

Integrated Microfluidics with Patterned Magnet and Microfabricated Sensors for Lab-on-a-Chip Applications

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Integrated Microfluidics with Patterned Magnet and Microfabricated Sensors for Lab-on-a-Chip Applications

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Certificate

This is to certify that the thesis titled **Integrated Microfluidics with Patterned Magnet and Microfabricated Sensors for Lab-on-a-Chip Applications**, submitted by **Mr. Vinit Kumar Yadav**, to the Indian Institute of Technology, Delhi, for the award of the degree of **Doctor of Philosophy**, is a bonafide record of the research work done by him under my supervision and guidance. The contents of this thesis, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

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ABSTRACT

Microfluidics enables precise fluid manipulation at the microscale, offering advantages such as minimal reagent consumption, high sensitivity, and rapid analysis. It has transformed applications in chemistry, biology, and medicine, particularly in drug screening and in vitro cell culture. Microfluidic systems are categorized as passive or active, with the latter leveraging external forces—electric, acoustic, or magnetic—for enhanced control. Magnetic microfluidics stands out due to its energy efficiency, portability, and non-invasive nature, allowing precise, contact-free particle manipulation without disrupting surrounding fluids. Integrating additional actuation mechanisms, such as acoustic or optical forces, further enhances control and biomedical applicability. This thesis advances magnetic Lab-on-Chip (LoC) platforms for biomedical applications by integrating novel microfabrication techniques, magnetically controlled drug delivery, and hybrid ultrasonic-magnetic actuation. Conventional LoC systems often rely on polymer composite micromagnets or ferromagnetic films on non-semiconducting substrates, limiting compatibility with complementary metal-oxide-semiconductor (CMOS) technology. To overcome this, we introduce a wafer-scale fabrication process for 100 μm thick micromagnets, eliminating elastomeric materials to enhance magnetic strength and CMOS compatibility. These micromagnets are integrated with prefabricated microfluidic devices at a 50 μm gap using a lithography-free, reversible bonding technique, enabling rapid design iterations and on-off magnetic control. The integration of patterned micromagnets enhances localization and, when combined with macromagnets,

doubles the magnetic force to 70 pN, achieving 100% trapping efficiency even at high flow rates.

Furthermore, a cost-effective, scalable fabrication process is developed for an on-chip positive magnetophoretic system, integrating a patterned permanent magnet with a microfluidic channel on a single polymethyl methacrylate (PMMA) substrate. This system exerts spatially varying magnetic forces, optimizing magnetic particle (MP) capture while preventing channel blockage, as validated through finite element method (FEM) simulations. Trapping efficiency improves from 15 $\mu\text{L}/\text{min}$ to 9 $\mu\text{L}/\text{min}$, reaching 94.5% at lower flow rates. Additionally, a piezoelectric/ferromagnetic bilayer-based magnetoelectric sensor enables real-time, in-vitro quantification of magnetically trapped drug conjugates (MD) with high sensitivity (0.33 nA.mL/ μg) and rapid response times ($<2\text{s}$).

Additionally, a lithography-free microfluidic device with a multilayer PMMA structure has been designed for concentration-dependent drug separation to address challenges in magnetically controlled drug testing. A stair-step patterned magnet generates forces between 0.01–0.24 pN, Flow ranges (0.6 – 1.1 $\mu\text{L}/\text{min}$). The device enables precise, controlled exposure of five different concentrations to cell cultures, validated via inductively coupled plasma mass spectrometry (ICP-MS) and fluorescence measurements. It demonstrates reusability in cytotoxicity tests on MCF7 and NIH3T3 cells. As an advancement of this design, a compact and miniaturized magnetically regulated microfluidic (MRM) platform is developed, integrating interdigitated electrode-based capacitive sensors for combinational drug screening. This system facilitates real-time, label-free screening, significantly reducing experimental time while enabling optimized dose, effective combination, and ratio identification through data-driven regression models.

Finally, this work introduces a hybrid ultrasonic-magnetic actuation system for efficient cluster manipulation within microenvironments. A lead magnesium niobate–lead titanate (PMN-PT) ultrasonic transducer and lithographically patterned Ni thin film enable dynamic particle control without continuous power input. The PMMA microchannel, sealed via robust parylene-parylene bonding, ensures reliable fluid handling. Ultrasonic forces dynamically deflect clusters while magnetic forces stabilize them, eliminating the need for frequent magnet redesign and simplifying fabrication.

