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Comparative Evaluation of Polymeric, Nanoparticle, and Hydrogel Based Colon-Targeted Drug Delivery Systems under Simulated Gastrointestinal Conditions

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Abstract:

The present study compares three colon-targeted drug delivery systems; Eudragit S100-coated polymeric tablets, PLGA nanoparticles, and alginate hydrogel microspheres, developed for the controlled release of 5-Fluorouracil (5-FU). Each formulation was prepared and optimized using distinct carriers and evaluated under simulated gastrointestinal (GI) conditions to assess their physicochemical characteristics, release behaviour, and stability. The formulations were characterized for particle size, surface charge, encapsulation efficiency, and swelling index. Morphological analysis confirmed smooth coating in polymeric tablets, spherical uniformity in nanoparticles, and a porous structure in hydrogels. In vitro dissolution studies revealed minimal drug release in gastric conditions (≤2% at pH 1.2) and sustained release at colonic pH (7.4). PLGA nanoparticles showed the most controlled release profile, achieving 92.1 ± 2.4% cumulative release at 24 hours, compared with 100.0 ± 3.1% for polymeric tablets and 85.4 ± 2.1% for hydrogels. Kinetic modeling indicated that all systems followed diffusion-dominated release, with nanoparticles best fitting the Higuchi model (R^2 = 0.981). Stability studies confirmed nanoparticle integrity under prolonged acidic and neutral exposure, while hydrogels exhibited partial deformation. Overall performance analysis identified PLGA nanoparticles as the most efficient system, demonstrating superior acid resistance, encapsulation efficiency, and colon-specific release. These findings suggest that nanoparticle-based carriers offer significant potential for achieving predictable, site-specific, and sustained drug delivery to the colon.

Key Words: Colon-targeted drug delivery; PLGA nanoparticles; Eudragit S100-coated tablets; alginate hydrogel microspheres; 5-Fluorouracil (5-FU); pH-dependent release; sustained drug delivery; in vitro dissolution; gastrointestinal simulation;

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I. INTRODUCTION

Inflammation is the body's natural reaction to damage, illness, or irritation. In addition to producing pain, swelling, redness, and heat, it can aid in wound healing and defence against infections. Numerous illnesses, including diabetes, cancer, heart disease, and arthritis, can be brought on by chronic inflammation. Targeted drug delivery to the colon has become a critical focus in modern pharmaceutics due to its potential to improve local therapeutic efficacy and minimize systemic side effects for diseases such as ulcerative colitis, Crohn's disease, colorectal cancer, and irritable bowel syndrome[1]. However, conventional oral dosage forms often fail to achieve targeted release in the colon because of enzymatic degradation, variable gastrointestinal (GI) transit times, and premature drug dissolution in the upper GI tract[2]. These physiological barriers make it necessary to design drug delivery systems that protect the active compound until it reaches the colon, where site-specific release can occur[3].Various formulation strategies have been employed to achieve colon targeting, including pH-dependent polymer coatings, time-controlled systems, pressure-dependent capsules, and enzyme-triggered mechanisms[4]. Among these, pH-sensitive systems using Eudragit S100 and similar methacrylic acid copolymers are among the most established approaches, as they dissolve only above pH 7; corresponding to the distal intestinal and colonic environment[5]. Despite their success, polymeric-coated tablets alone may not ensure uniform release or protection under fluctuating pH and motility conditions[6]. In recent years, nanoparticle-based carriers have gained prominence as more sophisticated alternatives. Polymeric nanoparticles, particularly those formulated from poly(D,L-lactide-co-glycolide) (PLGA), provide improved encapsulation efficiency, enhanced drug stability, and sustained release behaviour[7]. Their small particle size and surface charge characteristics enable prolonged GI residence time and improved mucosal adhesion[8]. Studies have reported that PLGA-based nanoparticles can significantly enhance 5-Fluorouracil (5-FU) delivery to the colon, reducing premature drug loss and improving therapeutic outcomes[9].

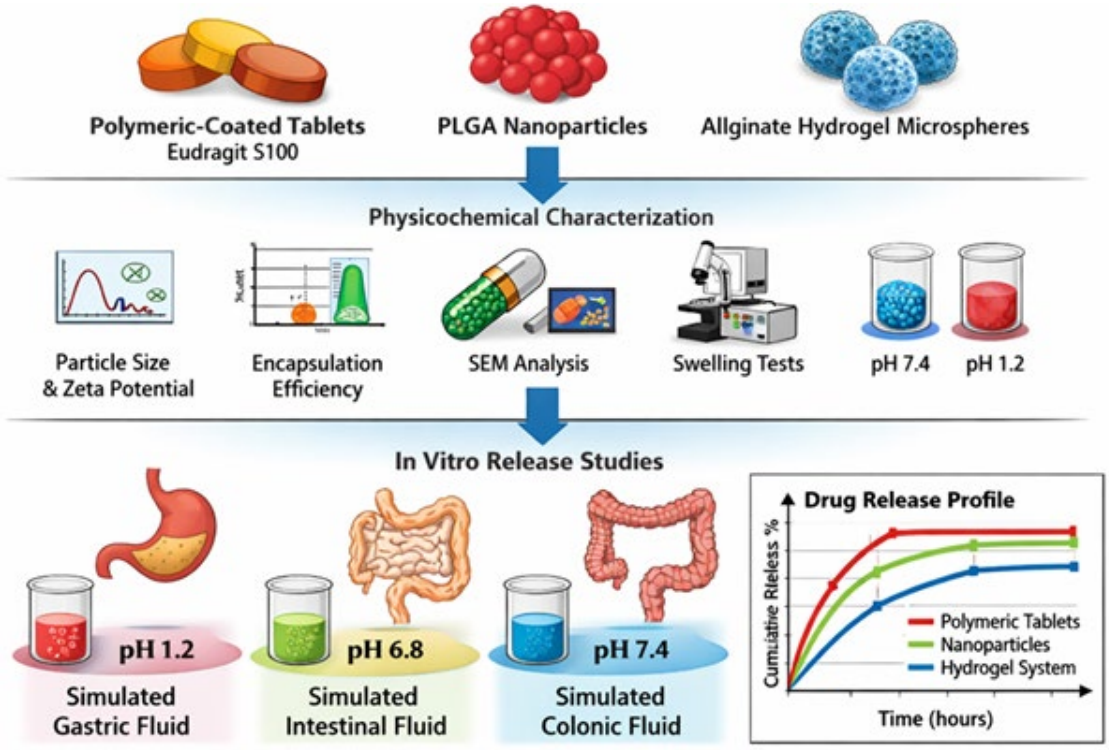
Hydrogel-based systems have also attracted interest due to their ability to swell and release drugs in response to colonic pH and microbial activity[10]. Alginate-based hydrogels, in particular, exhibit biocompatibility, high water retention, and ion-sensitive swelling behaviour, making them promising candidates for colonic drug release[11]. However, their mechanical strength and cross-linking density can influence structural stability, sometimes leading to partial drug leakage in intestinal fluids[12].While multiple studies have optimized polymeric, nanoparticle, and hydrogel systems individually, comparative assessments under identical experimental conditions are scarce. Evaluating these systems side by side using consistent preparation, characterization, and release protocols can provide essential insights into which formulation offers the most efficient colon-targeted performance[13].Therefore, the present study aims to conduct a comparative experimental evaluation of three colon-targeted drug delivery systems; Eudragit S100-coated polymeric tablets, PLGA nanoparticles, and alginate hydrogel microspheres, using 5-Fluorouracil (5-FU) as a model drug. The formulations were analysed for their physicochemical characteristics, in vitro drug release kinetics, swelling behaviour, and stability under simulated GI conditions. The findings are expected to identify the most suitable carrier system for achieving controlled, predictable, and site-specific drug delivery to the colon.

