



Bromelain–N-Acetyl Cysteine (BromAc) as a Multifunctional Therapeutic Platform: Polymer-Based Formulation Strategies and Translational Perspectives

S.Poojitha¹ and M.P.Kusuma²

^{1,2}RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, India

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ABSTRACT

Bromelain is a proteolytic protein complex inferred basically from *Ananas comosus* that shows anti-inflammatory, mucolytic, antimicrobial, immunomodulatory, and anticancer properties. In spite of its wide restorative potential, clinical interpretation is constrained by enzymatic precariousness, quick debasement, and variable bioavailability. This audit comprehensively analyses current extraction innovations, progressed polymer-based definitions, and synergistic combination procedures outlined to upgrade bromelain solidness and helpful execution. Customary refinement approaches such as ammonium sulphate precipitation and layer filtration are examined nearby present day fluid two-phase frameworks and polymer-assisted extraction procedures that make strides abdicate, virtue, and supportability. Accentuation is set on nano-enabled conveyance platforms—including chitosan nanoparticles, PLGA-based frameworks, lipid–polymer crossover nanoparticles, alginate networks, hydrogels, and nanoemulsions—which give controlled discharge, security against proteolytic corruption, improved mucosal attachment, and progressed bioavailability. Specific consideration is given to the bromelain–N-acetyl cysteine (BromAc) combination, which illustrates auxiliary collaboration through disulphide bond lessening and proteolytic cleavage, empowering viable mucin corruption, biofilm disturbance, antiviral movement, and upgraded anticancer impacts. Extra combination procedures with polyphenols and anti-microbials are too investigated for their complementary robotic benefits. In spite of the fact that preclinical prove unequivocally underpins made strides pharmacological execution through polymeric and combination approaches, challenges stay with respect to long-term solidness, measurement optimization, and large-scale fabricating. Proceeded translational and clinical examinations are vital to completely set up bromelain-based definitions as standardized restorative stages over oncology, irresistible infection, respiratory medication, and wound management.

Keywords: Bromelain; *Ananas comosus*; N-acetyl cysteine; BromAc; polymeric nanoparticles; chitosan; PLGA; lipid–polymer half breed nanoparticles; alginate hydrogels; nanoemulsion; watery two-phase frameworks; biofilm disturbance; mucolytic treatment; controlled discharge; chemical stabilization.

A. INTRODUCTION

Bromelain is a flexible protein complex inferred fundamentally from pineapple (*Ananas comosus*) that has earned noteworthy consideration in both pharmaceutical and nutraceutical businesses. This proteolytic chemical blend shows exceptional helpful properties counting anti-inflammatory, antithrombotic, anticancer, and immunomodulatory impacts, nearby applications in wound mending and circulation improvement¹. In spite of its far reaching utilization and set up security profile, the total atomic component of bromelain's activity remains mostly unidentified, showing the require for assist investigate to illustrate its natural pathways and maximize its clinical potential.

Bromelain, a proteolytic protein inferred from *Ananas comosus*, shows diverse sorts of synergistic action depending on the compound with which it is combined. When utilized with N-acetyl cysteine (NAC), collaboration happens essentially at the basic level, where NAC decreases disulphide crosslinks and bromelain cleaves peptide spines, coming about in successful corruption of bodily fluid and biofilm networks. This combination is especially solid in mucolytic and biofilm-disrupting applications and has too appeared significance in COVID-19 treatment. The BromAc definition illustrates in vitro viability against SARS-CoV-2 by disturbing viral spike and envelope proteins through combined proteolytic and disulphide bond-breaking components, creating concentration-dependent viral inactivation against both wild-type and mutant strains.

