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CHITOSAN-BASED NANOCARRIERS FOR ANTI-ASTHMATIC DRUG DELIVERY: FORMULATION PRINCIPLES, BIOLOGICAL RATIONALE AND TRANSLATIONAL CHALLENGES

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ABSTRACT

Asthma treatment depends on reliable drug delivery to control bronchoconstriction and chronic airway inflammation. Chitosan-based nanocarriers are being investigated because they combine biodegradability, modifiable cationic charge, mucoadhesion and the ability to form particles under mild ionic-gelation conditions. This review examines the physicochemical basis of chitosan nanocarriers, preparation routes, critical quality attributes, characterization methods, drug-release mechanisms, opportunities for pulmonary and mucosal delivery, and the evidence needed for translation. Particular attention is given to montelukast sodium, whose low aqueous solubility makes it a useful model for carrier-enabled formulation. Polymer molecular weight, degree of deacetylation, pH, chitosan-to-tripolyphosphate ratio, mixing energy and drying conditions jointly determine size, dispersity, charge, entrapment and release. Although nanoscale delivery can improve dispersion and sustain release, favorable particle size alone does not establish lung deposition, clinical benefit or safety. Development should integrate quality-by-design experiments, validated analytical methods, aerosol testing, disease-relevant pharmacology, toxicology and stability. Chitosan is a versatile platform, but successful products will require

reproducible raw materials and an explicit connection between manufacturing controls and therapeutic performance.

KEYWORDS: Asthma; chitosan; nanoparticles; pulmonary delivery; montelukast; quality by design; controlled release.

1. INTRODUCTION

Asthma is heterogeneous: patients differ in inflammatory phenotype, trigger pattern, severity, comorbid disease and response to therapy. Delivery systems cannot remove this biological complexity, but they may help a drug reach its intended compartment at an appropriate concentration and duration. The practical goal is therefore not nanotechnology for its own sake; it is a dosage form whose measurable attributes solve a defined clinical or pharmaceutical problem.

Nanocarriers can increase apparent dispersion of poorly soluble compounds, protect labile molecules and modulate release. For respiratory therapy, they may also support retention in airway mucus or uptake by relevant cells. These benefits are conditional. Particle aggregation, rapid clearance, dose loss in the device, macrophage uptake and local irritation can offset theoretical advantages.

Chitosan occupies a distinctive position among carrier polymers. It is obtained by deacetylation of chitin and contains primary amino groups that are protonated in acidic environments. This enables water-compatible processing, ionic cross-linking and interaction with negatively charged biological surfaces. Its properties vary with molecular weight, degree of deacetylation, purity and source, making material characterization central to reproducibility (Illum, 1998).

Montelukast sodium illustrates the formulation question. The drug blocks CysLT1 receptors and is used in asthma maintenance, allergic rhinitis and prevention of exercise-induced bronchoconstriction. Its limited aqueous solubility can complicate dispersion and dissolution. Encapsulation within chitosan can improve handling and release behavior, but a carrier must be evaluated against a clear route-specific target product profile.

2. Review Approach

This narrative review was structured around themes present in the attached thesis: asthma biology, montelukast pharmacology, chitosan chemistry, nanoparticle preparation, factorial

optimization, physicochemical characterization, release testing and preclinical evaluation. Foundational references reported in the thesis were retained where they directly support these themes. Because this is not a systematic review, it does not claim exhaustive retrieval, formal risk-of-bias grading or meta-analysis.

Evidence was interpreted by separating platform plausibility from demonstrated performance. Statements about polymer chemistry and measurement principles are distinguished from claims that require route-specific deposition, pharmacokinetic or efficacy data. This distinction is essential because many formulation studies stop at particle size, entrapment and *in vitro* release.

3. Asthma Biology and Therapeutic Targets

Airway epithelial activation initiates signals that shape innate and adaptive immune responses. In type 2-high disease, cytokine networks support immunoglobulin E production, eosinophil survival, mucus hypersecretion and airway hyperresponsiveness. Other phenotypes involve neutrophilic or paucigranulocytic patterns. A delivery strategy should therefore specify whether it is intended to relieve smooth-muscle constriction, suppress inflammation, alter mucus interaction or improve adherence.

Cysteinyl leukotrienes contribute to bronchoconstriction, edema and mucus secretion through the CysLT1 receptor. Montelukast selectively antagonizes this pathway. It is not a substitute for rapid-acting rescue therapy during an acute attack, and carrier development must not blur that clinical distinction. A sustained formulation is most logically positioned for maintenance rather than immediate bronchodilation.

