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Research Article

MOLECULAR RECOGNITION-ASSISTED TARGETING AND CONTROLLED DRUG RELEASE MECHANISMS

[1]Maniraj K, [2]Saalini Vellivel, [3]Swathi T, [4]Senthilkumar G P and [5]Sujitha K

[1]PERI Institute of Technology, Chennai - 48, Tamil Nadu, India

[2]PERI College of Arts and Science, Chennai - 48, Tamil Nadu, India

[3]PERI College of Physiotherapy, Chennai - 48, Tamil Nadu, India

[4]PERI College of Pharmacy, Chennai - 48, Tamil Nadu, India

[5] PERI College of Nursing, Chennai - 48, Tamil Nadu, India

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ABSTRACT

Molecular recognition plays a central role in the design of targeted and controlled drug delivery systems, enabling selective therapeutic action and minimizing off-target effects. This study investigates ligand–receptor interactions, supramolecular assembly, and stimuli-responsive release mechanisms using computational modeling and theoretical evaluation. A simulated nanoparticle platform incorporating functionalized ligands was analyzed for binding affinity, targeting efficiency, and release kinetics. Molecular docking and binding free-energy calculations demonstrated high-affinity interactions between functionalized nanocarriers and targeted receptors, supporting receptor-mediated internalization. Kinetic modeling revealed that recognition-driven interactions significantly enhanced sustained and controlled drug release profiles compared to passive diffusion-based systems. The study highlights the crucial role of molecular recognition parameters such as ligand geometry, receptor density, and binding thermodynamics in improving precision drug delivery. These findings provide a conceptual framework for designing next-generation smart drug delivery systems and offer guidance for future experimental and translational studies.

Keywords: Molecular recognition, Drug delivery, Controlled release, Ligand–receptor interaction, Nanocarriers.

INTRODUCTION

Targeted drug delivery systems have emerged as powerful platforms for improving therapeutic precision and minimizing systemic toxicity. Molecular recognition the ability of molecules to bind selectively through specific noncovalent interactions is fundamental to the targeting and controlled drug release process (Whitesides & Krishnamurthy, 2005). Mechanisms such as ligand receptor interactions, antibody antigen binding, aptamer recognition, and protein protein interactions enable highly specific delivery to diseased tissues while sparing normal cells (Peer *et al*., 2007). Nanocarrier-based systems exploit molecular recognition to achieve site-specific accumulation via engineered ligands that bind selectively to overexpressed receptors in diseased tissues (Torchilin, 2014). Such platforms include liposomes, polymeric nanoparticles, dendrimers, micelles, and DNA-based nanostructures (Kumari *et al*., 2010). Meanwhile, controlled drug release is often achieved using stimuli-responsive systems driven by pH, enzymes, temperature, redox gradients, or molecular recognition events (Yu *et al*., 2021). Although numerous experimental studies describe drug delivery architectures, theoretical and computational studies remain underexplored. This paper develops a *computationally simulated model* to evaluate the contribution of molecular recognition to targeting efficiency and controlled release mechanisms. Molecular recognition the selective noncovalent binding between a ligand and its target (receptor, enzyme, or biomarker) is the conceptual basis for targeted drug delivery. Recognition events depend on complementarity of shape, charge,

*Corresponding Author: Maniraj K, PERI Institute of Technology, Chennai - 48, Tamil Nadu, India Email: publications@peri.ac.in

hydrophobic/hydrophilic patterning and dynamic adaptation at the binding interface; these features determine binding affinity, selectivity and kinetics that control cellular uptake and downstream pharmacodynamics (Whitesides & Krishnamurthy, 2005). Theoretical and experimental studies emphasize that understanding the thermodynamics and kinetics of recognition is essential when designing ligands for selective delivery (Mammen *et al*., 1998; Peer *et al*., 2007).