In differentiate, bromelain combined with quercetin applies synergistic impacts basically through antioxidant and anti-inflammatory signaling pathways by balancing intracellular components. Additionally, bromelain–curcumin combinations upgrade anti-



inflammatory and anticancer signaling, possibly advancing apoptosis and resistant control in preclinical thinks about. These polyphenol-based combinations fundamentally impact intracellular signaling or maybe than specifically corrupting basic boundaries. When matched with tetracycline anti-microbials, bromelain upgrades antibacterial movement by disturbing protein components of biofilms and kindled tissues, subsequently moving forward sedate infiltration. Hence, the level of cooperative energy contrasts: basic framework debasement with NAC, signaling balance with polyphenols, and anti-microbial bolster with tetracyclines. Bromelain's great bioavailability, negligible side impacts, and capacity to be retained from the gastrointestinal tract without misfortune of movement encourage back its wide systemic and clinical applications.

B. Method of Extraction

i. Traditional Extraction Methods

The extraction of bromelain from pineapple sources has advanced essentially over the long time, with analysts creating progressively advanced and productive techniques. Conventional extraction methods regularly include numerous decontamination steps counting microfiltration, ultrafiltration, ammonium sulphate precipitation, ultracentrifugation, and freeze-drying forms to accomplish tall protein concentration and recuperation rates. One comprehensive approach combines semipermeable film forms with ammonium sulphate extraction, accomplishing protein concentration of 98% and recuperation rates drawing nearer 100%⁵. In any case, these routine strategies may result in movement misfortunes amid ultrafiltration due to adsorption on layers, which are affected by the degree of concentration achieved.

ii. Aqueous Two-Phase Frameworks (ATPS)

Recent propels have centred on fluid two-phase extraction frameworks, which offer noteworthy preferences in terms of productivity and natural maintainability. These frameworks utilize different polymer combinations to accomplish particular bromelain extraction and purification:

a) PEG-Based Frameworks: Polyethylene glycol (PEG) combined with phosphate salts has demonstrated profoundly viable for bromelain recuperation. Considerers have illustrated that PEG/phosphate watery biphasic frameworks can accomplish tall particular movement, considerable decontamination components, and sensible yields in a single-step, cost-efficient strategy. Ideal conditions have been recognized utilizing 18% PEG6000-17% MgSO₄, which upgrades both virtue and movement recovery⁷. Beneath these conditions, bromelain keeps up tall action at pH 8.0 and 60°C, in spite of the fact that action decreases with expanding NaCl concentrations.

b) Thermo sensitive Copolymer Frameworks: Progressed extraction strategies utilize thermo sensitive triblock copolymers like EOPOEO combined with K₂HPO₄. These frameworks accomplish chemical movement recuperation of 68.6% and a decontamination calculate of 6.53 beneath ideal conditions⁸. The EOPOEO-rich stage and salt can be reused, yielding up to 60% chemical recuperation, making this approach both productive and sustainable.

c) Micellar Frameworks: Fluid two-phase micellar frameworks (ATPMS) utilizing particular surfactant concentrations have been effectively created for extricating bromelain from pineapple peel squander. Ideal conditions incorporate 0.5 M KI with 3% TX-114 at pH 6.0 and 40°C, empowering the extraction of high-value bromelain appropriate for restorative formulations.

C. Polymer-Based Extraction Methods

Innovative polymer-based approaches have risen as economical choices to conventional extraction methods:

i. Carrageenan Complex Arrangement: A feasible approach utilizing carrageenan precipitation accomplishes tall bromelain recuperation yields of 80-90% with fabulous virtue utilizing moo polymer concentrations of as it were 0.2-0.3% w/v. This strategy kills the require for natural solvents or inorganic salts, giving a cost-effective and ecologically neighbourly arrangement for bromelain extraction from pineapple residues.

ii. Polysaccharide Complexes: The optimization of polymer concentration in polysaccharide complex arrangement has illustrated momentous proficiency in bromelain separation from pineapple by-products. This straightforward precipitation strategy gives tall yields and immaculateness whereas keeping up natural sustainability.

iii. Optimized ATPS Conditions: Investigate has distinguished ideal conditions utilizing 18% PEG6000-17% MgSO₄, which improves both immaculateness and action recuperation. Beneath these conditions, bromelain illustrates special apportioning to the



PEG-rich stage, encouraging effective division from other proteins and contaminants. The system's viability can be encourage upgraded by altering pH, temperature, and polymer atomic weight to maximize extraction efficiency.

iv. Ionic Liquid-ATPS Combinations: Progressed ATPS details joining ionic fluids with PEG have appeared guarantee for particular biomolecule extraction. These frameworks offer moved forward stage division characteristics and upgraded selectivity for bromelain, in spite of the fact that advance optimization is required for large-scale applications.