Current asthma care includes inhaled corticosteroids, beta2 agonists, muscarinic antagonists, leukotriene modifiers and biologics selected according to severity and phenotype. Nanocarriers may complement these pharmacological classes, but the route and device determine whether the formulation reaches conducting airways, peripheral lung or systemic circulation.

4. Chitosan as a Pharmaceutical Carrier

Chitosan is biodegradable, biocompatible in many contexts and capable of film, gel, bead and nanoparticle formation. Protonated amino groups confer positive charge and allow electrostatic interaction with polyphosphate anions. The polymer can also interact with

mucin, supporting mucoadhesion. These features explain its frequent use in mucosal delivery research (Lehr et al., 1992; Van der Lubben et al., 2001).

The same chemistry creates constraints. Chitosan is poorly soluble near neutral and alkaline pH unless chemically modified, and its viscosity rises with concentration and molecular weight. Batch-to-batch variation in deacetylation, residual protein, ash and endotoxin may change both processing and biological response. Specifications must therefore describe the actual grade rather than merely naming the polymer.

Degree of deacetylation influences charge density and cross-linking capacity. Molecular weight affects viscosity, chain entanglement and degradation. The distribution of acetylated residues may matter in addition to the mean degree of deacetylation. A robust study reports these attributes, supplier, lot and analytical method.

Biodegradability does not automatically guarantee safety at every dose or route. Particle charge, impurities, residual acid, cross-linker content, sterility and endotoxin can influence epithelial integrity and immune response. Pulmonary use requires a more demanding safety assessment than ordinary oral excipient use.

5. Preparation Technologies

Ionic gelation is widely used because particle formation occurs when positively charged chitosan encounters multivalent anions such as TPP. The process avoids harsh temperatures and can be compatible with sensitive drugs. pH, order of addition, mixing rate, addition rate and chitosan:TPP ratio determine the local balance between nucleation, growth and aggregation (Bhumkar & Pokharkar, 2006).

Emulsion-based methods can accommodate hydrophobic compounds by placing drug in an organic or dispersed phase before polymer stabilization. They may improve loading for selected molecules but introduce solvent removal, residual-solvent control and scale-up challenges. Spray drying and freeze drying are often applied downstream to obtain a stable powder, with cryoprotectants or matrix formers used to limit aggregation.

Microwave-assisted processing uses electromagnetic energy for rapid volumetric heating. Potential advantages include shorter reaction time and efficient energy use. Reproducibility depends on delivered energy, vessel geometry, sample volume, dielectric properties and temperature control. Translation from a laboratory unit requires calorimetric or temperature-

based process understanding rather than nominal wattage alone.

Microfluidic and impingement mixing can improve control over mixing time and local supersaturation. These continuous approaches may narrow particle distributions and support scale-up by numbering-up. Their value must be demonstrated using comparability data, throughput, fouling assessment and cleaning strategy.

Drying is not a neutral finishing step. Freezing rate, primary-drying pressure, shelf temperature and secondary drying affect cake structure, residual moisture and redispersibility. A dry powder intended for inhalation additionally requires control of geometric and aerodynamic particle properties, flow, emitted dose and moisture sorption.

6. Critical Quality Attributes and Analytical Methods

Particle size is commonly measured by dynamic light scattering, which reports a hydrodynamic diameter weighted by scattering intensity. A small population of large aggregates can dominate the signal. Number- or volume-based transformations should not replace the primary intensity result without explanation, and microscopy should be used as an orthogonal method.

Polydispersity index describes the breadth of a DLS distribution. Values below approximately 0.30 are often treated as acceptable for research dispersions, but the appropriate criterion depends on the intended product. Zeta potential estimates electrokinetic potential near the slipping plane. It can help compare formulations but does not independently prove shelf stability.

Entrapment efficiency and drug loading answer different questions. Entrapment is the fraction of the added drug retained by the carrier, whereas loading is drug mass relative to carrier or total solids. Indirect assays require complete separation of free drug and a mass-balance check. Direct extraction from nanoparticles provides a useful confirmation.

FTIR can identify major functional groups and changes in their environment. Peak shifts or broadening may reflect hydrogen bonding, ionic association, dilution or overlapping bands. DSC detects thermal transitions and can reveal changes in crystallinity or physical state. Neither method alone proves chemical compatibility; a stability-indicating assay is still required.

Electron microscopy describes dry-state morphology at high spatial resolution, whereas atomic-force microscopy can measure surface topology. Sample preparation can alter apparent structure, so image selection, scale bars and analysis of multiple fields are important. DLS size in dispersion should not be expected to equal dry microscopy diameter.

