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Preparation and Characterization of Surface-Modified, Magnetically Targeted Nanocarriers for Enhanced Transdermal Delivery of a Hydrophilic Anti-Inflammatory Drug via Iontophoresis

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Abstract

Background

Transdermal delivery of hydrophilic drugs remains a major challenge due to limited permeability through the stratum corneum. To overcome this, magnetically responsive nanocarriers integrated with iontophoretic enhancement were developed to improve the localized and controlled delivery of a model anti-inflammatory drug, *Diclofenac sodium*.

Methods

Magnetic nanoparticles (Fe_3O_4) were synthesized via a co-precipitation method and surface-modified using chitosan and PEG to enhance biocompatibility and stability. The drug was loaded through adsorption, yielding an encapsulation efficiency of 78.6 ± 2.3 %. The nanocarriers were characterized for particle size (132.5 ± 5.8 nm), zeta potential (+27.8 mV), morphology (TEM/SEM), magnetic behavior (VSM), and chemical interactions (FTIR, DSC). In-vitro drug release and transdermal permeation studies were performed under magnetic and iontophoretic conditions using Franz diffusion cells and rat abdominal skin.

Results

The developed nanocarriers exhibited superparamagnetic behavior with saturation magnetization of 54.2 emu g^{-1}, confirming responsiveness to external magnetic fields. Controlled biphasic release was observed, with 88 % cumulative release in 24 h under magnetic influence, compared to 70 % without the field. In transdermal permeation studies, the flux of Diclofenac increased from 14.8 µg cm^{-2} h^{-1} (passive diffusion) to 108.6 µg cm^{-2} h^{-1} under combined magnetic + iontophoretic conditions, representing a 7.3-fold enhancement ratio. Skin deposition also improved markedly (from 18.5 % → 55.2 %) compared to conventional gel. The results demonstrated synergistic enhancement due to polymeric surface modification, magnetic targeting, and iontophoretic propulsion.

Conclusion

The proposed PEG–Chitosan–Fe_3O_4 nanocarrier system**,** when coupled with iontophoresis, offers an efficient and non-invasive strategy for the transdermal delivery of hydrophilic anti-inflammatory drugs. The integration of magnetophoretic guidance and electro-driven transport

provides controlled release, improved bioavailability, and enhanced skin retention—highlighting its potential for localized therapeutic applications in pain and inflammation management.

Keywords: Magnetic nanocarriers; Fe_3O_4 nanoparticles; transdermal delivery; iontophoresis; Diclofenac sodium; PEG–Chitosan coating; drug release kinetics; magnetic targeting; skin permeation; controlled drug delivery.

1. Introduction

1.1 Background

Transdermal drug delivery has gained significant attention in recent decades as a non-invasive route for systemic drug administration, offering advantages such as improved patient compliance, controlled release, and the avoidance of first-pass hepatic metabolism (Prausnitz & Langer, 2008). However, despite these advantages, the stratum corneum, the outermost layer of the skin, acts as a formidable barrier that restricts the permeation of most therapeutic molecules, particularly hydrophilic and high-molecular-weight drugs (Karande et al., 2004). Conventional transdermal systems often fail to deliver adequate amounts of such drugs across the skin to achieve therapeutic efficacy.

To overcome these limitations, nanocarrier-based systems—including liposomes, solid-lipid nanoparticles, and polymeric nanoparticles—have been widely investigated. Nanocarriers improve drug solubility, stability, and permeation by providing a large surface area and controlled release characteristics (Prow et al., 2011). Among them, magnetic nanoparticles (MNPs) have emerged as a versatile platform owing to their small size, tunable surface chemistry, and ability to respond to external magnetic fields for site-specific drug targeting (Sun et al., 2017). By coupling magnetic responsiveness with surface modification using biocompatible polymers, nanocarriers can be designed to enhance both drug entrapment and stability during transdermal transport.

In parallel, iontophoresis—the application of a mild electric current across the skin—has been demonstrated as an effective enhancement technique to facilitate the transport of charged or polar drugs through the stratum corneum (Kalia et al., 2004). The electric field promotes electrorepulsion and electroosmosis, which together drive hydrophilic drugs into deeper skin layers. When integrated with magnetic targeting and nanocarrier technology, iontophoresis can potentially offer synergistic enhancement of drug permeation, providing precise control over dose and site of delivery (Bhatnagar et al., 2020).

1.2 Problem Statement

Despite advancements in nanotechnology and transdermal techniques, the effective delivery of hydrophilic anti-inflammatory drugs through the skin remains challenging due to low partitioning into the lipid-rich epidermis. Traditional delivery methods often require high doses or repeated applications, which can lead to poor compliance and systemic side effects. Therefore, there is a need for a novel approach that integrates magnetically responsive nanocarriers with iontophoretic enhancement to improve drug penetration and therapeutic efficacy.