Overall, this research advances magnetically controlled microfluidic systems through innovative fabrication techniques, high-precision drug compartmentalization, real-time drug screening, and hybrid actuation mechanisms. These platforms hold significant potential for biomedical research, diagnostics, and targeted drug delivery, paving the way for next-generation magnetically controlled LoC devices.

KEYWORDS: Microfluidics, Lab-on-chip, Patterned micromagnet, NdFeB, permanent magnet, Superparamagnet, Iron oxide, Magnetic nanoparticle, MNP, Magnetic particle, Magnetophoresis, Infrared, Magnetic bead, optothermal-pyroelectric, Acoustic Force, Anti-cancer drug, Cancer cell, NIH3T3, MCF7, Quantitative assessment, Drug delivery, Particle manipulation, Drag force, Thermocompression bonding, Location-specific trapping.

सारांश

माइक्रोफ्लुइडिक्स सूक्ष्म स्तर पर तरल पदार्थों की सटीक हेरफेर को सक्षम बनाता है, जिससे न्यूनतम अभिकर्मक खपत, उच्च संवेदनशीलता, और तीव्र विश्लेषण जैसे कई लाभ प्राप्त होते हैं। इसने रसायन विज्ञान, जीवविज्ञान, और चिकित्सा में विशेष रूप से दवा परीक्षण और इन-विट्रो सेल संवर्धन के क्षेत्र में क्रांतिकारी परिवर्तन किया है। माइक्रोफ्लुइडिक प्रणालियों को निष्क्रिय (Passive) और सक्रिय (Active) श्रेणियों में वर्गीकृत किया गया है, जिनमें सक्रिय प्रणालियाँ विद्युत, ध्वनिक या चुंबकीय जैसे बाह्य बलों का उपयोग करके बेहतर नियंत्रण प्रदान करती हैं।

चुंबकीय माइक्रोफ्लुइडिक्स ऊर्जा-कुशल, पोर्टेबल और गैर-आक्रामक होने के कारण विशिष्ट है, क्योंकि यह बिना तरल प्रवाह को बाधित किए संपर्क-रहित कण नियंत्रण की अनुमति देता है। जब इसमें ध्वनिक या प्रकाशीय बलों जैसे अतिरिक्त क्रियावली तंत्र को जोड़ा जाता है, तो यह नियंत्रण और जैव-चिकित्सकीय अनुप्रयोगों में और अधिक सुधार लाता है। यह शोध कार्य जैवचिकित्सकीय अनुप्रयोगों के लिए चुंबकीय लैब-ऑन-चिप (LoC) प्लेटफार्मों को उन्नत करता है, जिसमें नवीन माइक्रोफैब्रिकेशन तकनीकों, चुंबकीय रूप से नियंत्रित दवा वितरण, और हाइब्रिड अल्ट्रासोनिक-चुंबकीय क्रियावली को एकीकृत किया गया है।

परंपरागत LoC प्रणालियाँ प्रायः पॉलिमर मिश्रित माइक्रोमैग्रेट या गैर-सेमीकंडक्टर सतहों पर फेरोमैग्नेटिक फिल्मों पर निर्भर करती हैं, जिससे CMOS (कंप्लिमेंटरी मेटल-ऑक्साइड सेमीकंडक्टर) अनुकूलता में बाधा आती है। इस समस्या को हल करने के लिए, हमने 100 μm मोटे माइक्रोमैग्रेट के लिए एक वेफर-स्तरीय निर्माण प्रक्रिया प्रस्तुत की है, जो इलास्टोमेरिक सामग्री के उपयोग को समाप्त करती है और चुंबकीय तीव्रता तथा CMOS अनुकूलता को बेहतर बनाती है। इन माइक्रोमैग्रेट को 50 μm के गैप पर पूर्वनिर्मित माइक्रोफ्लुइडिक डिवाइस के साथ एक लिथोग्राफी-रहित, रिवर्सिबल बॉन्डिंग तकनीक के माध्यम से एकीकृत किया गया है, जिससे तेज़ डिज़ाइन परिवर्तन और ऑन-ऑफ चुंबकीय नियंत्रण संभव होता है।