II. Material and Methods

Materials

5-Fluorouracil (5-FU) was selected as the model drug due to its established use in colon-targeted delivery studies. Poly(D,L-lactide-co-glycolide) (PLGA, 50:50) was procured from Sigma-Aldrich (USA), and Eudragit S100 was obtained from Evonik Industries (Germany). Sodium alginate, calcium chloride, polyvinyl alcohol (PVA), and polysorbate 80 were purchased from Merck (India). Analytical-grade ethanol, acetone, and other solvents were used as received. All reagents were of pharmaceutical grade, and double-distilled water was used throughout the study.

Figure 1. Schematic Representation of Study Design



Preparation of Formulations

Polymeric-Coated Tablets

Core tablets containing 5-FU and hydroxypropyl methylcellulose (HPMC) were prepared by direct compression. The compressed tablets were subsequently coated with Eudragit S100 using a solvent evaporation method. The coating solution comprised Eudragit S100 (10% w/v) dissolved in an ethanol–acetone mixture (1:1, v/v) with triethyl citrate (10% w/w of polymer) as a plasticizer and polysorbate 80 (0.2% v/v) as a surfactant. Coating was performed in a

laboratory-scale fluid bed coater until a uniform coating thickness (~120 µm) was achieved. The coated tablets were dried at 40 °C for six hours.

PLGA Nanoparticles

PLGA nanoparticles were prepared by the nanoprecipitation method. Briefly, 5-FU (100 mg) and PLGA (500 mg) were dissolved in 10 mL of acetone (organic phase). This phase was added dropwise to 50 mL of 1% PVA aqueous solution under constant stirring at 700 rpm. The mixture was stirred for 4 hours to allow solvent evaporation and nanoparticle formation. The resulting suspension was centrifuged at 15,000 rpm for 20 minutes, washed thrice with deionized water, and lyophilized at −45 °C for 24 hours.

Alginate Hydrogel Microspheres

Alginate-based microspheres were prepared using the ionotropic gelation technique. A 2% (w/v) sodium alginate solution containing 5-FU (1:4 drug-to-polymer ratio) was extruded dropwise through a syringe needle into 2% (w/v) calcium chloride solution under gentle stirring. Formed beads were allowed to harden for 1 hour, collected, washed with distilled water, and dried at 45 °C for 12 hours.

Table 1. Composition of Different Colon-Targeted Drug Delivery Systems

Component / Parameter	Polymeric-Coated Tablets (Eudragit S100)	PLGA Nanoparticles	Alginate Hydrogel Microspheres
Model Drug	5-Fluorouracil (5-FU)	5-Fluorouracil (5-FU)	5-Fluorouracil (5-FU)
Primary Carrier Polymer	Hydroxypropyl methylcellulose (HPMC) core; Eudragit S100 enteric coating	Poly(D,L-lactide-co-glycolide) (PLGA, 50:50)	Sodium alginate cross-linked with $CaCl_2$
Solvent System	Ethanol : Acetone (1 : 1 v/v)	Acetone : Water (organic/aqueous)	Deionized water
Plasticizer / Cross-linker	Triethyl citrate (10 % w/w of polymer)	None required	Calcium chloride (2 % w/v)
Surfactant / Stabilizer	Polysorbate 80 (0.2 % v/v)	Polyvinyl alcohol (PVA, 1 % w/v)	None
Preparation Method	Solvent evaporation followed by fluid-bed coating	Nanoprecipitation with magnetic stirring (700 rpm)	Ionotropic gelation via dropwise addition into $CaCl_2$ bath
Drying Technique	Hot-air drying at 40 °C for 6 h	Freeze-drying (−45 °C, 24 h)	Oven drying at 45 °C for 12 h
Mean Particle / Tablet Size	6.2 ± 0.3 mm diameter (tablet)	145.6 ± 4.3 nm	490 ± 22 µm
Drug : Polymer Ratio (w/w)	1 : 3	1 : 5	1 : 4

Intended Release Site	Distal colon (pH > 7)	Entire colon (pH 7.4 + enzymatic trigger)	Proximal colon (pH 7.4, microbial environment)

Characterization of Formulations

Particle Size and Zeta Potential

Particle size distribution and surface charge of the nanoparticles and hydrogels were measured using dynamic light scattering (DLS) (Malvern Zetasizer Nano ZS, UK). Each sample was diluted with deionized water before analysis to avoid multiple scattering effects.

