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Synthesis And Characterization Of Thermo-responsive Magnetic Molecularly Imprinted Polymers For Selective Recognition Of Peptide–drug Conjugates

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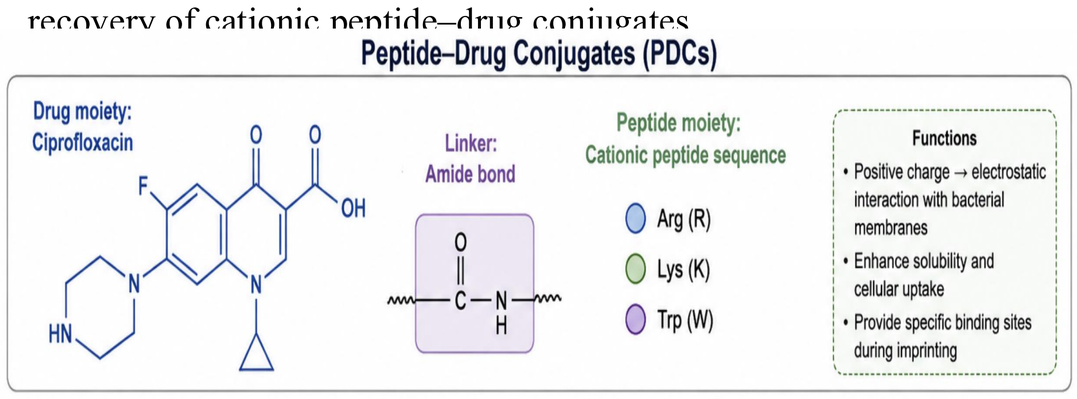
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Introduction

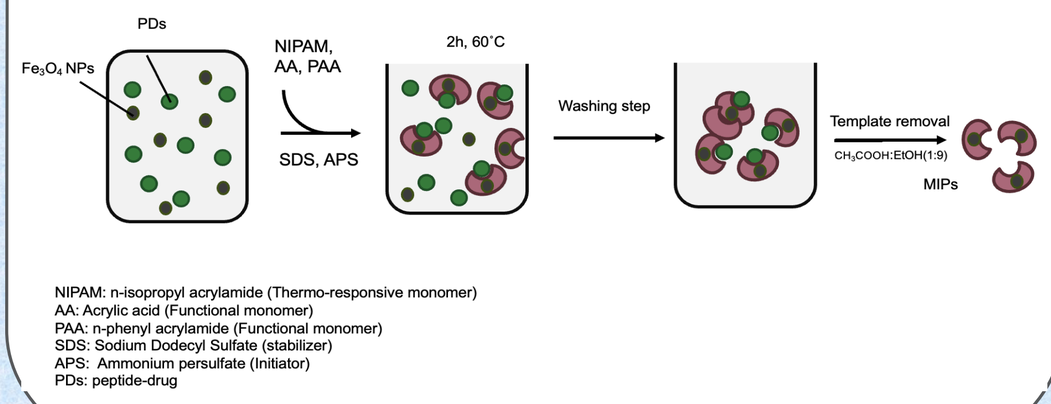
Peptide–drug conjugates (PDCs) are promising antimicrobial systems that combine the therapeutic activity of antibiotics with the targeting, membrane interaction, and cellular uptake properties of peptides. Incorporation of cationic amino acids such as arginine and lysine can enhance electrostatic interactions with negatively charged biological interfaces and provide additional hydrogen-bonding sites, potentially influencing the biological and physicochemical properties of the conjugates. In this study, two ciprofloxacin-based conjugates, Ciprofloxacin–Arg–Lys–Arg and Ciprofloxacin–Arg–Trp–Arg, were used as template molecules to develop thermo-responsive magnetic molecularly imprinted polymers (MMIPs).

The MMIPs were designed to provide selective recognition, temperature-controlled binding/release, and magnetic separation of the peptide–drug conjugates. The materials were characterized using FT-IR, TEM, and DLS, followed by adsorption and selectivity studies to evaluate their recognition performance.
This work explores thermo-responsive MMIPs as promising platforms for the selective extraction, separation, and controlled recovery of cationic peptide–drug conjugates.



Experimental

In this research, Fe_3O_4@poly(AA-*co*-PAA-*co*-NIPAM) MMIPs were synthesized via bulk polymerization in the presence of functional monomers capable of hydrogen bonding and ionic interactions. The integration of thermo-responsive polymer NIPAM with MMIP technology allows reversible modulation of polymer affinity around its lower critical solution temperature (LCST), enabling temperature-controlled binding and release of targets, while the magnetic core facilitates rapid separation under an external magnetic field.
Peptide-drug conjugates were prepared by solid-phase peptide synthesis (SPPS) with Fmoc/tBu strategy using triazine coupling reagent (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium toluene-4-sulfonate (DMT/NMM/$TosO^-$)).
In the last step, we characterized prepared nanoparticles by FT-IR, DLS, and TEM. Additionally, peptide-drug fragments were characterized by mass spectrometry techniques.