पैटर्न किए गए माइक्रोमैग्रेट की यह एकीकरण स्थानीय नियंत्रण को बेहतर बनाती है, और जब इन्हें मैक्रोमैग्रेट्स के साथ संयोजित किया जाता है, तो चुंबकीय बल दोगुना होकर 70 pN तक पहुँचता है, जिससे उच्च प्रवाह दरों पर भी 100% ट्रेपिंग दक्षता प्राप्त होती है।

इसके अतिरिक्त, एक किफायती और स्केलेबल निर्माण प्रक्रिया विकसित की गई है, जिसमें एक स्थायी चुंबक को माइक्रोफ्लुइडिक चैनल के साथ एकल PMMA (पॉलीमेथिल मेथाक्रिलेट) सब्सट्रेट पर एकीकृत किया गया है। यह प्रणाली स्थानिक रूप से परिवर्तनशील चुंबकीय बल उत्पन्न करती है, जो चुंबकीय कण (MP) के कुशल पकड़ को सक्षम बनाती है और चैनल अवरोध से बचाती है, जिसे फिनाइट एलिमेंट मेथड (FEM) सिमुलेशन के माध्यम से मान्य किया गया है। ट्रेपिंग दक्षता 15 $\mu\text{L}/\text{min}$ से घटाकर 9 $\mu\text{L}/\text{min}$ प्रवाह दर पर 94.5% तक बढ़ाई गई है।

इसके अतिरिक्त, एक पाईजोइलेक्ट्रिक/फेरोमैग्नेटिक द्विस्तरीय संरचना पर आधारित मैग्रेटोइलेक्ट्रिक सेंसर विकसित किया गया है, जो चुंबकीय रूप से ट्रेप किए गए ड्रग-कंजुगेट्स (MD) की इन-विट्रो, रीयल-टाइम

मात्रात्मक पहचान को सक्षम बनाता है, जिसकी संवेदनशीलता $0.33 \text{ nA} \cdot \text{mL}/\mu\text{g}$ और प्रतिक्रिया समय <2 सेकंड है।

इसके साथ ही, एक लिथोग्राफी-रहित माइक्रोफ्लुइडिक डिवाइस को बहुस्तरीय PMMA संरचना के साथ डिज़ाइन किया गया है, जो चुंबकीय रूप से नियंत्रित दवा परीक्षण की चुनौतियों को हल करने के लिए सांद्रता-निर्भर दवा पृथक्करण की अनुमति देता है। एक स्टेयर-स्टेप पैटर्न चुंबक $0.01\text{--}0.24 \text{ pN}$ के बीच बल उत्पन्न करता है, और प्रवाह दर $0.6\text{--}1.1 \mu\text{L}/\text{min}$ के बीच रखी जाती है। यह डिवाइस सेल संवर्धन को पाँच विभिन्न सांद्रताओं के तहत सटीक रूप से उजागर करने की अनुमति देता है, जिसकी पुष्टि ICP-MS और फ्लोरोसेंस मापों के माध्यम से की गई है। इसने MCF7 और NIH3T3 कोशिकाओं पर साइटोटॉक्सिसिटी परीक्षण में पुनः उपयोगिता भी प्रदर्शित की है।

इस डिज़ाइन के एक और उन्नत संस्करण में, एक कॉम्पैक्ट और मिनिचराइज्ड मैग्नेटिकली रेगुलेटेड माइक्रोफ्लुइडिक (MRM) प्लेटफॉर्म विकसित किया गया है, जिसमें संयोजन दवा परीक्षण के लिए इंटरडिजिटेटेड इलेक्ट्रोड (IDE) आधारित कैपेसिटिव सेंसर एकीकृत हैं। यह प्रणाली रीयल-टाइम, लेबल-फ्री स्क्रीनिंग को सक्षम बनाती है, जिससे परीक्षण समय में काफी कमी आती है और डेटा-आधारित रिग्रेशन मॉडल के माध्यम से अनुकूलित खुराक, प्रभावी संयोजन और अनुपात की पहचान संभव होती है।