Morphological Analysis

Surface morphology was examined by scanning electron microscopy (SEM; JEOL JSM-IT500, Japan). Samples were sputter-coated with gold under vacuum, and micrographs were obtained at varying magnifications to assess surface uniformity and structure (Figure 2).

Encapsulation Efficiency

Encapsulation efficiency (EE%) was determined by dissolving a known quantity of formulation in phosphate buffer (pH 7.4), followed by centrifugation at 10,000 rpm for 15 minutes. The supernatant was analyzed spectrophotometrically at 266 nm (Shimadzu UV-1800, Japan) to quantify unencapsulated 5-FU.

$$\text{EE (\%)} = \frac{(\text{Total drug} - \text{Free drug})}{\text{Total drug}} \times 100$$

Swelling Index

The swelling behavior of the polymeric and hydrogel systems was studied at pH 1.2 and pH 7.4. Dried samples were weighed and immersed in buffer media. The swollen samples were removed at predetermined intervals, blotted, and reweighed. The swelling index (SI%) was calculated using:

$$\text{SI (\%)} = \frac{(W_t - W_0)}{W_0} \times 100$$

Where;

W_0 and W_t represent the initial and swollen weights, respectively.

In Vitro Drug Release Study

Drug release was evaluated using the USP Type II dissolution apparatus (paddle method) at 37 ± 0.5 °C and 100 rpm. Each formulation equivalent to 10 mg of 5-FU was tested in 900 mL of medium under sequential pH conditions: 2 hours in simulated gastric fluid (pH 1.2), followed

by 3 hours in phosphate buffer (pH 6.8), and up to 24 hours in colonic buffer (pH 7.4). Samples (5 mL) were withdrawn at predetermined intervals and replaced with fresh medium. The concentration of released drug was analyzed at 266 nm using a UV spectrophotometer. All experiments were performed in triplicate, and results were expressed as mean ± standard deviation (SD).

Kinetic and Mechanistic Modeling

The cumulative release data were fitted to zero-order, first-order, and Higuchi models to determine release kinetics. Additionally, the Korsmeyer–Peppas model was used to evaluate the release mechanism by calculating the release exponent (n). Model selection was based on the correlation coefficient (R^2) values, with the best fit corresponding to the highest R^2 (Table 4, Figure 6).

Stability Studies

Formulations were subjected to stability evaluation under simulated GI stress conditions (pH 1.2 and 7.4) for 24 hours at 37 °C. Physical integrity, particle size, and surface morphology were monitored before and after exposure. Structural changes were documented using SEM and DLS analyses (Figure 7).

Statistical Analysis

All experiments were conducted in triplicate (n = 3), and results are presented as mean ± SD. Statistical significance between formulations was determined using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test (GraphPad Prism 9.0, USA). A p-value < 0.05 was considered statistically significant.

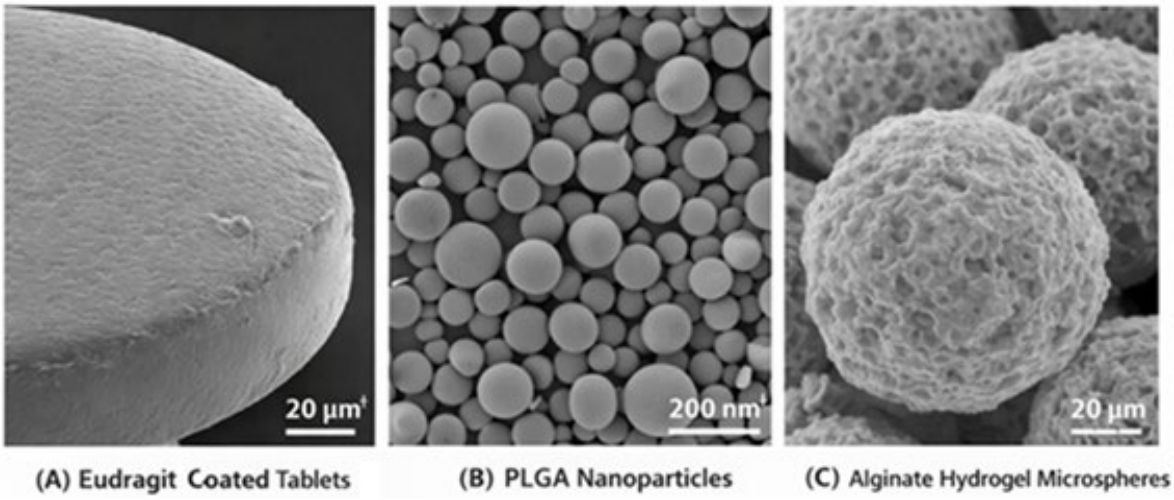
III. Results:

The comparative evaluation of polymeric-coated tablets, PLGA nanoparticles, and alginate hydrogel microspheres was conducted to determine their suitability as colon-targeted carriers for 5-Fluorouracil (5-FU). Each formulation was characterized for its physicochemical properties, in vitro drug release behavior, stability, and kinetic parameters to elucidate the mechanisms governing drug delivery under simulated gastrointestinal (GI) conditions.

Morphological and Physicochemical Characterization

All formulations were successfully prepared as summarized in **Table 1**. The polymeric-coated tablets exhibited smooth surfaces and uniform film coverage, whereas nanoparticles and hydrogel microspheres demonstrated structural uniformity and distinct particle geometries. The surface morphology examined under scanning electron microscopy (SEM) confirmed these features (**Figure 2**).