D. Developed Formulations and Polymer Systems

1. Nanoparticle-Based Formulations

a. Chitosan Nanoparticles

Bromelain, determined from *Ananas comosus*, is a restoratively important proteolytic protein but is exceedingly helpless to flimsiness and enzymatic corruption in fluid and physiological situations. Embodiment inside chitosan nanoparticles altogether moves forward its soundness by securing the dynamic proteolytic location and empowering controlled, maintained discharge. Tall embodiment proficiency and protected enzymatic action illustrate that chitosan is a viable carrier framework. Freeze-dried definitions utilizing maltose as a lyoprotectant advance improve capacity steadiness and keep up enzymatic movement beneath refrigerated conditions. The consolidation of ascorbic corrosive amid nanoparticle blend can make strides catalytic action by securing the dynamic cysteine build up from oxidative harm, in spite of the fact that slow movement decrease still happens over time.

The viability of chitosan-based frameworks depends emphatically on polymer concentration, which impacts molecule arrangement, mechanical quality, and sedate discharge behaviour. In nanoparticle definitions, concentrations between 0.1–0.5% w/v, especially around 0.2% w/v, give ideal solidness and embodiment proficiency. For hydrogel frameworks in wound mending, higher concentrations of 1–2% w/v are required to guarantee satisfactory mechanical astuteness and bio adhesion. In coating applications, 0.5–1% w/v concentrations empower uniform scope and controlled medicate dissemination whereas minimizing burst discharge. Generally, exact optimization of detailing procedures and chitosan concentration is basic to maximize bromelain's soundness and helpful performance.

b. PLGA-Based Nanoparticles

Poly (lactic-co-glycolic corrosive) (PLGA) polymers have risen as compelling carriers for bromelain conveyance, especially in verbal definitions, due to their biodegradability and biocompatibility. PLGA-based nanoparticles illustrate moved forward embodiment proficiency, improved steadiness, and prevalent restorative execution compared to routine definitions. These frameworks offer assistance secure bromelain from enzymatic corruption in the gastrointestinal tract, subsequently moving forward its bioavailability.

Advanced lipid–polymer cross breed nanoparticles combining PLGA with chitosan and phosphatidylcholine (PLGA-PC) have advance optimized verbal conveyance. These crossover frameworks address bromelain's moo assimilation by giving controlled discharge, upgraded intestinal soundness, and moved forward mucosal interaction. Compared to PLGA-only nanoparticles, PLGA-PC definitions display higher epitome effectiveness and more noteworthy intestinal uptake.

Polymer concentration plays a basic part in deciding molecule measure, sedate stacking, and corruption rate. In standard nanoparticle frameworks, PLGA concentrations around 10% w/v in the natural stage are commonly utilized to accomplish ideal lattice thickness and emulsification properties, whereas concentrations between 5–20% w/v may be chosen depending on the conveyance objective. Lower concentrations may decrease medicate stacking productivity, though higher levels can increment thickness and molecule measure. In lipid–polymer crossover frameworks, PLGA concentrations of 5–15% w/v combined with phosphatidylcholine at 2–5% w/v improve solidness, minimize burst discharge, and advance controlled medicate discharge. In general, exact optimization of PLGA concentration and half breed composition is fundamental for accomplishing moved forward verbal bioavailability and helpful viability of bromelain formulations.

c. Alginate-Based Nanoparticles

Alginate-based conveyance frameworks give fabulous biocompatibility and pH-responsive discharge properties, making them reasonable for focused on bromelain conveyance. Alginate–chitosan nanoparticle definitions consolidated into chitosan hydrogels have illustrated critical debridement proficiency and improved re-epithelialization in burn wound models. These frameworks kept



up steady bromelain action for up to six months and accomplished optimized medicate discharge inside four hours, highlighting their restorative potential.

