gel formation under physiological conditions. Such behavior may increase residence time at the target site compared with a formulation that remains freely mobile after administration.

Human fibroblast testing described in the source indicated favorable cellular responses at NAC concentrations of 1–10%, while viability decreased at the highest tested concentration of 20%. The concentration-dependent finding is important because it shows why formulation optimization cannot be separated from dose optimization. Increasing the amount of NAC does not necessarily produce a proportional increase in biological benefit and may adversely affect cell responses at sufficiently high concentrations.

For local wound or oral-ulcer applications, thermo-responsive gelation may also reduce formulation leakage and improve contact time. The system therefore combines a physical trigger—temperature—with a pharmaceutical objective—localized NAC delivery. Further studies are required to establish long-term stability, release behavior and in-vivo tissue compatibility.

7. NACESOL™ and multifunctional antibiofilm delivery

NACESOL™ is described in the supplied material as a NAC–resveratrol–cyclodextrin multicomposite. The formulation concept combines NAC with additional components intended to modify stability and antioxidant or antibiofilm performance. Against P. aeruginosa biofilms, free NAC produced approximately 19.42%, 20.87% and 89.52% biofilm reduction at 0.5, 2 and 4 mg/mL, respectively. NACESOL™ produced approximately 51.41% and 68.98% reduction at 0.5 and 2 mg/mL, respectively.

The supplied dataset does not provide a NACESOL™ value at 4 mg/mL, so no direct conclusion should be made for that concentration. At the two concentrations where both formulations were reported, the multicomposite showed higher numerical biofilm reduction than free NAC. This finding is consistent with the formulation objective of modifying the local chemical and physical environment of NAC. It also demonstrates why a delivery system should be evaluated at multiple concentrations rather than at a single dose.

Biofilm results should be interpreted together with the assay design. The source describes biofilms grown on stainless-steel discs for 48 hours, with viable bacteria assessed using CFU/mL and structural information obtained using SEM–EDS. These methods provide complementary information: viable counts address bacterial survival, whereas microscopy provides information about changes in biofilm structure and morphology.

8. Other formulation and stability observations

The supplied material also includes NAC stability observations. A NAC solution at 25 mg/mL remained stable for approximately 24 hours at room temperature and four days under refrigeration in the reported conditions. Addition of zinc gluconate extended the reported stability to four days at room temperature and eight days at 5 ± 3°C. These observations illustrate a general formulation principle: stability is affected by both storage conditions and the composition of the formulation.

NAC has additionally been investigated during refrigerated platelet storage. The source describes antioxidant and potential antiplatelet effects during storage at approximately 4°C, including reduction of oxidative damage and platelet activation and preservation of platelet characteristics. This application is conceptually different from nanoparticle drug delivery, but it reinforces the relevance of NAC's redox activity in pharmaceutical and biological storage environments.

The source also mentions an intratympanic NAC hydrogel designed to form a gel within the middle ear after administration. The intended objective was controlled and prolonged local release while potentially

reducing drug leakage and repeated administration. Because the supplied material does not provide a complete set of numerical results for this formulation, it is presented here as a formulation concept rather than as a quantitatively compared system.