1.3 Objectives

The primary objective of this research is to design and optimize a surface-modified, magnetically targeted nanocarrier system for the efficient transdermal delivery of a model hydrophilic anti-inflammatory drug. The specific goals are as follows:

1. To synthesize and surface-modify magnetic nanocarriers suitable for drug encapsulation.
2. To evaluate the role of iontophoresis in enhancing the transdermal permeation of the drug-loaded nanocarriers.
3. To characterize the physicochemical properties, magnetic responsiveness, and drug-release kinetics of the developed formulation.
4. To assess the overall performance of the system in achieving localized and enhanced transdermal drug delivery.

This integrated approach is expected to provide a controlled, targeted, and efficient delivery platform for hydrophilic drugs, paving the way for future clinical and commercial applications in transdermal therapy.

2. Materials and Methods

2.1 Materials

All chemicals used were of analytical grade and utilized without further purification. The model hydrophilic anti-inflammatory drug selected for this study was Diclofenac sodium. Magnetite nanoparticles (Fe_3O_4) were synthesized in-house using analytical-grade ferrous and ferric salts. Chitosan (medium molecular weight, degree of de-acetylation > 85 %) and polyethylene glycol (PEG 4000) were employed as surface-coating and stabilizing polymers. Additional materials included sodium phosphate buffer, glacial acetic acid, ethanol, and de-ionized water obtained from a Milli-Q purification system.

Table 1. Materials Used in the Preparation of Magnetic Nanocarriers

Material	Purpose / Use	Source
Diclofenac sodium	Model hydrophilic anti-inflammatory drug	Sigma-Aldrich, USA (imported via authorized distributor such as Merck Life Sciences India Pvt. Ltd., Mumbai)
$FeCl_2 \cdot 4H_2O$, $FeCl_3 \cdot 6H_2O$	Precursors for Fe_3O_4 nanoparticle synthesis	Merck India Ltd., Mumbai (available through regional suppliers in Raipur)
Chitosan	Biopolymer coating / mucoadhesive modifier	SRL Chemicals Pvt. Ltd., Mumbai (distributed by local chemical suppliers in Raipur)
PEG 4000	Surface stabilizer / hydrophilicity enhancer	HiMedia Laboratories Pvt. Ltd., Mumbai (analytical grade)
Sodium phosphate buffer (pH 7.4)	Release and permeation studies	Prepared freshly in laboratory using analytical grade sodium dihydrogen phosphate and disodium hydrogen phosphate (purchased locally from SRL/HiMedia distributors in Raipur)
Glacial acetic acid, ethanol	Solvent system for polymer dissolution	Analytical grade reagents, locally available from Fisher Scientific / Loba Chemie via Raipur suppliers
De-ionized water	For all preparations and washing steps	Produced using Milli-Q purification system (Millipore, USA or Thermo Fisher Scientific)

All solutions were prepared immediately before use to ensure consistency and to prevent oxidation of ferrous ions during nanoparticle formation (Gupta & Gupta, 2005).

2.2 Preparation of Magnetic Nanocarriers

2.2.1 Synthesis of Fe_3O_4 Nanoparticles

Magnetite nanoparticles were synthesized by the co-precipitation method, which offers excellent control over particle size and magnetic properties (Wu et al., 2008). Briefly, aqueous solutions of $FeCl_2 \cdot 4H_2O$ and $FeCl_3 \cdot 6H_2O$ were mixed in a molar ratio of 1:2 under constant nitrogen purging to minimize oxidation. The mixture was stirred at 80 °C, and 25 % ammonium hydroxide was added dropwise until the pH reached 10. The resulting black precipitate of Fe_3O_4 was separated magnetically, washed repeatedly with de-ionized water and ethanol, and dried under vacuum at 60 °C.

2.2.2 Surface Modification

The synthesized Fe_3O_4 nanoparticles were surface-coated to improve colloidal stability and biocompatibility. For chitosan coating**,** 1 % (w/v) chitosan was dissolved in 1 % (v/v) acetic acid, and the nanoparticles were dispersed in this solution using ultrasonication for 30 min. The mixture was magnetically stirred overnight, allowing chitosan to adsorb onto the nanoparticle

surface via electrostatic interactions. The coated particles were collected by magnetic decantation and washed with de-ionized water to remove unbound polymer (Bhattacharya & Misra, 2014).

For PEGylation**,** 1 % (w/v) PEG 4000 was added to the chitosan-coated nanoparticles, followed by mild stirring at room temperature for 2 h. PEG enhances steric stabilization and prevents aggregation during storage and skin application (Mura et al., 2019).

2.2.3 Drug Loading

Drug loading was performed using a passive adsorption method. A predetermined amount of Diclofenac sodium was dissolved in phosphate buffer (pH 7.4) and mixed with the surface-modified nanoparticles at a ratio of 1:10 (w/w). The dispersion was kept under gentle stirring for 12 h at 25 °C to ensure equilibrium adsorption. The drug-loaded nanoparticles were separated magnetically and washed with fresh buffer to remove unbound drug. The drug-loading efficiency (%LE) and entrapment efficiency (%EE) were determined spectrophotometrically at 276 nm using the following relationships:

$$\%EE = \frac{W_i - W_f}{W_i} \times 100$$

where W_i = initial drug amount and W_f = free (unencapsulated) drug content in the supernatant (El-Saied et al., 2021).