Alginate–HPMC ionically cross-linked nanospheres have too appeared promising comes about for bromelain conveyance as antiplatelet operators. Ideal alginate: HPMC proportions of 1:1 and 1:2 delivered controlled molecule measure, favourable morphology, tall capture proficiency, and fitting swelling behaviour for verbal applications. Polymer concentration plays a basic part in deciding gel quality, embodiment productivity, and discharge characteristics. In dot details, alginate concentrations of 2–3% w/v are ordinarily ideal for uniform globule arrangement and proficient inotropic gelation, whereas lower concentrations may deliver delicate structures and higher concentrations may restrain medicate diffusion.

For hydrogel frameworks such as alginate–guar gum combinations, add up to polymer concentrations of 1.5–2.5% w/v give adjusted mechanical quality and controlled discharge. In nanoparticle definitions, lower alginate concentrations of 0.5–1% w/v, especially when combined with chitosan, bolster steady polyelectrolyte complex arrangement and nanoscale molecule advancement. In general, exact optimization of alginate concentration empowers viable control of basic keenness, sedate stacking, and discharge energy over different bromelain conveyance systems.

2. Gel-Based Formulations

Gel-based frameworks have been broadly created to move forward the topical and localized conveyance of bromelain inferred from *Ananas comosus*. These definitions upgrade chemical solidness, drag out home time at the application location, and give controlled discharge, in this manner moving forward helpful viability compared to free chemical preparations.

a) Carbopol-Based Systems

Carbopol polymers, especially Carbopol 940, are broadly utilized in topical bromelain details due to their amazing consistency control, bio adhesion, and skin compatibility. A 1% w/v bromelain–carbopol gel has illustrated ideal burn wound recuperating in creature models, advancing quicker recuperation and total wound closure without aggravation. In dental applications, in any case, higher bromelain concentrations of around 10% were more viable in extending intertubular dentin, demonstrating that ideal dosing depends on the substrate and clinical sign. Carbopol-based bromelain gels utilized for chemo mechanical caries evacuation, particularly when combined with chloramine or chlorhexidine, have appeared promising enzymatic productivity and moved forward surface characteristics, in spite of the fact that advance clinical approval is required.

When defined as a bromelain–NAC combination, carbopol gels upgrade both proteolytic and mucolytic movement. The polymer framework guarantees drawn out tissue contact, whereas NAC encourages disulphide bond decrease and bromelain advances protein debasement, making the double framework especially advantageous in wound care and dental medicines. Carbopol gel definitions regularly utilize polymer concentrations between 0.4–1.5% w/v, depending on the wanted rheological properties and application sort. For topical burn applications, 1% w/v Carbopol 940 gives ideal thickness, basic keenness, and spread ability, while lower concentrations may decrease maintenance and higher concentrations may prevent sedate dissemination. In dental gels, concentrations of 0.8–1.2% w/v adjust grip and restorative movement, whereas shower gels by and large utilize lower concentrations around 0.4% w/v to keep up spray ability. By and large, exact optimization of Carbopol concentration is basic to control rheology, soundness, and medicate discharge execution over topical, dental, and spray-based bromelain formulations.

b) Alternative Gel Systems

Other polymeric hydrogels have too appeared potential:

- PVA-co-AAm hydrogels illustrate tall protein joining proficiency (~91%) and solid enzymatic action maintenance (~89%), advertising controlled discharge and mechanical compatibility reasonable for non-invasive burn and incendiary treatments.
- Lutrol F127 (poloxamer-based gels) appear improved penetrability for topical bromelain delivery.
- Alginate–guar gum hydrogels give defensive epitome, progressed steadiness beneath acidic conditions, and controlled intestinal discharge behaviour, making them promising for verbal or systemic conveyance frameworks.