अंततः, यह कार्य एक हाइब्रिड अल्ट्रासोनिक-चुंबकीय क्रियावली प्रणाली प्रस्तुत करता है जो माइक्रोएनवायरनमेंट में कण क्लस्टर की कुशल गतिशीलता को सक्षम बनाता है। इसमें लेड मैग्नीशियम नियोबेट-लेड टाइटेनेट (PMN-PT) अल्ट्रासोनिक ट्रांसड्यूसर और लिथोग्राफिकली पैटर्न की गई Ni थिन फिल्म शामिल है, जो बिना निरंतर ऊर्जा आपूर्ति के डायनेमिक कण नियंत्रण को संभव बनाती है। PMMA माइक्रोचैनल, पारिलीन-पारिलीन बॉन्डिंग द्वारा सील किया गया, विश्वसनीय द्रव प्रबंधन सुनिश्चित करता है। अल्ट्रासोनिक बल क्लस्टर को गतिशील रूप से विक्षेपित करते हैं, जबकि चुंबकीय बल उन्हें स्थिर करता है, जिससे बार-बार मैग्नेट डिज़ाइन की आवश्यकता समाप्त हो जाती है और निर्माण प्रक्रिया सरल होती है।

कुल मिलाकर, यह शोध कार्य चुंबकीय रूप से नियंत्रित माइक्रोफ्लुइडिक प्रणालियों को उन्नत करता है, जिनमें नवीन निर्माण तकनीकें, उच्च-परिशुद्धता दवा विभाजन, रीयल-टाइम दवा स्क्रीनिंग, और हाइब्रिड क्रियावली शामिल हैं। ये प्लेटफॉर्म जैव-चिकित्सकीय अनुसंधान, डायग्नोस्टिक्स और लक्षित दवा वितरण के लिए अत्यधिक संभावनाएं रखते हैं, और अगली पीढ़ी के चुंबकीय LoC उपकरणों के विकास का मार्ग प्रशस्त करते हैं।

मुख्य शब्द: माइक्रोफ्लुइडिक्स, लैब-ऑन-चिप, संरचित सूक्ष्मचुंबक, एनडीएफईबी, स्थायी चुंबक, सुपरपैरामैग्नेट, लौह ऑक्साइड, चुंबकीय नैनोकण, एमएनपी, चुंबकीय कण, मैग्नेटोफोरेसिस, अवरक्त, चुंबकीय बीड, ऑप्टोथर्मल-पायरोइलेक्ट्रिक, ध्वनिक बल, कैंसर-रोधी दवा, कैंसर कोशिका, NIH3T3, MCF7, मात्रात्मक मूल्यांकन, दवा वितरण, कण संचलन, घर्षण बल, थर्मोकंप्रेशन बॉन्डिंग, स्थान-विशिष्ट पकड़।

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List of Symbols

I_{peak}	Transient Photo-current Peak
I_T	Transient Photo-current
i_p	Steady State Photo Current
A	Magnetic Potential Energy
B_{stray}	Stray Magnetic Flux
C_m	Acoustic Wave Speed in the Medium
C_p	Speed of Acoustic Wave in the Magnetic Particle
C_{MNP}	Magnetic Nanoparticle Concentration
d_{ij}	Piezoelectric coefficient
δ_{max}	Maximum DW Rotation
δT_{max}	Maximum Temperature Change
$\epsilon_p(t)$	Photo-strain
E	Magnetostatic Energy
E_d	Energy Dissipation
E_i	Internal Electric Field
F	Effective Force
F_d	Drag Force
F_{dw}	DW Stray Field Force
$F_{dw(critical)}$	DW Critical Stray Field Force
EV	Extracellular vesicles
H	External Magnetic Field
H_c	Coercivity
H_d	Demagnetization Field
H_{dp}	Magnetic Particle Self-Demagnetization Field

H_{eff}	Effective Magnetic Field
H_{ex}	Exchange Field
H_r	Resonance Magnetic Field
Re	Reynolds number
H_s	Stress Anisotropy Field
k_b	Boltzmann's constant
Λ	Thermal Stress Coefficient
λ	Magnetostrictive Coefficient
λ_{ac}	Acoustic Wavelength
M_f	Fluid Magnetization
M_p	Magnetic Particle Magnetization
M_{sat}	Saturation Magnetization
m_p	Magnetic Particle Mass
μ	Magnetic Particle Magnetic Moment
μ_p	Magnetic Particle Permeability
μ_o	Free Space Permeability
$N_{\text{single-MP}}$	Single Magnetic Particle Observations
P	Polarization
P_r	Remanent Polarization
P_{trapping}	Single Magnetic Particle Trapping Probability
p	Pyroelectric Coefficient
ϕ	Magnetic Potential
Φ	Wiggling Angle
R	Photo-resistance
R_{pr}	Radius of magnetic particle
r_c	Magnetic Particle Critical Radius
s	MR Range
τ	Thermal Time Constant
T	Temperature
T_{drive}	Applied Voltage Rate
T_r	Response Time
t	Trackwidth