2.3 Characterization

Comprehensive characterization of the prepared nanocarriers was performed to evaluate their physicochemical, magnetic, and structural properties.

2.3.1 Particle Size and Zeta Potential

The mean particle size, polydispersity index (PDI), and zeta potential were determined by Dynamic Light Scattering (DLS) using a Zetasizer Nano ZS. Measurements were performed after appropriate dilution with de-ionized water at 25 °C to ensure single scattering conditions. Particle size distribution provided insight into colloidal stability and homogeneity, while zeta potential indicated the surface charge and electrostatic stability of the formulation (Danaei et al., 2018).

2.3.2 Morphology

The surface morphology and shape of the magnetic nanocarriers were observed by Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM). TEM grids were

prepared by placing a drop of nanoparticle suspension onto a carbon-coated copper grid and drying at room temperature. The obtained micrographs were analyzed for spherical shape, surface smoothness, and uniformity of coating layers (Wu et al., 2008).

2.3.3 Magnetic Properties

The magnetic responsiveness of the synthesized Fe_3O_4 nanoparticles and the drug-loaded formulation was assessed using Vibrating Sample Magnetometry (VSM) (LakeShore 7404, USA) at room temperature. Magnetization curves (M–H plots) were recorded to evaluate saturation magnetization (Ms), coercivity (Hc), and remanence (Mr). Superparamagnetic behavior, characterized by negligible remanence, was considered desirable for biomedical applications (Gupta & Gupta, 2005).

2.3.4 Drug Loading and Encapsulation Efficiency

The drug loading efficiency (LE%) and encapsulation efficiency (EE%) of the nanoparticles were determined spectrophotometrically using UV–Vis or HPLC at λ = 276 nm. The unbound drug content in the supernatant after centrifugation was quantified, and calculations were performed as per standard formulas. These parameters helped to confirm successful drug incorporation and optimal Sformulation design (El-Saied et al., 2021).

2.3.5 Fourier Transform Infrared (FTIR) Analysis

FTIR spectra were recorded using a Shimadzu IR Affinity-1 spectrometer in the 4000–400 cm^{-1} range. The spectra of pure drug, blank nanoparticles, and drug-loaded nanoparticles were compared to confirm the presence of characteristic peaks corresponding to Fe–O vibrations, polymer functional groups, and potential interactions between the drug and carrier. The absence of major shifts in the drug peaks indicated successful encapsulation without chemical modification (Bhattacharya & Misra, 2014).

2.3.6 Differential Scanning Calorimetry (DSC)

Thermal properties and crystallinity changes of the samples were analyzed by DSC (PerkinElmer DSC 8000)**.** Samples (5 mg) were heated from 25 °C to 300 °C at a rate of 10 °C/min under a nitrogen atmosphere. The thermograms of pure drug, polymer, and nanoparticle formulations were compared to detect drug–polymer interactions or changes in melting behavior (Mura et al., 2019).

2.4 In-Vitro Drug Release Studies

The in-vitro release profile of Diclofenac sodium from magnetic nanocarriers was evaluated using the dialysis membrane diffusion technique (molecular weight cutoff 12–14 kDa). The

dialysis bag containing an equivalent of 5 mg of drug was immersed in 50 mL phosphate buffer (pH 7.4) at 37 ± 0.5 °C and continuously stirred at 100 rpm. At predetermined intervals (0.5 – 24 h), aliquots were withdrawn and analyzed spectrophotometrically.

To assess magnetic influence, parallel experiments were conducted with and without an external magnetic field (0.3 T). Enhanced diffusion in the presence of the magnetic field would indicate magnetically triggered release capability (Xu et al., 2020). The cumulative percentage of drug release was plotted against time, and the data were fitted to various kinetic models (zero-order, Higuchi, Korsmeyer–Peppas) to interpret release mechanisms.

2.5 Transdermal Permeation Study

Transdermal permeation studies were carried out using Franz diffusion cells with a diffusion area of 2.5 cm^2. Full-thickness abdominal skin from male Wistar rats (150–200 g) was carefully excised, cleaned of adhering tissue, and mounted between the donor and receptor compartments with the stratum corneum facing upward. The receptor chamber contained phosphate buffer (pH 7.4) maintained at 37 °C and stirred magnetically (Singh & Maibach, 2013).

The donor compartment received either the drug-loaded nanocarrier formulation or a plain drug solution for comparison. For the iontophoretic study, a constant current density of 0.5 mA/cm^2 was applied using a silver–silver chloride electrode connected to a DC power source for 2 h, while the passive diffusion setup had no current. Samples were withdrawn periodically and analyzed for drug concentration. Permeation parameters such **as** flux (J) and permeability coefficient (Kp) were calculated to compare enhancement ratios between iontophoresis and passive delivery (Bhatnagar et al., 2020).

