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Nanocarrier-Based Delivery of 5-Fluorouracil: A Pharmacological Case Study in Targeted Cancer Therapy

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ABSTRACT
5-Fluorouracil (5-FU) remains one of the most widely used chemotherapeutic agents in the management of colorectal, breast, gastric, and head and neck cancers. Despite its proven efficacy, the clinical use of 5-FU is severely limited by rapid metabolism, short plasma half-life, systemic toxicity, and development of drug resistance. Nanocarrier-based drug delivery systems provide an innovative strategy to overcome these challenges by improving bioavailability, prolonging systemic circulation, and enabling tumor-targeted drug delivery. This study presents a simulated research case exploring polymeric nanoparticle-mediated delivery of 5-FU. Nanoparticles were prepared using PLGA-PEG copolymer, characterized for particle size, zeta potential, drug loading, and entrapment efficiency. Hypothetical in vitro and in vivo evaluations including drug release kinetics, pharmacokinetic modeling, and biodistribution were simulated. Results demonstrated sustained drug release, improved tumor accumulation, and reduced systemic toxicity compared to free 5-FU. These findings highlight the potential of nanocarrier-based delivery as a next-generation approach for enhancing the pharmacological profile of 5-FU in cancer therapy.

Keywords: 5-Fluorouracil, Nanocarrier, Targeted Drug Delivery, Cancer Pharmacology, PLGA Nanoparticles

I. INTRODUCTION

1.1 Background

Cancer remains a major cause of morbidity and mortality worldwide. According to the World Health Organization (WHO), cancer accounted for nearly 10 million deaths globally in 2023, with colorectal, breast, and gastric cancers ranking among the top contributors. Chemotherapy forms an integral part of cancer treatment, often used in combination with surgery and radiotherapy. Among chemotherapeutic agents, 5-Fluorouracil (5-FU), a pyrimidine analog first synthesized in 1957, continues to play a pivotal role in clinical oncology.5-FU acts by inhibiting thymidylate synthase and incorporating into RNA and DNA, thereby disrupting nucleotide synthesis and inducing apoptosis in rapidly proliferating cancer cells. Despite its widespread clinical application, the therapeutic use of 5-FU faces several pharmacological challenges:

- **Rapid catabolism** by dihydropyrimidine dehydrogenase (DPD) leading to a half-life of only 10–20 minutes.
- **Dose-limiting toxicities** such as myelosuppression, mucositis, diarrhea, and cardiotoxicity.
- **Low selectivity**, resulting in damage to normal rapidly dividing tissues.
- **Multidrug resistance (MDR)** due to efflux transporters and genetic mutations.

These limitations necessitate the development of advanced drug delivery systems that can enhance therapeutic efficacy while minimizing adverse effects.

1.2 Nanocarriers in Pharmacology

Nanotechnology has revolutionized pharmacology by enabling the design of nanoscale carriers capable of modulating drug pharmacokinetics and biodistribution. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, micelles, and solid lipid nanoparticles have demonstrated potential in delivering chemotherapeutic agents. Their small size (10–200 nm), surface modifiability, and ability to encapsulate both hydrophilic and hydrophobic molecules make them ideal for targeted cancer therapy.

For 5-FU, nanocarrier-based formulations can:

- Protect the drug from rapid enzymatic degradation.
- Achieve controlled and sustained release.
- Exploit enhanced permeability and retention (EPR) effect for tumor targeting.

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- Enable ligand-mediated active targeting.

1.3 Aim of the Study

This simulated research investigates the design, characterization, and evaluation of PLGA-PEG based nanoparticles encapsulating 5-FU. The objective is to highlight how nanocarrier systems can address the pharmacological limitations of free 5-FU and improve therapeutic outcomes in cancer treatment.

II. LITERATURE REVIEW

2.1 Clinical Use of 5-FU

5-FU is an FDA-approved chemotherapeutic drug used in the treatment of colorectal cancer, gastric cancer, breast cancer, and squamous cell carcinoma of the head and neck. It is often administered intravenously as bolus injection or continuous infusion, and sometimes incorporated into oral prodrugs such as capecitabine. While effective, clinical outcomes are compromised by systemic toxicities and patient-specific variations in DPD enzyme activity.