For inhaled products, geometric nanoparticle size is only one level of structure. Nanoparticles are often incorporated into micron-scale aggregates or carrier-based powders that deaggregate during inhalation. Cascade impaction, emitted dose, fine-particle fraction and mass median aerodynamic diameter are required to support deposition claims.

7. Quality-by-Design Optimization

A quality target product profile translates the proposed clinical use into measurable product attributes. For a chitosan nanocarrier, plausible critical attributes include assay, impurities, particle size distribution, surface charge, entrapment, release, redispersibility, residual moisture, microbial quality and route-specific performance.

Risk assessment links material attributes and process parameters to those outputs. Chitosan grade, drug solubility, TPP concentration, pH, mixing intensity, addition rate, microwave exposure and drying cycle are common high-risk variables. A factorial or response-surface design then estimates main effects, curvature and interactions more efficiently than sequential one-factor experiments.

Optimization should use a desirability function or prespecified decision rule that balances competing responses. Maximizing entrapment alone can produce particles that are too large or release too slowly. A design-space claim requires confirmation runs, prediction intervals and evidence that control is maintained across normal manufacturing variability.

Scale-up changes shear, heat transfer, hold time and mixing length. A control strategy should state which inputs are fixed, which are adjusted and how in-process measurements trigger action. Process analytical technology may include temperature monitoring, turbidity, particle-size sampling or spectroscopic checks where justified.

8. Drug Release and Mechanistic Interpretation

Release from chitosan matrices may combine desorption of surface-associated drug, diffusion through water-filled channels, polymer swelling, ion exchange and matrix erosion. The dominant mechanism can change with time. A biphasic profile is therefore common and

should not be reduced to a single descriptive phrase without examining the entire curve.

Zero-order, first-order, Higuchi and Korsmeyer-Peppas models are frequently applied. A high correlation coefficient does not prove the underlying mechanism, especially when sampling is sparse or multiple models fit similarly. Model selection should consider residuals, parameter plausibility and the assumptions of each equation (Fu & Kao, 2010).

Sink conditions are essential for a poorly soluble drug. If the receptor medium approaches saturation, declining concentration gradient can mimic sustained release. Solubility in the selected medium, membrane recovery, adsorption, drug stability and total mass recovered should be reported. Discriminatory power is more valuable than achieving a visually smooth curve.

In vitro-in vivo relationships require matched mechanisms and exposure measures. A release profile may guide batch comparison, but it cannot by itself predict lung residence, absorption or clinical duration. Mechanistic pharmacokinetic studies are needed to establish whether slower release changes local or systemic exposure.

9. Preclinical Pharmacology and Safety

Ovalbumin sensitization is commonly used to model allergic airway inflammation. Useful endpoints include direct pulmonary mechanics, bronchoalveolar lavage differentials, cytokines, immunoglobulins, mucus staining and histopathological scoring. Whole-body plethysmography can be supportive, but indirect Penh measurements should not be treated as equivalent to airway resistance.

A carrier-control group helps distinguish the effect of chitosan from that of the encapsulated drug. A conventional drug group establishes whether the formulation adds value at the same dose. Dose-response testing, randomization, blinding and prespecified endpoints reduce bias and improve interpretability.

Safety evaluation should cover local tolerance, inflammation, epithelial injury, systemic exposure and immunogenicity. Repeated administration may produce effects that are absent after a single dose. Histology, bronchoalveolar biomarkers, serum chemistry, hematology and organ examination provide complementary information.

Nanoparticle uptake depends on size, shape, charge, protein adsorption and cell type (Desai et

al., 1997; Chithrani et al., 2006). Uptake is not automatically desirable: intracellular delivery may help some targets but can also increase persistence or toxicity. The desired biological interaction must be defined before interpreting uptake data as a benefit.

10. Stability, Manufacturing and Regulation

Physical stability includes resistance to aggregation, sedimentation, crystal growth and irreversible changes after drying. Chemical stability covers drug potency, degradants and polymer changes. Microbiological quality and container compatibility are additional requirements. Accelerated conditions are useful for screening but do not replace long-term data.

Lyophilized systems require controls for residual moisture, cake appearance, reconstitution time and post-reconstitution particle size. Inhalable powders require moisture-protective packaging and testing after device actuation. Storage specifications should be linked to attributes that predict clinical performance.

Manufacturing feasibility depends on raw-material supply, batch reproducibility, sterile or low-bioburden processing, solvent control, cleaning and analytical throughput. Chitosan's natural origin makes supplier qualification and lot comparability especially important.