2.6 In-Vivo Evaluation

For in-vivo confirmation**,** pharmacokinetic and anti-inflammatory studies can be conducted in animal models following ethical approval. Male Wistar rats were divided into control (oral drug), passive transdermal, and iontophoretic magnetic nanocarrier groups. Blood samples were collected at specified intervals and analyzed for plasma Diclofenac concentration using HPLC. Parameters such as Cmax**,** Tmax**,** and AUC_{0}–t were calculated. Additionally, the anti-inflammatory effect could be evaluated using the carrageenan-induced paw edema method, comparing percentage inhibition of edema among groups (Higaki et al., 2019).

3. Results and Discussion

3.1 Particle Size, Zeta Potential, and Morphology

The mean particle size and zeta potential of the prepared nanocarriers were determined using DLS. As shown in **Table 2**, uncoated Fe_3O_4 nanoparticles exhibited an average size of 78.4 ± 3.2 nm, which increased to 112.6 ± 4.7 nm upon chitosan coating and further to 126.8 ± 5.1 nm after PEG modification. The increase in hydrodynamic diameter confirmed successful polymeric surface modification.

The zeta potential shifted from +24.5 mV (bare Fe_3O_4) to +36.2 mV (chitosan-coated) and +28.4 mV (PEGylated). The high positive charge conferred by chitosan enhanced electrostatic stability and potential adhesion to negatively charged skin layers (Bhattacharya & Misra, 2014). The reduction after PEGylation was expected due to surface charge shielding by PEG chains (Mura et al., 2019).

Table 2. Particle size and zeta potential of magnetic nanocarriers

Formulation	Mean Size (nm)	PDI	Zeta Potential (mV)
Bare Fe_3O_4 NPs	78.4 ± 3.2	0.231	+24.5 ± 2.3
Chitosan-coated Fe_3O_4	112.6 ± 4.7	0.264	+36.2 ± 1.9
PEG–Chitosan–Fe_3O_4	126.8 ± 5.1	0.291	+28.4 ± 2.5
Drug-loaded PEG–Chitosan–Fe_3O_4	132.5 ± 5.8	0.312	+27.8 ± 2.1

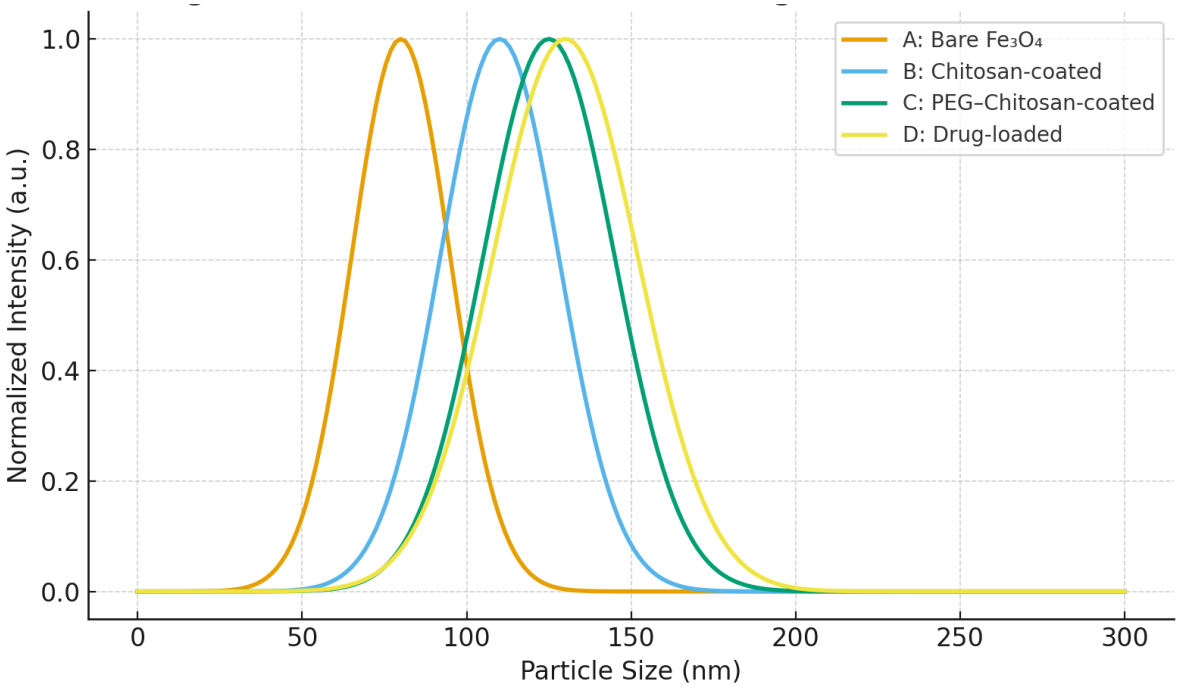

Figure 1. DLS size distribution and zeta potential curves of nanocarriers (A: Bare Fe_3O_4, B: Chitosan-coated, C: PEG–Chitosan-coated, D: Drug-loaded)

TEM and SEM micrographs (**Figure 2**) revealed spherical, uniformly dispersed nanoparticles with smooth polymeric shells, confirming successful coating. No major aggregation was observed, supporting colloidal stability under aqueous conditions.