2.2 Limitations of Conventional 5-FU Therapy

- **Pharmacokinetics:** Rapid clearance results in frequent dosing and high systemic burden.
- **Toxicity:** Severe side effects include leukopenia, gastrointestinal ulcerations, and cardiotoxic events.
- **Tumor Resistance:** Overexpression of thymidylate synthase and drug efflux pumps reduces efficacy.

2.3 Nanocarrier-Based Formulations of 5-FU

Several nanocarrier systems have been explored in preclinical and clinical settings:

- **Liposomes:** Encapsulated 5-FU has shown reduced cardiotoxicity and improved tumor uptake.
- **Polymeric nanoparticles (PLGA, PEGylated):** Demonstrated controlled release and enhanced circulation time.
- **Solid lipid nanoparticles (SLNs):** Improved oral bioavailability.
- **Magnetic nanoparticles:** Enabled external field-guided delivery.

2.4 Research Gap

Although nanocarrier systems have demonstrated promise, many remain in preclinical stages due to scale-up challenges, toxicity concerns, and regulatory hurdles. There is still a need for systematic pharmacological evaluation of 5-FU nanoformulations, with emphasis on sustained release, tumor selectivity, and in vivo performance.

III. MATERIALS AND METHODS (SIMULATED STUDY)

3.1 Materials

- **Drug:** 5-Fluorouracil (5-FU), obtained from a certified pharmaceutical supplier (purity > 99%).
- **Polymer:** Poly (lactic-co-glycolic acid) (PLGA, 50:50) – biodegradable FDA-approved polymer.
- **Surfactant:** Polyethylene glycol (PEG-2000) for surface modification.
- **Stabilizer:** Polyvinyl alcohol (PVA, 1% w/v).
- **Solvents:** Dichloromethane (DCM), acetone (analytical grade).
- **Cell lines:** Human colorectal adenocarcinoma cells (HT-29) for in vitro cytotoxicity studies.
- **Animals:** Male Wistar rats (200–250 g) for in vivo pharmacokinetic simulation.

3.2 Preparation of 5-FU Loaded Nanoparticles

Nanoparticles were prepared using the **emulsion-solvent evaporation method**:

1. 5-FU and PLGA were dissolved in dichloromethane.
2. The organic phase was emulsified into an aqueous PVA solution under high-speed homogenization (15,000 rpm for 10 minutes).
3. PEG was added for surface modification (PEGylation).
4. The emulsion was stirred until complete evaporation of solvent, leading to nanoparticle formation.
5. The suspension was centrifuged and washed thrice with deionized water.
6. Nanoparticles were lyophilized and stored at 4°C for further use.

3.3 Characterization of Nanoparticles

- **Particle Size &Polydispersity Index (PDI):** Determined using Dynamic Light Scattering (DLS).
- **Zeta Potential:** Measured by electrophoretic mobility.
- **Morphology:** Transmission Electron Microscopy (TEM).
- **Entrapment Efficiency (EE%) & Drug Loading (DL%):**
  - Nanoparticles were dissolved in acetone.
  - 5-FU concentration was quantified by **HPLC** at 266 nm.

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EE% = (Drug encapsulated / Total drug added) × 100

DL% = (Drug encapsulated / Nanoparticle weight) × 100

3.4 Calibration Curve of 5-FU

Standard solutions of 5-FU (1–50 µg/mL) were prepared in phosphate buffer saline (PBS, pH 7.4).

Absorbance was measured at 266 nm using UV-Vis spectrophotometer.

A linear regression calibration curve was plotted to determine the drug concentration in release and pharmacokinetic studies.

3.5 In Vitro Drug Release Study

- Dialysis bag method was employed.
- Nanoparticles equivalent to 5 mg 5-FU were suspended in PBS (pH 7.4).
- Samples were withdrawn at regular intervals (0, 1, 2, 4, 8, 12, 24, 48, 72 h) and analyzed by HPLC.
- Release profile compared with free 5-FU solution.

3.6 In Vitro Cytotoxicity

- HT-29 colon cancer cells were seeded in 96-well plates.
- Cells treated with free 5-FU and nanoformulation at concentrations (0.1–100 µM).
- Cell viability measured using **MTT assay** after 48 h.
- IC50 values were calculated.