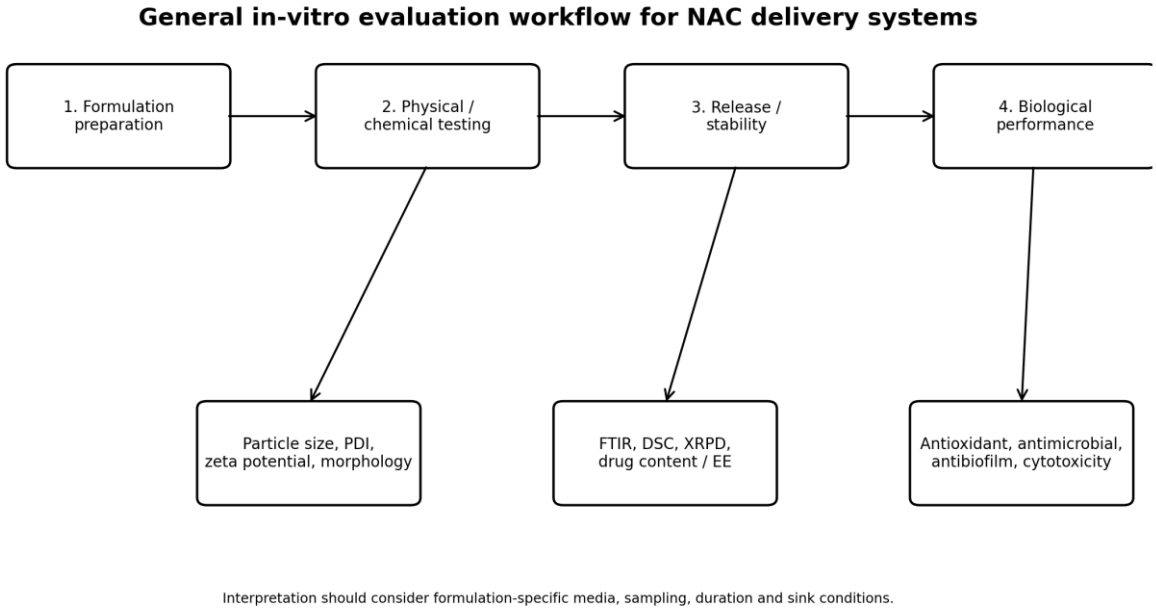

Figure 3: Generalized in-vitro evaluation workflow synthesized from the characterization methods described in the supplied material.

9. Comparative formulation considerations

Delivery platform	Primary purpose	Reported/expected evaluation focus	Key observation from supplied material
Lipid nanoparticles	Biofilm-directed delivery	Size, PDI, loading, stability, cytotoxicity, hemolysis, antibiofilm assays	~200 nm optimized system; activity reported against P. aeruginosa
PLGA nanoparticles	Pulmonary sustained delivery	Particle properties, encapsulation, morphology, release, deposition	Double-emulsion preparation; lactose coating; release reported to ~48 h
Magnetic nanoparticles	Delivery plus imaging	Size, PDI, zeta potential, magnetic properties, cytotoxicity, MRI	154 nm, PDI 0.22, +32 mV in optimized sample
Alginate–guar gum hydrogel	Localized wound delivery	pH, density, release, antimicrobial and cell studies	F3 reported pH 6.2 ± 0.168 and density 1.026 ± 0.21
Thermo-responsive hydrogel	Localized, temperature-triggered gelation	Gelation, release, fibroblast response	Favorable fibroblast response at 1–10% NAC; lower viability at 20%
NACESOL™	Multicomponent antibiofilm activity	Biofilm reduction, microbial viability, structural analysis	Higher reported reduction than free NAC at 0.5 and 2 mg/mL

10. Overall interpretation of the reviewed results

Across the reviewed systems, the major recurring advantage of advanced delivery is the ability to separate the pharmacological activity of NAC from the limitations of a simple solution. Nanoparticles can modify the spatial distribution and duration of exposure. Hydrogels can retain NAC at a local site. Thermo-responsive systems add a physical trigger for gel formation. Magnetic nanoparticles can add an imaging function. Combination systems can alter the local chemical environment and potentially increase biological activity at selected concentrations.

The results also show that there is no single universal formulation parameter that predicts biological performance. Particle size alone does not establish

antibiofilm activity; a hydrogel's pH does not establish wound-healing efficacy; and a high encapsulation efficiency does not necessarily mean that release will be optimal. Formulation development therefore requires a chain of evidence linking physical properties to release behavior and then to biological performance.

Another important observation is the influence of concentration. The thermo-responsive hydrogel study showed reduced viability at the highest tested NAC concentration, while the NACESOL™ data demonstrate concentration-dependent antibiofilm activity. These findings support careful dose selection and controlled exposure. A formulation that provides sustained or localized delivery may allow a target concentration to be maintained while avoiding unnecessarily high exposure elsewhere.

Finally, the literature remains heterogeneous. Different studies use different polymers, carrier structures, biological models, concentrations and release methods. The supplied source explicitly cautions against comparing release percentages without considering the experimental conditions. Standardized reporting would improve the ability to compare future NAC delivery systems and identify reproducible formulation advantages.

CONCLUSION

N-acetylcysteine remains a versatile therapeutic molecule whose antioxidant, mucolytic and anti-inflammatory properties support investigation across multiple pharmaceutical applications. The literature summarized in the supplied material demonstrates a broad range of formulation strategies intended to improve how NAC is delivered rather than changing the fundamental activity of the molecule.

The reported in-vitro findings are encouraging but formulation-specific. NAC-loaded lipid nanoparticles showed activity against P. aeruginosa biofilms, the alginate–guar gum hydrogel demonstrated antimicrobial and cell-supporting potential, and the methylcellulose hydrogel showed temperature-dependent gelation with concentration-dependent fibroblast responses.

For future development, greater standardization is needed in particle characterization, release testing, stability protocols and biological assays. Comparative studies should use clearly defined concentrations, matched experimental conditions and appropriate controls. In-vitro findings should then be followed by suitable in-vivo studies before therapeutic conclusions are generalized. Overall, the evidence supports continued investigation of NAC delivery systems, particularly those that integrate controlled release, localized administration, biological compatibility and measurable targeting or monitoring functions.

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