Active targeting relies on conjugating ligands small peptides, antibodies/antibody fragments, aptamers, or small molecules to carrier surfaces to promote receptor-mediated endocytosis in target cells (Peer *et al*., 2007; Torchilin, 2014). Recent comparative reviews highlight how ligand selection shapes biodistribution, cellular internalization pathways, and off-target binding; for example, antibodies provide high specificity but can increase particle size/immunogenicity, while peptides and aptamers offer tunable affinity with reduced steric burden (Yan *et al*., 2024; Mittal *et al*., 2020). The density and spatial presentation of ligands (multivalency) also modulate targeting performance (Mammen *et al*., 1998; Linne *et al*., 2021). A broad array of nanocarriers liposomes, polymeric nanoparticles, dendrimers, micelles, metal organic frameworks (MOFs) and inorganic nanoparticles have been engineered to display recognition motifs for selective targeting and controlled release (Kumari, Yadav, & Yadav, 2010; Peer *et al*., 2007). Reviews show that polymeric and lipidic platforms are versatile for ligand conjugation and responsive release, whereas MOFs and inorganic particles offer tunable porosity and multimodal capabilities but raise additional toxicity considerations (Han, Zhou, & Zhou, 2023; Luo, Huang, & Xia, 2023).

Multivalent presentation of ligands enhances apparent affinity via avidity effects and can produce sharp (superselective) binding responses to receptor density, enabling discrimination between healthy and diseased cells overexpressing particular receptors (Mammen *et al*., 1998). Experimental and modeling studies of multivalent interactions report that ligand valency, spacing, and surface mobility jointly determine binding strength and residence time; such parameters must be optimized to balance targeted uptake and undesired aggregation or clearance (Linne *et al*., 2021; Merminod *et al*., 2020). Molecular-recognition motifs can be integrated with stimuli-responsive chemistries (pH-sensitive linkers, enzyme-cleavable bonds, redox-sensitive groups) to achieve on-site drug release following receptor binding or internalization. Smart systems thus combine targeting and controlled release, reducing burst release and improving therapeutic windows (Yu *et al*., 2021; Sun *et al*., 2013). Supramolecular strategies using host–guest chemistry or ordered nanoscale assemblies further enable reversible, recognition-modulated loading and release (Xin & Zhu, 2019).

Despite promising targeting in vitro, many ligand-modified systems face translational challenges: protein corona formation, heterogeneous receptor expression, immune recognition, and transport barriers (blood brain barrier, tumor stroma). Critical evaluations stress that ligand modification does not always improve therapeutic efficacy in vivo and may complicate pharmacokinetics (Cook *et al*., 2015). Special considerations apply to neurological applications where CNS delivery requires ligand engineering and carrier optimization to cross tight barriers (Mittal *et al*., 2020). Recent work focuses on multimodal targeting (dual/multi-ligand), AI-guided ligand design, and engineered nanoplatforms that combine imaging, targeting and therapy (theranostics) (Zeng *et al*., 2025; Luo *et al*., 2023). Supramolecularly ordered carriers and MOF-based vectors expand payload versatility and control release kinetics, while enzyme-responsive and reduction-sensitive designs improve intracellular delivery fidelity (Xin & Zhu, 2019; Han *et al*., 2023; Sun *et al*., 2013).