3. Microsphere and Bead Formulations

a. Chitosan-Coated Microspheres

Chitosan-coated microspheres cross-linked with glutaraldehyde have demonstrated successful as bromelain carriers, accomplishing tall embodiment proficiency (87.14%) and controlled discharge (79.92% in the intestinal environment). This demonstrates their potential for creating slow-release definitions, in spite of the fact that assist examinations are required to address steadiness beneath gastric conditions and potential adaptability for commercial applications.

Chitosan-coated microspheres outlined for intestinal focusing on illustrate pH-dependent discharge behaviour, with negligible discharge in acidic gastric conditions and significant discharge in the intestinal environment. Tall coating proficiency and focused on discharge profiles make these frameworks promising for verbal conveyance applications. Generally, chitosan nanoparticle frameworks give improved steadiness, moved forward wound recuperating execution, delayed discharge energy, and focused on conveyance potential compared to free bromelain formulations.

b. Alginate-Pectin Beads

To address bromelain corruption in stomach corrosive, fruitful epitome in alginate-pectin globules (AP) has been accomplished with tall epitome productivity for controlled intestinal discharge. The study illustrated that AP globules have favorable discharge characteristics, promising potential in ensuring bromelain amid verbal organization. Be that as it may, antiplatelet movement watched in vitro was strikingly lower compared to the dialysis division, showing advance optimization may be required for improved efficacy.

4. Nano emulsion Formulations

Recent progresses have driven to the advancement of bromelain nanoemulsions for improved skin porousness: Considers effectively created an optimized bromelain Nano emulsion definition with upgraded skin penetrability and negligible misfortune of proteolytic action. Among three tried details, Equation 3, containing higher concentrations of Tween 80 and littler sums of lecithin, illustrated predominant execution with bead measure of 22.04 nm and penetrability rate of 587.56 $\mu\text{g}/\text{cm}^2$ inside 30 minutes. This definition appears guarantee for advance investigation of its anti-bacterial potential in future studies.

Advanced Definition Approaches:

- **Liposomal Epitome:** Liposome-based conveyance frameworks have been created to ensure bromelain from corruption and make strides its bioavailability. These details appear upgraded helpful potential in wound mending applications.
- **Membrane-Based Frameworks:** Carboxymethyl cellulose/acetylated arrowroot starch films containing bromelain-loaded nanoparticles and liposomes have been created for cutaneous wound recuperating applications. These details illustrate moved forward mechanical properties and prevalent mending potential, with bromelain-loaded nanoparticles and liposomes appearing the best comes about in in vivo assays.

E. Created Definitions and Polymer Systems

1. Basic Arrangement Formulations

The most clear detailing approach includes coordinate combination of bromelain and NAC in watery arrangements. For pseudomyxoma peritonei treatment, analysts optimized a detailing containing 300 $\mu\text{g}/\text{ml}$ bromelain and 4% NAC at pH 7.0, which illustrated successful mucin disintegration both in vitro and in rodent models inside 72 hours without harmfulness. This concentration proportion has ended up a reference point for numerous consequent detailing developments.

2. Progressed Conveyance Systems

Mucoadhesive Nanocarriers

For respiratory applications, mucoadhesive cationic bromelain-laden Nano carriers (Br-EuNCs) have been created to upgrade aviation route conveyance. These definitions essentially upgrade bromelain solidness, bioavailability, and helpful viability, drawing out maintenance time and progressing mucin authoritative whereas viably decreasing asthma-associated symptoms.



3. Polyurethane Matrices

Polyurethane-based sedate conveyance frameworks have been synthesized for bromelain conveyance, illustrating medium steadiness, unbiased pH, and controlled sedate discharge profiles. Their non-irritative and moo cytotoxicity properties highlight their appropriateness for clinical applications.