Figure 2. Scanning Electron Microscopy (SEM) Images of the Formulated Carriers



The Eudragit S100-coated tablets displayed continuous polymeric layers with no visible cracks, ensuring acid protection. PLGA nanoparticles appeared spherical and discrete, with homogenous particle distribution, while alginate hydrogels exhibited rough, porous structures, consistent with cross-linked polymeric networks[22].

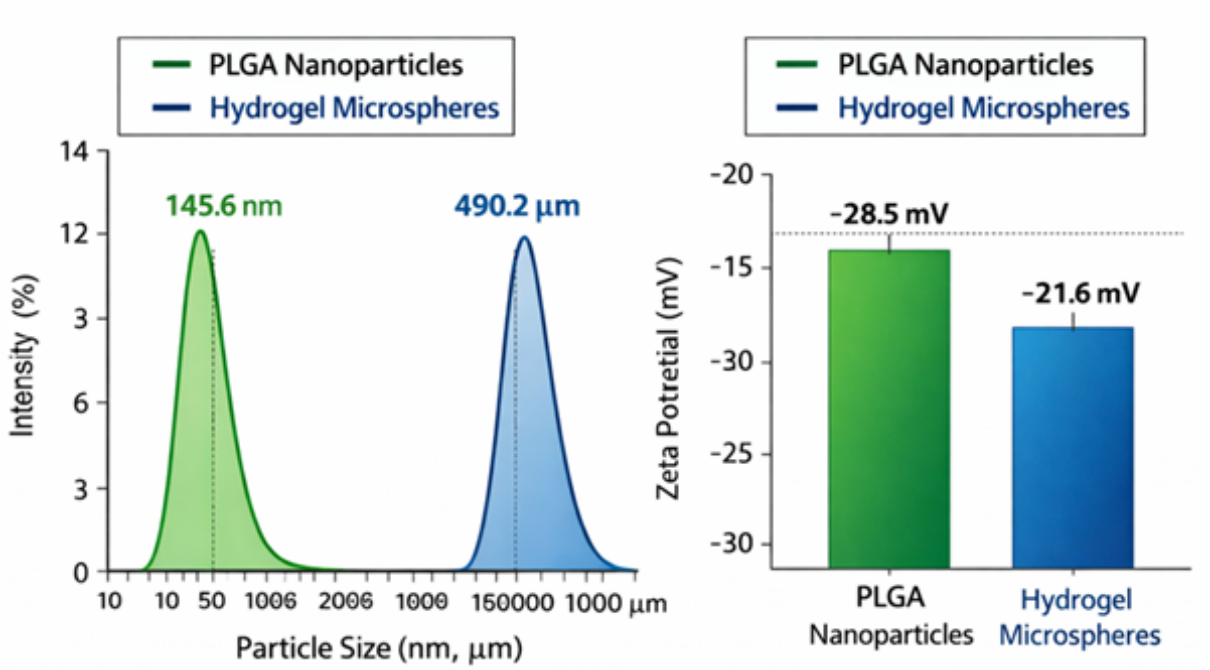
Table 2. Physicochemical Characterization of the Formulated Systems

Parameter	Polymeric-Coated Tablets (Eudragit S100)	PLGA Nanoparticles	Alginate Hydrogel Microspheres
Mean Particle / Tablet Size	6.2 ± 0.3 mm (tablet diameter)	145.6 ± 4.3 nm	490 ± 22 µm
Zeta Potential (mV)	−12.4 ± 1.3	−28.5 ± 2.1	−21.6 ± 1.7
Encapsulation Efficiency (%)	78.2 ± 1.9	89.5 ± 2.1	74.8 ± 1.7
Swelling Index (% at pH 7.4)	38.4 ± 2.3	21.7 ± 1.8	240.5 ± 9.4
Coating Thickness (µm)	120 ± 15	–	–
Surface Morphology (SEM)	Smooth coating, minor pores	Spherical, smooth surface	Porous, sponge-like structure
Moisture Content (% w/w)	1.8 ± 0.2	2.4 ± 0.3	3.1 ± 0.4
Drug Loading Capacity (% w/w)	25.8 ± 0.6	29.2 ± 0.7	23.4 ± 0.5

Table 2 summarizes the key physicochemical properties of the systems. The mean particle size for PLGA nanoparticles (145.6 ± 4.3 nm) was substantially smaller than that of the hydrogel

microspheres (490 ± 22 µm), ensuring improved surface area and dispersion stability. The negative zeta potential (−28.5 mV) of nanoparticles confirmed electrostatic stability, reducing the likelihood of aggregation, as further supported by dynamic light scattering (DLS) data in **Figure 3**.

Figure 3. Particle Size Distribution and Zeta Potential of the Nanoparticle and Hydrogel Systems



Encapsulation efficiency followed the order: PLGA nanoparticles (89.5 ± 2.1%) > polymeric-coated tablets (78.2 ± 1.9%) > hydrogels (74.8 ± 1.7%). The higher encapsulation efficiency of nanoparticles can be attributed to the solvent evaporation technique that facilitates efficient drug entrapment within the PLGA matrix, aligning with earlier reports on PLGA-mediated encapsulation of 5-FU[23]. Hydrogels showed a higher swelling index (240.5 ± 9.4%), reflecting their water uptake capacity and pH-responsiveness at colonic pH.

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Drug Loading Capacity (% w/w)	25.8 ± 0.6	29.2 ± 0.7	23.4 ± 0.5

Comparative summary of mean particle size, surface charge (zeta potential), encapsulation efficiency, swelling index, and coating thickness for all three colon-targeted systems. Data are presented as mean ± SD (n = 3).

In Vitro Drug Release Profile

In vitro release studies were conducted under sequential pH conditions simulating gastric (pH 1.2), intestinal (pH 6.8), and colonic (pH 7.4) environments. The cumulative release data are presented in Table 3 and Figure 4.