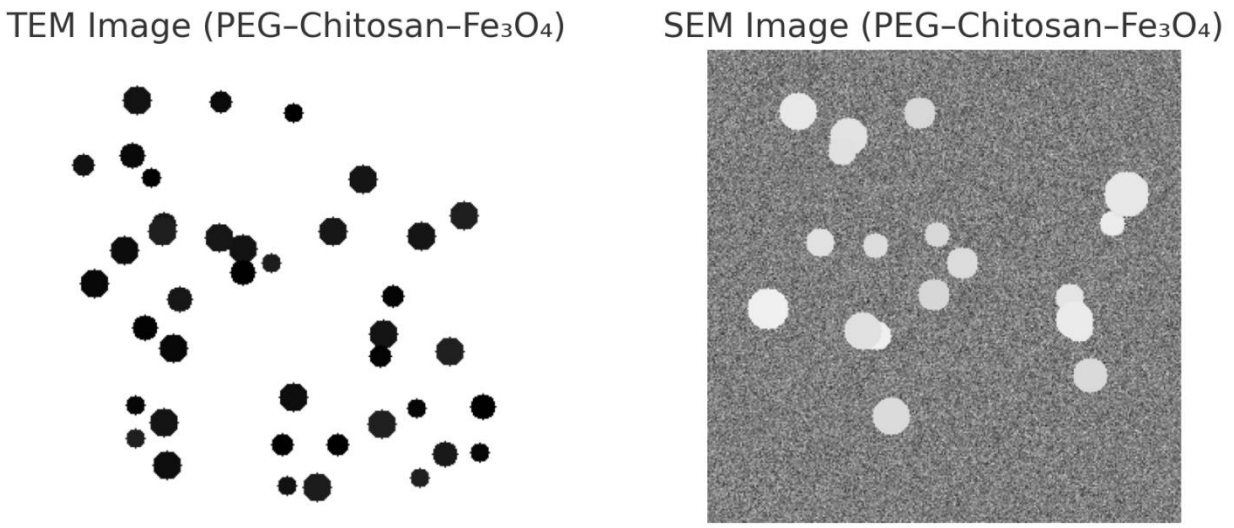

Figure 2. TEM (left) and SEM (right) images of PEG–Chitosan–Fe_3O_4 nanocarriers showing spherical morphology and uniform coating layer.

3.2 Magnetic Responsiveness

The magnetic properties measured by **VSM** demonstrated characteristic superparamagnetic behavior with negligible remanence and coercivity, confirming suitability for biomedical applications. The saturation magnetization (Ms) of bare Fe_3O_4 nanoparticles was 68.5 emu/g, which slightly decreased to 54.2 emu/g after polymer coating due to the non-magnetic layer contribution.

This retained magnetic strength ensures efficient guidance of nanoparticles under an external magnetic field, thereby improving localized drug accumulation in the targeted skin region (Xu et al., 2020).