Regulatory evaluation focuses on the complete product rather than the novelty of the carrier. Developers must justify excipient safety for the proposed route, characterize critical attributes, validate manufacturing and demonstrate that the formulation's benefit outweighs its added complexity. Early dialogue with regulators can clarify whether the product is treated as a conventional drug, a complex formulation or a drug-device combination.

Problem definition: state the limitation of the existing drug product in measurable terms, such as inadequate dissolution, short airway residence, dose variability or poor usability. Select chitosan only if its properties directly address that limitation. A general wish to make a nanoparticle is not a sufficient product rationale.

Material characterization: document drug solid form and solubility; chitosan molecular weight, degree of deacetylation and viscosity; cross-linker identity and strength; and the quality of all solvents and stabilizers. Establish acceptance criteria before optimization so raw-material drift is not confused with process variation.

Process definition: specify solution pH, concentrations, order and rate of addition, mixing geometry, energy input, temperature history, separation, washing and drying. Identify hold times and conditions under which the dispersion can change. Record actual values rather than nominal equipment settings alone.

Analytical strategy: use orthogonal methods for attributes that can be method-dependent. Combine DLS with microscopy, indirect entrapment with direct extraction or mass balance, and FTIR/DSC with a stability-indicating chemical assay. Qualify methods for precision, range, recovery and interference before using them to rank formulations.

Performance strategy: make the release test discriminatory and route relevant. For pulmonary delivery, evaluate the complete formulation-device system using emitted dose and cascade impaction. Demonstrate that redispersion, aerosolization or dilution does not destroy the optimized nanoparticle structure.

Biological strategy: include a conventional drug comparator and an empty carrier. Connect exposure with response using pharmacokinetics or biodistribution. Predefine primary outcomes, randomize treatment, blind assessments, justify group sizes and report every exclusion. Treat efficacy and safety as parallel development questions.

Stability strategy: monitor physical, chemical, microbiological and functional attributes. A stable assay value is insufficient if particles aggregate or aerosol performance shifts. Conversely, unchanged particle size does not exclude drug degradation. Package selection and moisture protection should reflect the most sensitive attribute.

Translation strategy: define the manufacturing scale, clinical route, dosing device and patient population early. Evaluate whether the added complexity produces a clinically meaningful benefit over established dosage forms. Stop or simplify development when the carrier does not improve a decision-relevant endpoint.

Table 1: Chitosan attributes and formulation consequences.

Attribute	Potential benefit	Development concern
Primary amino groups	Ionic cross-linking and positive charge	Strong pH dependence
Molecular weight	Tunable viscosity and matrix strength	Batch variation and difficult mixing
Degree of	Controls charge	Requires reliable

deacetylation	density	characterization
Mucoadhesion	May extend mucosal residence	Can impede diffusion through mucus
Biodegradability	Supports clearance	Rate varies with grade and environment

Table 2: Preparation methods.

Method	Strength	Limitation	Key controls
Ionic gelation	Mild, aqueous processing	Sensitive to pH and mixing	Polymer/TPP ratio; addition rate
Emulsion	Useful for hydrophobic drugs	Solvent and surfactant residues	Phase ratio; solvent removal
Microwave-assisted	Rapid volumetric heating	Scale-dependent energy distribution	Temperature; energy per mass
Spray drying	Continuous powder formation	Thermal and shear stress	Inlet/outlet temperature; feed
Freeze drying	Low-temperature stabilization	Long cycle and redispersion risk	Freezing rate; pressure; protectant

Table 3: Characterization framework.

Attribute	Primary method	Interpretive caution
Hydrodynamic size/PDI	Dynamic light scattering	Intensity emphasizes aggregates
Morphology	TEM/SEM/AFM	Drying can change structure
Surface potential	Electrophoretic mobility	Not a stand-alone stability test
Entrapment/loading	Validated drug assay	Indirect methods need mass balance
Solid state	DSC and diffraction	Peak change is not proof of degradation
Compatibility	FTIR plus stability-indicating assay	Band overlap can mask changes
Release	Discriminatory dissolution/release test	Confirm sink and drug stability
Aerosol performance	Cascade impaction	Geometric size cannot predict deposition

Table 4: Translational evidence ladder.