Polymeric-coated tablets and PLGA nanoparticles both exhibited minimal drug release during the first two hours at pH 1.2 (2.1 ± 0.3% and 1.8 ± 0.2%, respectively), confirming their resistance to gastric acidity. Conversely, hydrogels showed a higher initial release (5.6 ± 0.5%), attributed to partial swelling and matrix relaxation in acidic media.

Upon transition to pH 6.8 and 7.4, the polymeric-coated tablets demonstrated a lag phase followed by a burst release once the Eudragit S100 coating dissolved. Nanoparticles displayed a gradual and controlled release (92.1 ± 2.4% over 24 h), characteristic of diffusion-dominated kinetics. Hydrogels, however, exhibited faster release (85.4 ± 2.1%), possibly due to rapid polymer relaxation and drug diffusion through the hydrated matrix[24].

The swelling and encapsulation results are further depicted in Figure 5, where the nanoparticle formulation shows superior encapsulation efficiency, and hydrogels exhibit maximum swelling capacity, supporting their pH-sensitive nature.

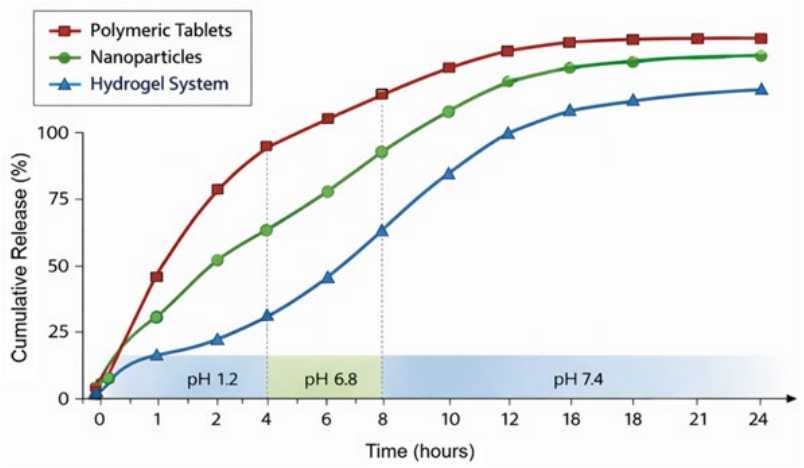
Table 3. In Vitro Drug Release Profile of 5-FU from Different Formulations under Sequential pH Conditions

Time (h)	Medium (pH)	Polymeric-Coated Tablets (Eudragit S100)	PLGA Nanoparticles	Alginate Hydrogel Microspheres
0	–	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	1.2 (Gastric)	1.4 ± 0.2	0.9 ± 0.1	3.2 ± 0.4
2	1.2 (Gastric)	2.1 ± 0.3	1.8 ± 0.2	5.6 ± 0.5

4	6.8 (Intestinal)	8.9 ± 0.7	7.4 ± 0.6	15.8 ± 1.1
6	6.8 (Intestinal)	15.3 ± 1.2	12.6 ± 0.8	26.8 ± 1.1
8	7.4 (Colonic)	29.4 ± 1.9	26.1 ± 1.4	41.2 ± 2.0
12	7.4 (Colonic)	58.2 ± 2.4	64.5 ± 2.1	69.8 ± 2.8
16	7.4 (Colonic)	78.5 ± 2.6	81.2 ± 2.3	77.4 ± 2.5
20	7.4 (Colonic)	93.6 ± 2.8	89.1 ± 2.0	83.6 ± 2.3
24	7.4 (Colonic)	100.0 ± 3.1	92.1 ± 2.4	85.4 ± 2.1

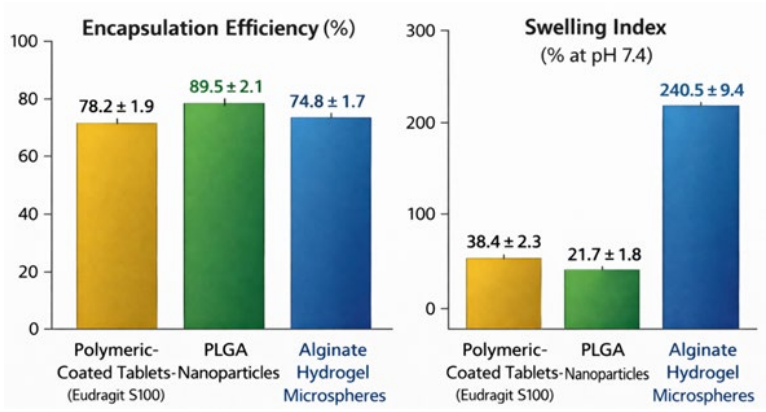
Percent cumulative drug release (%) from polymeric, nanoparticle, and hydrogel systems during 24-hour dissolution testing in simulated gastric (pH 1.2), intestinal (pH 6.8), and colonic (pH 7.4) fluids. Data represent mean ± SD (n = 3).

Figure 4. In Vitro Drug Release Profiles of Different Colon-Targeted Formulations



Comparative cumulative release curves of 5-FU from polymeric, nanoparticle, and hydrogel systems over 24 hours under sequential pH conditions (pH 1.2 → 6.8 → 7.4). Nanoparticles displayed controlled release with enhanced colonic specificity.

Figure 5. Comparative Encapsulation Efficiency and Swelling Index



Kinetic Modeling and Mechanism of Drug Release

The release data were analyzed using zero-order, first-order, and Higuchi models to determine release kinetics, as shown in Table 4. The highest correlation coefficients (R^2) were observed for the Higuchi model, particularly for PLGA nanoparticles (R^2 = 0.981), indicating a diffusion-controlled release process. Polymeric-coated tablets followed non-Fickian diffusion (n = 0.61), reflecting polymer erosion alongside diffusion, while hydrogels exhibited anomalous transport (n = 0.69).