NIPAM: n-isopropyl acrylamide (Thermo-responsive monomer)
AA: Acrylic acid (Functional monomer)
PAA: n-phenyl acrylamide (Functional monomer)
SDS: Sodium Dodecyl Sulfate (stabilizer)
APS: Ammonium persulfate (Initiator)
PDs: peptide-drug

Results and discussion

Table 1.Results of peptide synthesis (LC-Mass analysis):

No.	Conjugate	Molecular Formula	Monoisotopic Mass (g/mol)	$[M+H]^+$ (m/z)	Purity %
1	Ciprofloxacin–Arg–Lys–Arg	$C_{35}H_{54}FN_{13}O_6$	771.4304	772.4377	96
2	Ciprofloxacin–Arg–Trp–Arg	$C_{40}H_{52}FN_{13}O_6$	829.4148	830.4220	94

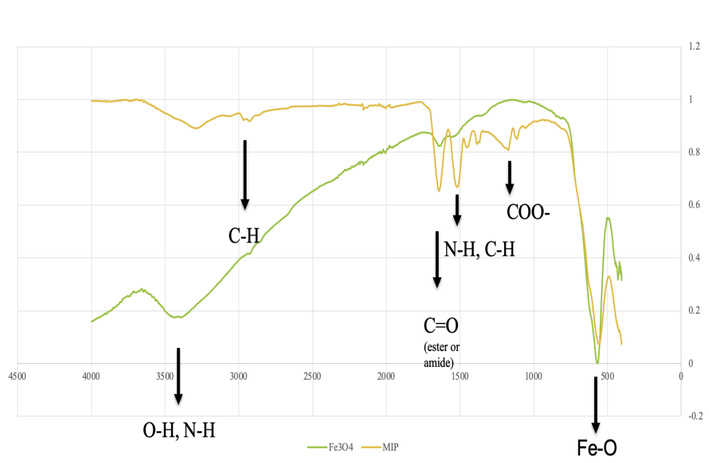
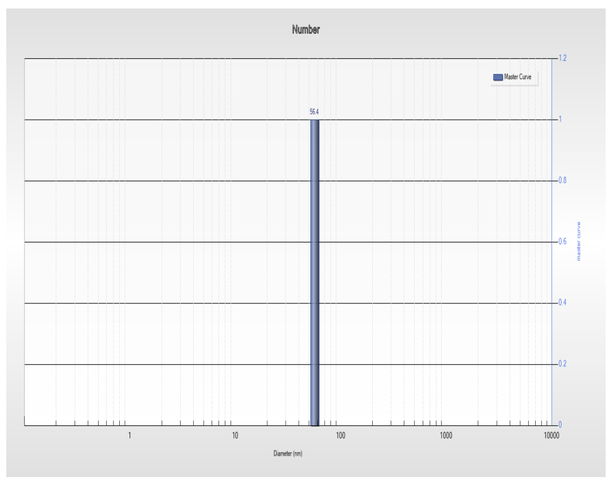


Fig 1. FTIR Spectra of MMIPs



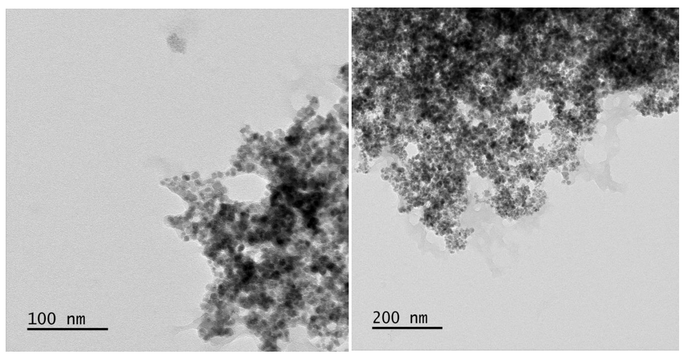


Fig 2. TEM images of MMIPs

Parameter	Mean ± SD
Z-Average (nm)	56.4 ± 0.02
PDI	0.23 ± 0.05

Fig 3. DLS result of MMIPs

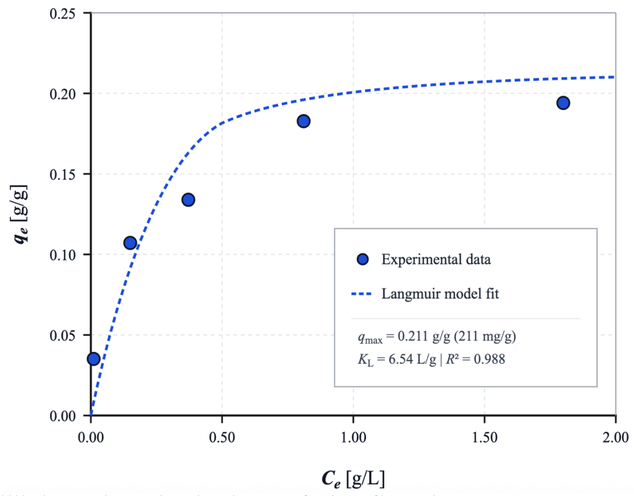


Fig 4. Equilibrium adsorption isotherm of Ciprofloxacin–Arg–Lys–Arg on MMIPs fitted with the Langmuir model

Conclusions

Core-shell thermo-responsive MMIPs (Fe_3O_4@poly(AA−*co*−PAA−*co*−NIPAM)) with a mean hydrodynamic size of 56.4 nm were successfully prepared. The material demonstrated high binding affinity toward Ciprofloxacin–Arg–Lys–Arg, conforming to the Langmuir isotherm ($R^2 = 0.988$) with a maximum capacity of 211 mg/g, highlighting its strong potential for selective magnetic separation of cationic peptide–drug conjugates.

Acknowledgment

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