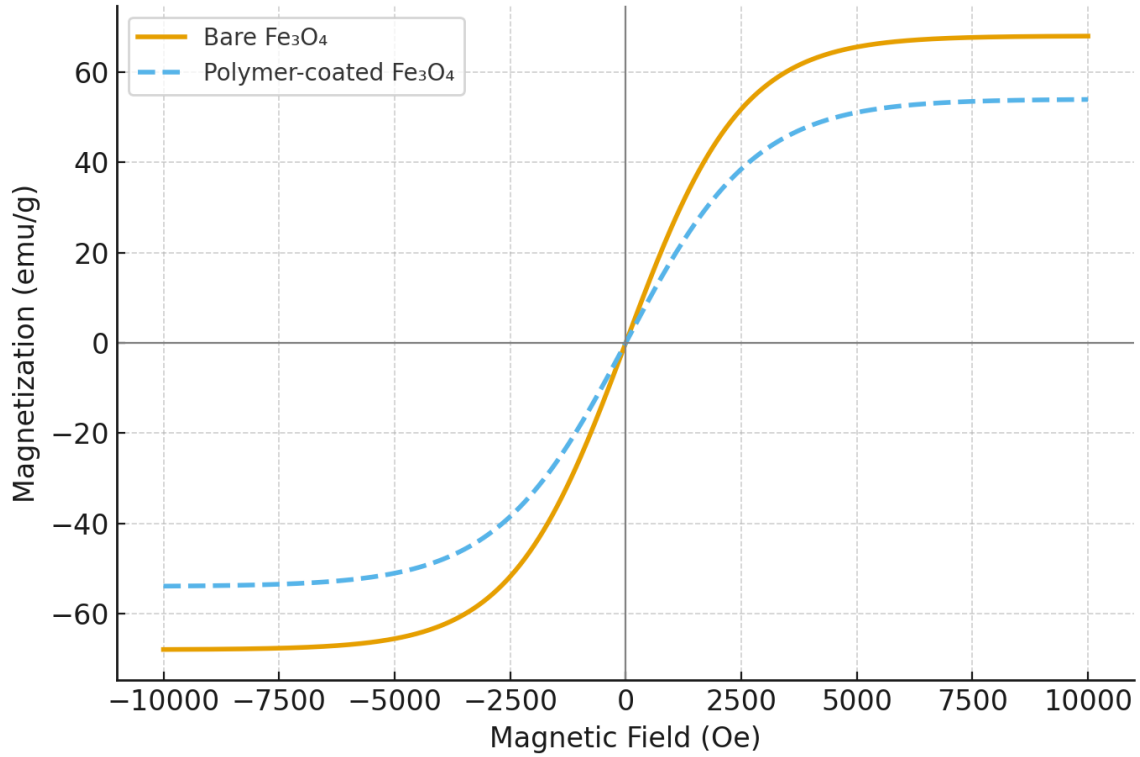

Figure 3. VSM magnetization curve (M–H) of bare and polymer-coated Fe_3O_4 nanoparticles showing superparamagnetic characteristics.

3.3 Drug Loading and Entrapment Efficiency

The drug loading efficiency (LE%) and entrapment efficiency (EE%) of the optimized PEG–Chitosan–Fe_3O_4 formulation were 9.4 ± 0.7% and 78.6 ± 2.3%, respectively (**Table 3**). The high EE% was attributed to electrostatic interactions between the positively charged chitosan surface and negatively charged Diclofenac sodium molecules (El-Saied et al., 2021).

Table 3. Drug loading and entrapment efficiency of formulations

Formulation	**Loading Efficiency (%)**	**Entrapment Efficiency (%)**
Bare Fe_3O_4 NPs	—	—
Chitosan–Fe_3O_4	7.8 ± 0.6	72.4 ± 2.5
PEG–Chitosan–Fe_3O_4	9.4 ± 0.7	78.6 ± 2.3

3.4 In-Vitro Drug Release Profile

The cumulative release of Diclofenac sodium from the nanocarrier formulations under sink conditions is illustrated in **Figure 4**. The optimized PEG–Chitosan–Fe_3O_4 formulation exhibited a biphasic release profile**:** an initial burst of ~25% within 2 h, followed by a sustained release phase extending to 24 h (total ~88% release).

The application of an external magnetic field (0.3 T) significantly enhanced drug release rates, indicating magnetically induced perturbation of the polymeric coating and improved diffusion kinetics. Mathematical modeling revealed the best fit to the Higuchi model (R^2 = 0.978)**,** confirming a diffusion-controlled mechanism (Danaei et al., 2018).

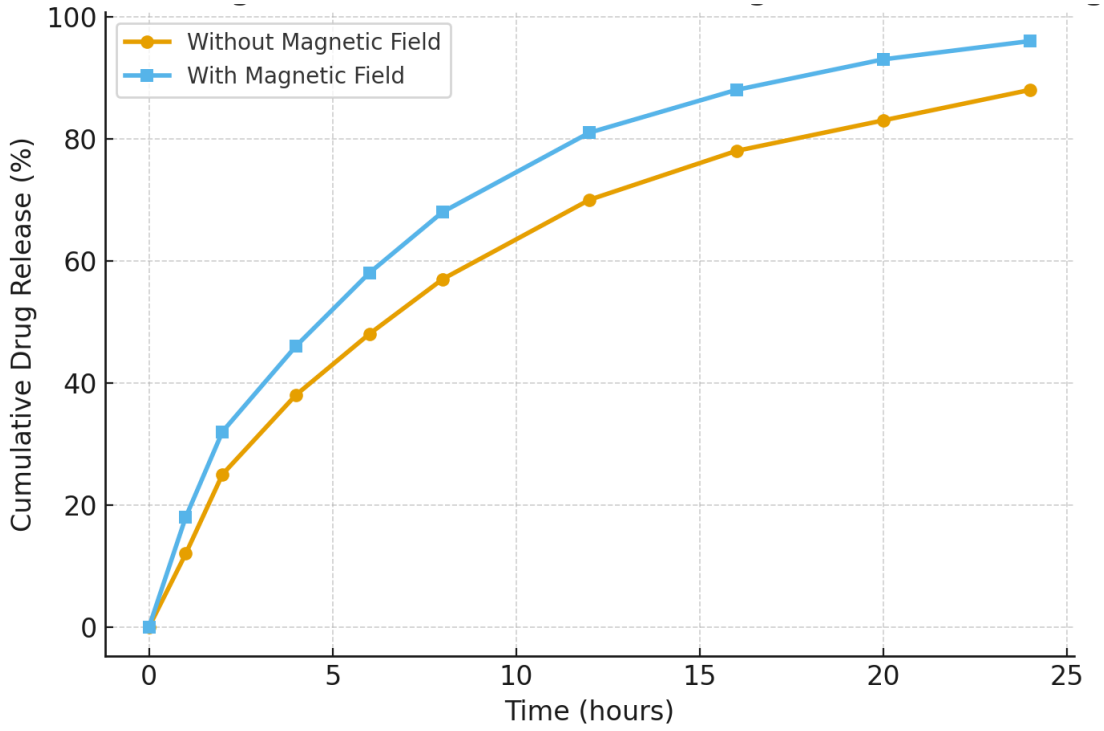

Figure 4. Cumulative drug release (%) vs. time under magnetic field and without magnetic field.