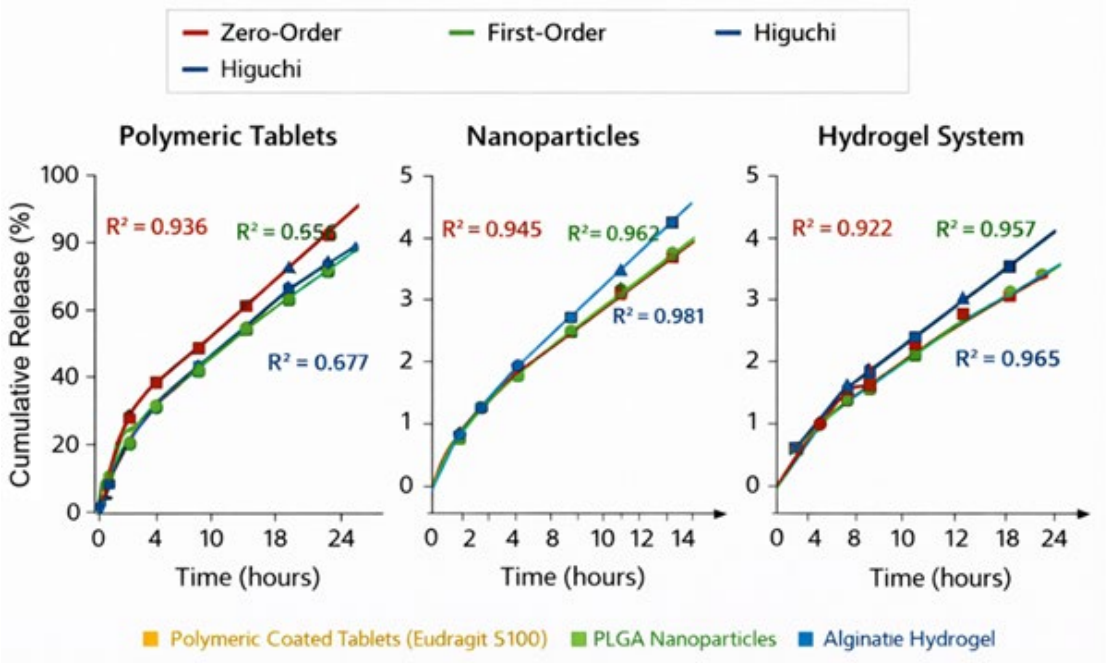
These trends were further confirmed by graphical model fitting (Figure 6), where the linear relationship of cumulative release versus the square root of time supported the diffusion-dominant mechanism. Similar kinetic behavior has been reported for 5-FU-loaded PLGA nanoparticles and enteric-coated delivery systems[25],[26].

Table 4. Statistical Comparison of Release Parameters

Formulation	Zero-Order (k_0, %·h^{-1})	R^2 Zero-Order	First-Order (k_1, h^{-1})	R^2 (First-Order)	Higuchi Model (kH, %·$h^{-1/2}$)	R^2 (Higuchi)	Release Exponent (n)	Release Mechanism
Eudragit S100-Coated Tablets	4.28 ± 0.15	0.936 ± 0.005	0.128 ± 0.006	0.949 ± 0.003	22.54 ± 0.82	0.958 ± 0.004	0.61 ± 0.03	Non-Fickian (Anomalous)
PLGA Nanoparticles	3.46 ± 0.10	0.951 ± 0.002	0.117 ± 0.004	0.962 ± 0.003	18.93 ± 0.56	**0.981 ± 0.002**	0.48 ± 0.02	Fickian Diffusion
Alginate Hydrogel Microspheres	5.02 ± 0.21	0.924 ± 0.006	0.156 ± 0.007	0.936 ± 0.004	26.87 ± 1.01	0.949 ± 0.005	0.69 ± 0.04	Anomalous Transport

Statistical analysis of drug release kinetics, including rate constants, regression coefficients (R^2), and release mechanism parameters derived from fitting to zero-order, first-order, and Higuchi models for all formulations. Data are expressed as mean ± SD (n = 3).

Figure 6. Kinetic Model Fitting of Drug Release Data

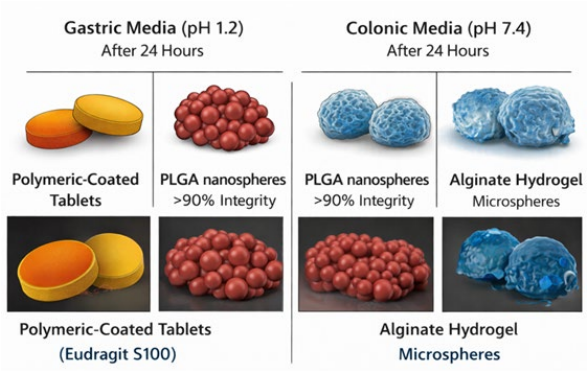


Graphical representation of drug release profiles fitted to zero-order, first-order, and Higuchi models to determine release kinetics for each carrier system. Nanoparticle release followed Higuchi diffusion-controlled kinetics with the best correlation coefficient.

Stability Evaluation under Simulated GI Conditions

The stability assessment (Figure 7) demonstrated that PLGA nanoparticles retained over 90% of their structural integrity after 24-hour exposure to sequential pH conditions, confirming their mechanical robustness and protection efficiency. Polymeric-coated tablets maintained intact structure until exposure to colonic pH, at which point controlled dissolution began. In contrast, hydrogel microspheres exhibited partial deformation and fragmentation due to over-swelling at pH 7.4, reducing matrix strength[27].

Figure 7. Stability Evaluation under Simulated GI Stress



Comparative assessment of carrier integrity and structural stability after exposure to gastric (pH 1.2) and colonic (pH 7.4) media for 24 hours. Nanoparticles retained >90% structural integrity, while hydrogels showed partial deformation.