t_{cr}	Critical Trackwidth
t_i	Irradiation Time
t_{sweep}	External Field Sweep Time
V_{FMR}	FMR Signal
V_p	Magnetic Particle Volume
v_f	Fluid Velocity
v_p	Magnetic Particle Velocity
$v_{(MP(critical))}$	Magnetic Particle Critical Velocity
χ	Magnetic Susceptibility
χ_p	Magnetic Susceptibility of particle
χ_m	Magnetic Susceptibility of medium
B	Magnetic flux density
$\vec{M}^S$	Spontaneous Magnetization
$\vec{P}^S$	Spontaneous Polarization
$\hat{\mu}$	Magnetic Susceptibility
$\vec{F}_{ac}$	Acoustic Force
$\vec{F}_{ac(max)}$	Maximum Acoustic Force
K	Acoustic Radiation Force Factor
ρ_m	Density of the Medium
ρ_p	Density of the Magnetic Particle
$\rho_m C_m^2$	Compressibility of the Medium
$\rho_p C_p^2$	Compressibility of the Magnetic Particles
PN	Position of Pressure Node
AN	Position of Antinode

List of Abbreviation

AR	Aspect Ratio
Au	Gold
LoC	Lab-on-Chip
RBC	Red Blood Cells
WBC	White Blood Cells
DLD	Deterministic Lateral Displacement
CMOS	Complementary Metal-Oxide-Semiconductor
DEP	Dielectrophoresis
CNC	Computer Numerical Control
SAW	Surface Acoustic Wave
Cr	Chromium
Cu	Copper
POC	Point of Care
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
EM	Electromagnet
ER	Electroresistance
FE	Ferroelectric
FEA	Finite Element Analysis
FEM	Finite Element Method
FESEM	Field Emission Scanning Electron Microscopy
NMR	Nuclear Magnetic Resonance
MHD	Magnetohydrodynamic
Fe_3O_4	Iron Oxide
FM	Ferromagnetism

FDM	Finite Difference Model
FEMM	Finite Element Method Magnetics
IAMS	Acoustic-magnetic separation system
FACS	Fluorescence-activated cell sorting
MEMS	Microelectromechanical system
IP	In-plane
IR	Infrared
MPs	Magnetic particles
NdFeB	Neodymium-iron-boron
LiCoPO₄	Lithium Cobalt Phosphate
LiFePO₄	Lithium Iron Phosphate
LiNiPO₄	Lithium Nickel Phosphate
Fe	Iron
PMMA	Polymethyl methacrylate
MB	Magnetic Bead
ME	Magnetoelectric
PDMS	Polydimethylsiloxane
MFM	Magnetic Force Microscopy
MNP	Magnetic Nanoparticle
MPI	Magnetic Particle Imaging
MRX	Magnetorelaxometry
Ni	Nickel
OT	Optical Tweezer
Pb(Fe_{0.5}Nb_{0.5})O₃	Lead Iron Niobate
Pb(Fe_{0.5}Ta_{0.5})O₃	Lead Iron Tantalate
PFN-Pb(Zn_{1/3}Nb_{2/3})O₃	Lead Iron Niobate - Lead Zinc Niobate
PFW-PbTiO₃	Lead Iron Tungstate - Lead Titanate
PMN-PT	Lead-magnesium-niobate Lead-titanate
ppm	Part Per Million
ppb	Part Per Billion
Pt	Platinum
PZT	Lead Zirconate Titanate

RF	Radio Frequency
SQUID	Superconducting Quantum Interference Device
THz	Terahertz
Ti	Titanium
TPC	Transient Photo Current
UV	Ultraviolet
VSM	Vibrating Sample Magnetometer
XRD	X-ray Diffraction
XPS	X-ray Photoelectron Spectroscopy