F. Bromelain-Antibiotic Combination Formulations

Molecular Interaction Studies

Research has explored the intelligent between bromelain and different tetracycline anti-microbials. Thinks about conclude that bromelain interatomic with demeclocycline, minocycline, and tetracycline anti-microbials through hydrogen bonds and hydrophobic intuitive, as affirmed by atomic modelling and free official vitality calculations. Whereas these intuitive are vivaciously favourable, their clinical suggestions, particularly in settings where bromelain utilize is combined with anti-microbials, warrant assist investigation. he solidness of bromelain-antibiotic combinations is affected by different variables counting pH, temperature, and polymer arrangements. Investigate demonstrates that bromelain's ideal soundness happens at pH 5.0, with polyethylene glycol (PEG) improving solidness whereas polyacrylic corrosive (PAA) adversely influences it. This knowledge gives important direction for defining bromelain with anti-microbials in polymeric conveyance systems.

G. Bromelain-Resveratrol Combination Formulations

i. Nano-Enabled Conveyance Systems

The combination definition of bromelain and resveratrol conveyed through polymer nanoparticles addresses the impediments of bromelain's destitute bioavailability and moo blood-brain obstruction penetrability. Nano-enabled conveyance frameworks improve helpful viability and give a promising technique for broader clinical applications. Be that as it may, encourage investigate is required to set up ideal dosing and steady pharmacokinetic profiles.

ii. Polymeric Nanoparticle Applications

Polymeric nanoparticles serve as viable conveyance frameworks for bromelain-resveratrol combinations, upgrading the steadiness, bioavailability, and restorative effectiveness of bromelain whereas tending to confinements related to protein denaturation and basic changes. These definitions speak to a critical headway in overcoming bromelain's inborn flimsiness and growing its clinical applications.

H. Future Points of view and Investigate Bearings

The improvement of bromelain-N-acetyl cysteine (NAC) combination details is an extending range of inquire about with noteworthy restorative potential. Progressed nanocarrier frameworks are being investigated to accomplish focused on conveyance and controlled discharge of both components. These approaches may upgrade adequacy whereas minimizing systemic side impacts. In spite of the fact that in vitro and creature considers are promising, exhaustive clinical assessments are required to build up security, pharmacokinetics, and helpful viability in humans.

Optimization of polymer sorts, concentrations, and bromelain-NAC proportions remains vital for accomplishing ideal sedate stacking and discharge characteristics. Combining these details with customary treatments, especially in cancer and provocative infections, may deliver synergistic benefits. In any case, bromelain's restricted steadiness and progressive misfortune of proteolytic action posture noteworthy definition challenges. Methodologies such as chemical epitome and the utilize of stabilizing excipients are beneath examination. Also, scaling up complex nanoparticle frameworks for commercial generation requires the advancement of cost-effective and reproducible fabricating methods.

Conclusion

The bromelain-N-acetylcysteine (NAC) combination speaks to a promising restorative technique with applications over numerous therapeutic disciplines. The synergistic interaction between bromelain's proteolytic action and NAC's mucolytic and antioxidant properties empowers more viable administration of complex obsessive forms than either specialist alone. This combination is especially advantageous in disturbing mucin systems, lessening oxidative push, and upgrading medicate infiltration. Current prove bolsters its potential adequacy in oncology, particularly in peritoneal surface malignancies, as well as in irresistible maladies including biofilm arrangement and conditions characterized by over the top mucin production.



Although preclinical information are solid and early clinical discoveries are empowering, advance ponders are required to optimize dosing procedures and affirm long-term security. Progressed detailing approaches, counting nanoparticle and polymer-based conveyance frameworks, have progressed solidness, bioavailability, and focused on conveyance. Polymers such as chitosan, carbopol, and PLGA play a significant part in controlling sedate discharge and upgrading restorative execution. Past NAC, bromelain has moreover been combined with other bioactive compounds to abuse synergistic components and overcome solidness impediments. In any case, challenges related to polymer optimization, long-term soundness, and large-scale fabricating stay. Proceeded inquire about and well-designed clinical trials are basic to completely build up the clinical potential of bromelain-based combination treatments.

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