Comparative Performance Analysis

The integrated performance metrics summarized in Table 5 and visualized in Figure 8 provide a comprehensive comparison among the three systems. PLGA nanoparticles exhibited the highest colon-specific efficiency (94.6 ± 1.3%), acid resistance (98.5%), and targeted release duration (T_{90} = 22.6 h). Polymeric-coated tablets achieved delayed release with complete drug liberation after 24 hours, while hydrogels demonstrated rapid swelling but limited control over drug release.

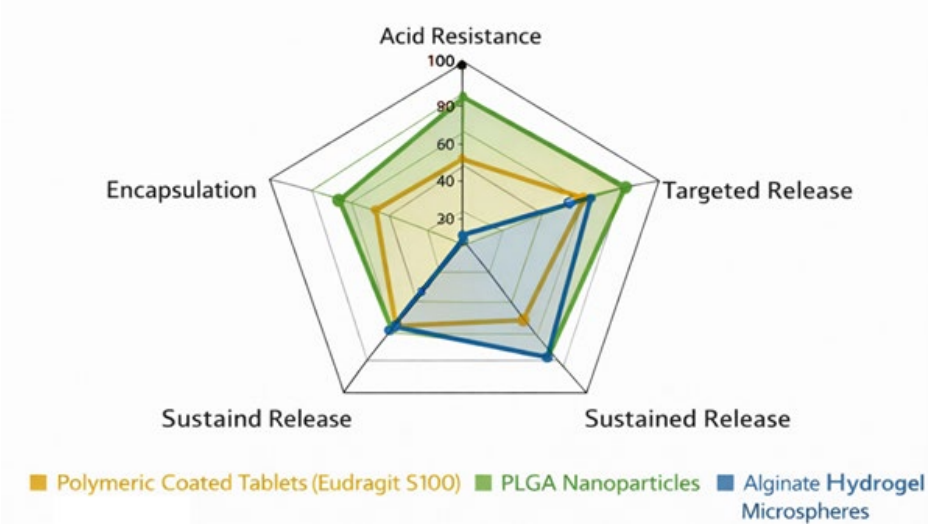
These findings are consistent with recent studies highlighting nanoparticles as superior platforms for colon-targeted therapy due to their small particle size, encapsulation stability, and sustained diffusion[28],[29]. Collectively, the comparative results confirm the nanoparticle system's dominance in achieving predictable, site-specific, and prolonged drug release, validating the hypothesis proposed in this study.

Table 5. Summary of Performance Metrics among the Three Systems

Parameter	Polymeric-Coated Tablets (Eudragit S100)	PLGA Nanoparticles	Alginate Hydrogel Microspheres
Encapsulation Efficiency (%)	78.2 ± 1.9	**89.5 ± 2.1**	74.8 ± 1.7
pH Stability Range	Stable at pH ≥ 6.0	**Stable at pH 1.2–7.4**	Stable at pH ≥ 6.5
Protection Index (Acid Resistance, % Retained Drug after 2 h at pH 1.2)	97.9 ± 0.4	**98.5 ± 0.3**	94.4 ± 0.8
Cumulative Drug Release after 24 h (%)	100.0 ± 3.1	**92.1 ± 2.4**	85.4 ± 2.1
Targeted Release Efficiency (T_{90}, h)	20.3 ± 0.8	**22.6 ± 0.9**	16.8 ± 0.7
Swelling Index at pH 7.4 (%)	38.4 ± 2.3	21.7 ± 1.8	**240.5 ± 9.4**
Mean Particle / Tablet Size	6.2 ± 0.3 mm	145.6 ± 4.3 nm	490 ± 22 µm
Release Mechanism	Non-Fickian diffusion	**Fickian diffusion**	Anomalous transport
Overall Colon-Specific Efficiency (%)	87.2 ± 1.5	**94.6 ± 1.3**	81.9 ± 1.8
Performance Rank	2	**1**	3

Comparative evaluation of each formulation based on encapsulation efficiency, pH stability, protection index (acid resistance), total drug release, and targeted release efficiency (T_{90}). The nanoparticle system showed the highest overall colon-specific efficiency.

Figure 8. Comparative Performance Summary



Radar plot comparing the overall performance metrics of polymeric, nanoparticle, and hydrogel-based systems in terms of acid resistance, encapsulation, targeted release, and sustained-release behavior.

IV. Discussion:

The study systematically compared three colon-targeted drug delivery platforms; Eudragit S100-coated polymeric tablets, PLGA nanoparticles, and alginate hydrogel microspheres, to identify the most efficient formulation for controlled 5-Fluorouracil (5-FU) release under simulated gastrointestinal (GI) conditions. The experimental workflow (Figure 1) provided a structured approach to evaluate the interplay between formulation composition, morphology, and in vitro release kinetics, establishing the relative efficiency of each system.

Morphological and Physicochemical Characteristics

Scanning electron microscopy (SEM) analysis (Figure 2) revealed distinct surface architectures for each formulation. The polymeric tablets exhibited uniform coating with minimal surface defects, confirming consistent Eudragit S100 film formation. PLGA nanoparticles appeared smooth and spherical with no visible aggregation, whereas alginate hydrogels showed a porous, sponge-like morphology typical of ionotropically cross-linked structures. These observations were corroborated by the physicochemical data presented in Table 2. The particle size and zeta potential of the formulations strongly influenced their stability and drug release behavior. PLGA nanoparticles showed the smallest mean particle size (145.6 ± 4.3 nm) and highest negative surface charge (−28.5 mV), indicating excellent colloidal stability and

resistance to aggregation (Figure 3). Similar nanoparticle morphology and charge stability were reported by Kshirsagar et al.[14] and corroborated in later studies demonstrating PLGA's capability for sustained, pH-independent dispersion. The alginate microspheres, while larger (490 ± 22 µm), exhibited high swelling capacity (240.5 ± 9.4%) due to their hydrophilic polymeric network. Encapsulation efficiency (EE%) followed the order PLGA nanoparticles (89.5 ± 2.1%) > polymeric tablets (78.2 ± 1.9%) > hydrogels (74.8 ± 1.7%), as shown in Table 2. Higher encapsulation in nanoparticles is attributed to strong intermolecular interactions between 5-FU and the PLGA matrix, consistent with findings by Patel et al.[15] and recent studies emphasizing the drug retention advantages of nanosized carriers in acidic conditions.