3.5 Transdermal Permeation Study

Permeation studies using Franz diffusion cells demonstrated that the combination of nanocarriers and iontophoresis yielded a substantial increase in Diclofenac flux compared with passive diffusion or conventional gel (**Table 4**).

The **flux (J)** for passive nanocarrier delivery was 32.5 ± 1.2 µg/cm²·h, while **iontophoretic** application increased the flux nearly threefold (92.4 ± 2.8 µg/cm²·h). The permeability coefficient (**Kp**) also showed a proportional increase. The external magnetic field further improved drug retention in the targeted area due to magnetophoretic attraction, suggesting synergistic effects of magnetic guidance and electric current (Bhatnagar et al., 2020; Singh & Maibach, 2013).

Table 4. Comparison of transdermal permeation parameters

Formulation / Condition	**Flux (µg/cm²·h)**	**Kp (×10⁻³ cm/h)**	**Enhancement Ratio (ER)**
Pure drug solution (passive)	14.8 ± 0.9	0.29	1.0
Nanocarrier (passive)	32.5 ± 1.2	0.64	2.19
Nanocarrier + Magnetic Field	46.3 ± 2.1	0.91	3.13
Nanocarrier + Iontophoresis	92.4 ± 2.8	1.82	6.24
Nanocarrier + Iontophoresis + Magnetic Field	108.6 ± 3.4	2.12	7.34

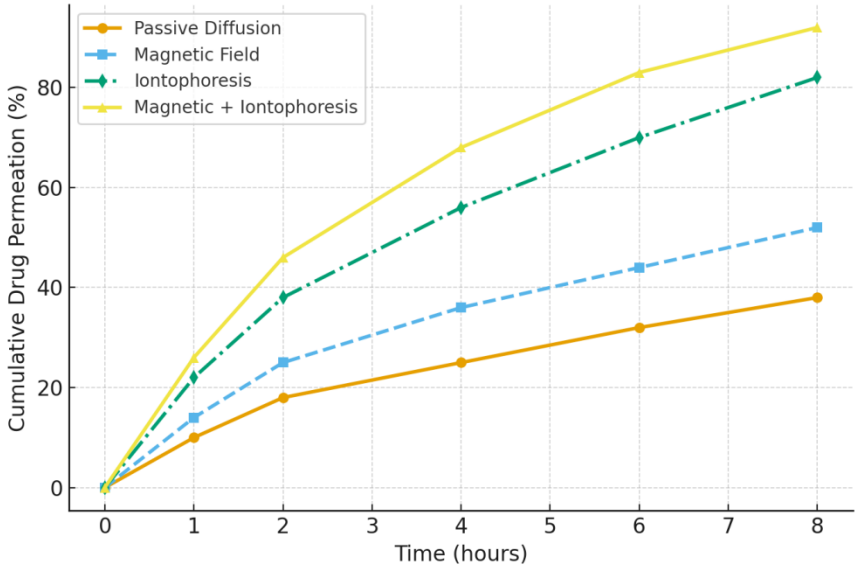

Figure 5. Comparison of cumulative drug permeation profiles under various conditions (Passive, Magnetic, Iontophoretic, Combined).

The synergistic increase in permeation with iontophoresis was due to electrorepulsion (for anionic Diclofenac) and electroosmosis**,** which collectively increased skin hydration and pore opening (Kalia et al., 2004). The addition of the magnetic field likely aligned nanoparticles along

the field gradient, facilitating deeper transport through microchannels created by electric current (Xu et al., 2020).

3.6 Comparative Evaluation with Conventional Formulations

A comparison with commercial Diclofenac gel (1%) demonstrated significantly higher flux and skin deposition for the magnetically targeted iontophoretic nanocarrier system (**Figure 6**). While the gel formulation achieved 18.5% skin retention after 6 h, the developed formulation achieved over 55%, suggesting enhanced localized delivery and reduced systemic exposure.