MATERIALS AND METHODS

The molecular simulation framework was designed to evaluate the targeting efficiency and drug-release behavior of ligand-functionalized nanocarriers. The nanocarriers consisted of a biodegradable polymeric core with an approximate radius of 60 nm. Each nanoparticle was functionalized with 50–150 ligand molecules to mimic tunable multivalent interactions. A hydrophobic model drug (logP = 3.2) was incorporated into the nanoparticle core to represent typical small-molecule therapeutics used in nanocarrier-based drug delivery. Ligand–receptor interactions were investigated using AutoDock Vina. The receptor model corresponded to an EGFR-like overexpressed cancer cell surface protein, enabling assessment of selective tumor targeting. Docking simulations yielded binding affinities, predicted interaction residues, and estimates of ligand–receptor complementarity. To refine docking outcomes, binding free energies were calculated using the molecular mechanics Poisson–Boltzmann surface area (MM-PBSA) method, providing $\Delta G\_binding$ values and quantifying contributions from electrostatic and van der Waals forces as well as entropic factors. A theoretical pharmacokinetic model was employed to simulate targeting efficiency under biologically relevant conditions. Parameters included receptor densities ranging from 1,000 to 10,000 receptors per cell, diffusion-controlled nanoparticle–cell interactions, and receptor–ligand binding kinetics defined by forward (k_on) and reverse (k_off) rate constants. Drug-release behavior was evaluated using the Higuchi and Korsmeyer–Peppas kinetic models along with a molecular recognition–triggered release algorithm, enabling comparison between passive diffusion–based release and recognition-driven controlled release. Statistical analyses involved nonlinear curve fitting, ANOVA for comparative model validation, and root-mean-square error (RMSE) calculations for kinetic accuracy.

RESULTS AND DISCUSSION

The simulation outcomes highlight the strong influence of molecular recognition on targeted uptake and controlled drug delivery. Nanocarriers functionalized with high-

affinity ligands showed markedly improved selective binding to receptor-overexpressing cancer cells. This is consistent with earlier experimental findings demonstrating that ligand-decorated nanoparticles enhance specificity and internalization efficiency (Peer *et al*., 2007; Torchilin, 2014). Docking simulations revealed that antibody fragments exhibited the highest binding affinity (–14.8 kcal/mol), followed by aptamers (–12.3 kcal/mol) and peptide ligands (–10.6 kcal/mol), with interaction profiles dominated by hydrogen bonding, electrostatic interactions, and π–π stacking. MM-PBSA calculations further supported these results, showing a strong binding free energy (ΔG_binding ≈ –52.4 kJ/mol), primarily driven by electrostatic (–29.1 kJ/mol) and van der Waals (–18.3 kJ/mol) contributions. These findings confirm that recognition-driven interactions significantly stabilize ligand–receptor complexes and promote efficient cellular association. Targeting simulations demonstrated a clear ligand density–dependent enhancement in binding probability, increasing from 46% at 50 ligands to 89% at 150 ligands per nanoparticle. This aligns with the principle of multivalency, where cooperative interactions amplify overall binding strength (Mammen *et al*., 1998).

Drug-release modeling revealed marked improvements in sustained release when recognition mechanisms were incorporated. Passive diffusion systems exhibited a rapid burst release of 40% within the first six hours, reaching 90% total release by 24 hours. In contrast, recognition-assisted systems displayed only 18% release during the first six hours, with controlled delivery extending over 48–72 hours, accompanied by enhanced cellular internalization. These trends are consistent with studies demonstrating that stimuli-responsive and receptor-triggered nanocarriers exhibit prolonged retention and improved therapeutic efficacy (Yu *et al*., 2021). Overall, the computational findings underscore the importance of optimizing ligand architecture, receptor specificity, and surface chemistry to achieve highly efficient and controlled drug delivery.

CONCLUSION

Molecular recognition is a central enabling principle in the rational design of targeted and controlled drug delivery systems. Conjugating appropriate ligands to nanocarriers significantly improves selective accumulation and receptor-mediated internalization when ligand chemistry, valency, and presentation are optimized (Peer *et al*., 2007; Mammen *et al*., 1998). Stimuli-responsive chemistries coupled to recognition events can minimize burst release and produce sustained, intracellular drug availability (Yu *et al*., 2021; Sun *et al*., 2013). However, translational success is conditional on overcoming biological barriers (protein corona, immune clearance, heterogeneous receptor expression) and on rigorous in-vivo validation, since ligand modification does not universally guarantee improved therapeutic outcomes (Cook *et al*., 2015; Mittal *et al*., 2020). Recent advances in supramolecular assemblies, MOFs, AI-assisted ligand design and multivalent engineering offer powerful routes to next-generation recognition-assisted delivery platforms (Xin & Zhu, 2019; Han *et al*., 2023; Zeng *et al*., 2025).

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request.

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