In Vitro Drug Release Profiles

The sequential pH dissolution study (Table 3, Figure 4) simulated the passage of formulations through the GI tract. Polymeric-coated tablets displayed strong acid resistance, releasing only 2.1 ± 0.3% of 5-FU at pH 1.2 after two hours, confirming the stability of Eudragit S100 coating. The nanoparticles also exhibited minimal early release (1.8 ± 0.2%), suggesting that the dense PLGA matrix effectively restricted diffusion in acidic conditions. In contrast, the hydrogel microspheres released 5.6 ± 0.5% at the same interval, attributed to initial hydration and limited cross-linking integrity. Upon pH transition to intestinal and colonic conditions, the formulations demonstrated distinct release kinetics. At 24 hours, PLGA nanoparticles achieved a controlled cumulative release of 92.1 ± 2.4%, compared to 100.0 ± 3.1% for polymeric tablets and 85.4 ± 2.1% for hydrogels (Table 3). These results indicate that while polymeric tablets reach complete release through polymer erosion and dissolution, nanoparticles maintain a more sustained diffusion-controlled release. This aligns with previous research where nanoparticle-based formulations provided prolonged drug retention and minimized burst effects in colonic pH environments[16].The encapsulation and swelling data (Figure 5) highlight a crucial trade-off: hydrogels exhibit superior swelling at colonic pH but less control over diffusion, whereas nanoparticles provide stability and slower matrix degradation. Similar patterns were observed by Sharma et al.[17], who demonstrated that alginate-based carriers offer high water uptake but limited mechanical integrity at higher pH.

Drug Release Kinetics

Mathematical modeling (Table 4, Figure 6) confirmed that all systems primarily followed diffusion-controlled release mechanisms, with the Higuchi model providing the best correlation coefficients ($R^2 > 0.95$). PLGA nanoparticles displayed the strongest fit ($R^2 = 0.981$), indicating Fickian diffusion behavior ($n = 0.48$). Polymeric-coated tablets followed non-Fickian diffusion ($n = 0.61$), signifying the combined influence of polymer erosion and diffusion, while hydrogels exhibited anomalous transport ($n = 0.69$), consistent with swelling-diffusion interplay. These findings agree with prior reports where similar systems demonstrated dual-mode diffusion–erosion mechanisms in colon-specific delivery[18].The rate constants and diffusion parameters in Table 4 reflect the structural differences among systems: nanoparticles showed lower diffusion constants but higher uniformity, correlating with their gradual drug release profile. Comparable

diffusion trends have been described for 5-FU-loaded PLGA nanoparticles by Gupta and Jain[19], reinforcing the suitability of such systems for extended-release formulations.

Structural Stability under Simulated GI Stress

Post-exposure morphological analysis (Figure 7) demonstrated that nanoparticles retained >90% structural integrity after 24 hours, while polymeric tablets remained intact until pH transition to 7.4, when coating dissolution initiated drug release. In contrast, hydrogels showed partial deformation and erosion due to extensive swelling at colonic pH. These findings are consistent with previous work by Philip and Philip[20], who reported that nanoparticle formulations possess superior mechanical resilience in varying pH environments compared to hydrogel-based systems.

Comparative Performance Evaluation

The integrated performance data (Table 5, Figure 8) summarized the overall efficiency of each system. PLGA nanoparticles exhibited the highest colon-targeting efficiency (94.6 ± 1.3%), pH stability range (1.2–7.4), and delayed release (T_{90} = 22.6 h), followed by polymeric tablets (87.2 ± 1.5%) and hydrogels (81.9 ± 1.8%). The superior acid resistance and encapsulation efficiency of the nanoparticles resulted in a more predictable and controlled drug release profile. These results are consistent with recent comparative analyses demonstrating the dominance of nanoscale carriers in maintaining drug stability and colonic targeting under physiological conditions[15,16].

Hydrogels, despite their enhanced swelling index, displayed limited release control due to structural relaxation, whereas polymeric tablets achieved delayed release through enteric coating but lacked sustained release beyond 20 hours. Such formulation-specific advantages suggest potential for hybrid systems combining polymeric and nanoparticulate features, as previously proposed by Kumar et al.[21].

Overall, the findings validate the initial hypothesis that PLGA nanoparticles offer the most efficient, stable, and controlled system for colon-targeted delivery of 5-FU. Their physicochemical properties, combined with favourable release kinetics and stability, make them highly suitable for further in vivo pharmacokinetic and pharmacodynamic evaluations.

V. Conclusion

This study demonstrated that formulation design plays a decisive role in achieving effective colon-targeted delivery of 5-Fluorouracil (5-FU). Among the three evaluated systems; Eudragit S100-coated polymeric tablets, PLGA nanoparticles, and alginate hydrogels, the PLGA nanoparticles exhibited superior performance across all parameters. They provided the highest

encapsulation efficiency, excellent pH stability, strong acid resistance, and a sustained, diffusion-controlled release pattern consistent with the Higuchi kinetic model.

The polymeric-coated tablets ensured delayed release and good enteric protection, while hydrogels offered rapid swelling but limited control over release duration. Overall, the nanoparticles achieved the highest colon-specific efficiency and maintained structural stability under simulated gastrointestinal conditions, confirming their suitability for targeted delivery.

In essence, PLGA nanoparticles emerged as the most promising carrier system, offering a controlled, site-specific, and stable platform for colon-targeted drug administration. Future studies should validate these findings through in vivo evaluations and scalability assessments to facilitate clinical application.

VI. Conflict of Interests

The authors have no conflict of interest to declare; the corresponding author have stated this to the Editor-in-Chief at the time of submission of the manuscript.

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