Stage	Question	Minimum evidence
Formulation	Can the carrier be made reproducibly?	Defined materials, process and batch data
Analytical	Are attributes measured accurately?	Validated or qualified orthogonal methods
Functional	Does the product release and aerosolize as intended?	Discriminatory release and device testing
Preclinical	Does exposure improve efficacy safely?	PK/PD, carrier control, toxicology
Manufacturing	Can the process scale without drift?	Control strategy and comparability
Clinical	Does added complexity benefit patients?	Appropriate efficacy, safety and usability endpoints

11. Future Directions

Future platforms may use trimethylated, thiolated or ligand-modified chitosan to tune solubility, mucoadhesion and targeting. Responsive systems can release drug in reaction to pH, enzymes or redox conditions. Each modification adds characterization and toxicology requirements, so complexity should be introduced only when it solves a demonstrated limitation.

Combination nanocarriers could co-deliver anti-inflammatory drugs, bronchodilators or nucleic acids. Coordinated delivery is attractive for multifactorial disease, but fixed ratios can restrict dose flexibility and complicate pharmacokinetics. Combination claims require evidence that co-encapsulation provides an advantage over separately optimized products.

Human-relevant models, including airway epithelial cultures, organoids and precision-cut lung slices, can improve mechanism testing before animal studies. These systems are most informative when exposure at the cell surface is measured and compared with achievable clinical doses.

The decisive advance will be integration rather than another isolated formulation. Material specifications, scalable processing, validated analytics, aerosol performance, exposure, pharmacology and safety must form a connected evidence package. That integration can convert chitosan from a promising laboratory polymer into a reproducible therapeutic platform.

12. CONCLUSION

Chitosan provides a flexible foundation for anti-asthmatic nanocarriers because its charge, biodegradability, mucoadhesion and mild cross-linking chemistry can be tuned to drug and route. The platform can improve dispersion and sustain release, particularly for poorly soluble agents such as montelukast. Translation depends on controlling polymer variability, proving route-specific performance and connecting critical quality attributes with exposure, efficacy and safety. Carefully designed comparative studies are more valuable than reporting favorable nanoparticle metrics in isolation.

13. Declarations

This narrative review was prepared from the themes and references contained in the attached thesis. It presents no new experimental dataset. Before journal submission, the authors should

update the literature search, verify every bibliographic record against the source publication and adapt the manuscript to the target journal's review methodology and disclosure requirements.

REFERENCES

1. Bhumkar, D. R., & Pokharkar, V. B. Studies on the effect of pH on cross-linking of chitosan with sodium tripolyphosphate. AAPS PharmSciTech, 2006; 7(2): Article 50.
2. Fu, Y., & Kao, W. J. Drug release kinetics and transport mechanisms of polymeric delivery systems. Expert Opinion on Drug Delivery, 2010; 7(4): 429-444.
3. Illum, L. Chitosan and its use as a pharmaceutical excipient. Pharmaceutical Research, 1998; 15: 1326-1331.
4. Lehr, C. M., Bouwstra, J. A., Schacht, E. H., & Junginger, H. E. In vitro evaluation of mucoadhesive properties of chitosan and other natural polymers. International Journal of Pharmaceutics, 1992; 78: 43-48.
5. Panyam, J., & Labhasetwar, V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Advanced Drug Delivery Reviews, 2003; 55: 329-347.
6. Van der Lubben, I. M., Verhoef, J. C., Borchard, G., & Junginger, H. E. Chitosan and its derivatives in mucosal drug and vaccine delivery. Advanced Drug Delivery Reviews, 2001; 52: 139-144.
7. Desai, M. P., Labhasetwar, V., Walter, E., Levy, R. J., & Amidon, G. L. Size-dependent uptake of biodegradable microparticles in Caco-2 cells. Pharmaceutical Research, 1997; 14: 1568-1573.
8. Gao, L., Zhang, D., & Chen, M. Drug nanocrystals for poorly soluble drugs and their application as delivery systems. Journal of Nanoparticle Research, 2008; 10: 845-862.
9. Chithrani, B. D., Ghazani, A. A., & Chan, W. C. W. Size and shape dependence of nanoparticle uptake into mammalian cells. Nano Letters, 2006; 6(4): 662-668.
10. Chen, M., Liu, Y., Yang, W., Li, X., Liu, L., & Zhou, Z. Self-assembled nanoparticles of cholesterol-modified chitosan for drug delivery. Carbohydrate Polymers, 2011; 84: 1244-1251.
11. Kawashima, Y., Handa, T., Takenaka, H., Lin, S. Y., & Ando, Y. Controlled-release granules coated with a sodium polyphosphate-chitosan complex. Journal of Pharmaceutical Sciences, 1985; 74: 264-268.
12. Ma, Z., Yeoh, H. H., & Lim, L. Y. Formulation pH modulates drug interaction with chitosan nanoparticles. Journal of Pharmaceutical Sciences, 2002; 91: 1396-1404.