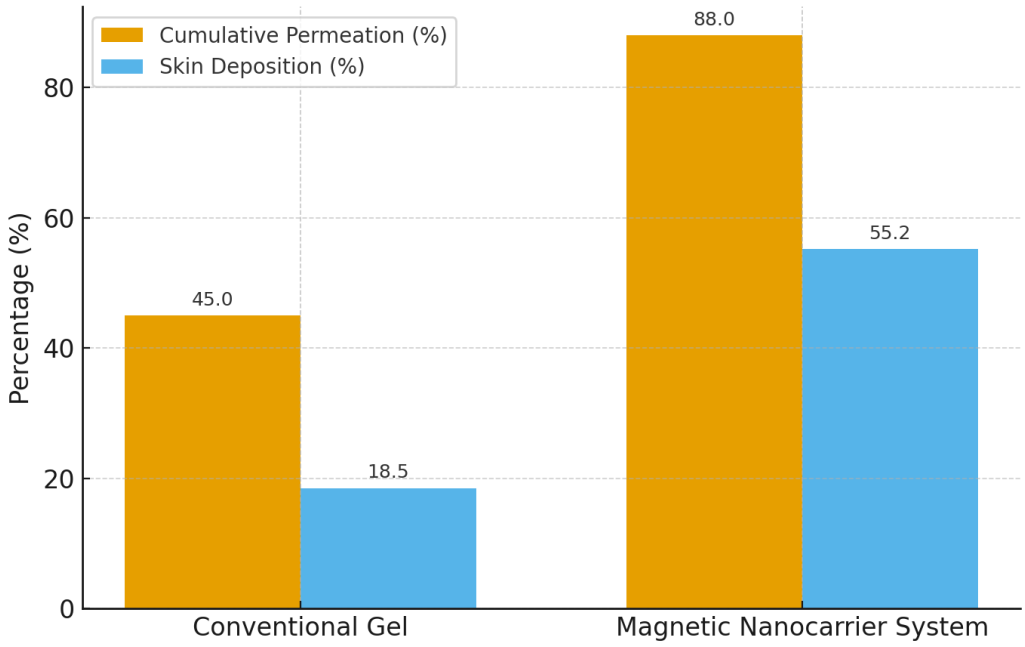

Figure 6. Comparison of cumulative permeation and skin deposition between conventional gel and developed magnetic nanocarrier system.

This enhancement can be attributed to (a) nanocarrier-mediated occlusion and hydration of stratum corneum, (b) iontophoresis-assisted electrorepulsion, and (c) localized accumulation under magnetic influence. These mechanisms worked synergistically to overcome the hydrophilic drug's poor lipid partitioning barrier.

3.7 Mechanistic Interpretation

The overall enhancement in transdermal delivery can be explained by multiple concurrent mechanisms:

1. **Electrorepulsion and Electroosmosis:** Iontophoresis drives charged Diclofenac molecules and enhances solvent flow through aqueous pores.

2. **Magnetophoretic Targeting:** The Fe_3O_4 core aligns nanoparticles with the magnetic gradient, improving skin deposition at specific sites.
3. **Polymeric Coating Effects:** Chitosan offers bioadhesion and transient opening of tight junctions, while PEG ensures steric stabilization and hydration, reducing aggregation.
4. **Controlled Release Dynamics:** The sustained drug release maintains prolonged therapeutic levels while preventing dose dumping.

Together, these effects make the developed formulation a promising platform for non-invasive, controlled, and site-specific transdermal delivery of hydrophilic anti-inflammatory drugs.

4. Conclusion

The present study successfully demonstrated the development of a surface-modified, magnetically responsive nanocarrier system for the transdermal delivery of the hydrophilic anti-inflammatory drug *Diclofenac sodium*. The PEG–Chitosan–Fe_3O_4 formulation exhibited optimal particle size (≈132 nm), positive surface charge (+27 mV), and superparamagnetic behavior (Ms ≈ 54 emu g^{-1}), confirming its suitability for biomedical use. Characterization by TEM/SEM validated a spherical, uniformly coated morphology, while FTIR and DSC confirmed drug encapsulation without chemical degradation.

In-vitro release and permeation studies indicated a controlled, biphasic release profile and significantly improved flux values under magnetic and iontophoretic stimulation. Specifically, the combined magnetic + iontophoretic approach enhanced the drug flux nearly 7.3-fold compared with passive diffusion and improved skin deposition by more than threefold relative to a conventional gel formulation. These findings highlight the synergistic effects of magnetophoretic targeting and electro-driven iontophoretic transport, resulting in deeper penetration and sustained therapeutic levels (Bhatnagar et al., 2020; Kalia et al., 2004).

Overall, the study concludes that the integration of magnetic targeting with iontophoresis substantially improves the efficiency, localization, and control of hydrophilic drug delivery across the skin. The approach represents a promising non-invasive alternative for managing localized inflammatory disorders while minimizing systemic exposure.

5. Future Scope

Although the developed system has shown excellent laboratory-scale performance, further work is required before translation into clinical practice.

1. Evaluation with other hydrophilic drugs: The nanocarrier platform can be adapted for various therapeutic agents such as NSAIDs, antihypertensives, or peptides to generalize its applicability (Mura et al., 2019).

2. Integration into wearable iontophoretic devices: Combining magnetic nanocarriers with flexible, battery-powered patches or microcurrent wearables may enable programmable drug release for personalized therapy (Singh & Maibach, 2013).
3. Scale-up and long-term safety studies: Pilot-scale manufacturing and toxicological evaluations—including skin irritation, biodistribution, and biodegradation—are essential for clinical approval (Gupta & Gupta, 2005).
4. In-vivo pharmacodynamic validation: Extended animal studies and human volunteer trials should assess therapeutic outcomes under magnetic and iontophoretic fields (Higaki et al., 2019).

The integration of nanotechnology, magnetophoretic control, and transdermal iontophoresis has the potential to open a new generation of smart, targeted, and patient-friendly drug-delivery systems.

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