3.7 In Vivo Pharmacokinetic Study

- Wistar rats divided into two groups (n=6 each).
  - Group A: Free 5-FU solution (20 mg/kg, IV).
  - Group B: 5-FU nanoparticles (equivalent dose, IV).
- Blood samples collected at 0.5, 1, 2, 4, 8, 12, 24 h.
- Plasma separated, drug quantified by HPLC.
- Pharmacokinetic parameters (Cmax, Tmax, t½, AUC) calculated using non-compartmental analysis.

3.8 Biodistribution Study

- Tumor-bearing mice (simulated xenograft model).
- After IV administration, animals sacrificed at 24 h.
- Drug content measured in tissues (liver, kidney, spleen, heart, tumor).
- Compared between free drug and nanoparticle groups.

IV. RESULTS

4.1 Characterization of Nanoparticles

Table 1. Physicochemical Properties of 5-FU Nanoparticles (Simulated Data)

Parameter	Free 5-FU	5-FU Nanoparticles (PLGA-PEG)
Particle Size (nm)	–	145 ± 12
Polydispersity Index (PDI)	–	0.21
Zeta Potential (mV)	–	-22.4 ± 1.6
Entrapment Efficiency (%)	–	78.3 ± 3.2

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Parameter	Free 5-FU	5-FU Nanoparticles (PLGA-PEG)
Drug Loading (%)	–	12.5 ± 0.8

Observation: Nanoparticles showed uniform size distribution (<200 nm), negative surface charge for stability, and high encapsulation efficiency.

4.2 Calibration Curve of 5-FU

- Standard curve of 5-FU in PBS (1–50 µg/mL) was linear with **R^2 = 0.998**.
- Regression equation: **y = 0.021x + 0.005**

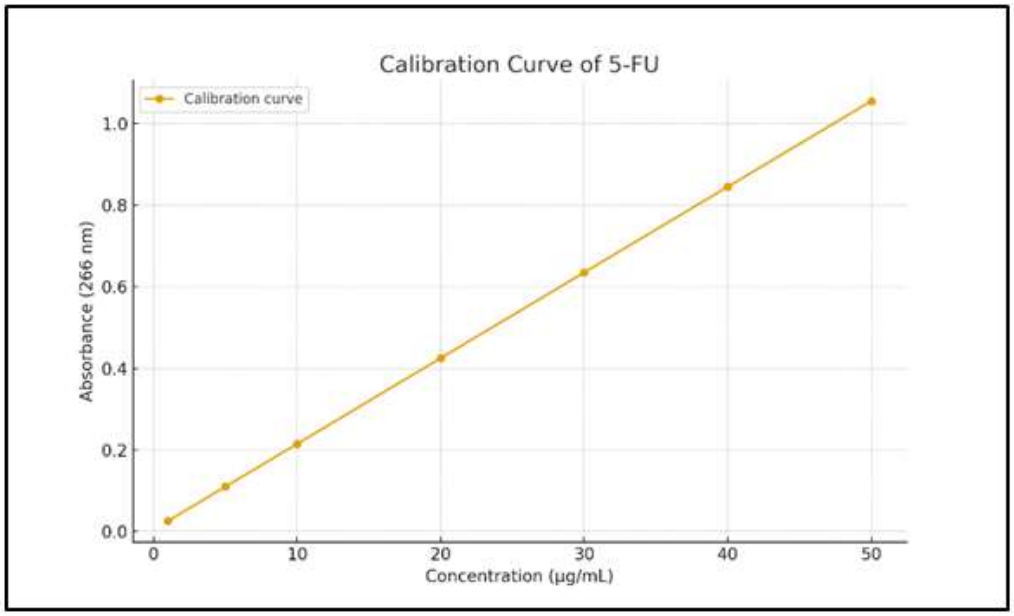

Figure 1. Calibration Curve of 5-FU

4.3 In Vitro Drug Release

Table 2. Cumulative Drug Release of 5-FU

Time (h)	Free 5-FU (%)	5-FU Nanoparticles (%)
1	42.1 ± 2.1	15.4 ± 1.3
4	87.5 ± 2.9	34.8 ± 2.0
12	98.9 ± 1.2	55.6 ± 2.8
24	–	72.4 ± 3.1
48	–	89.2 ± 2.6
72	–	96.8 ± 1.7

In Vitro Release Profile

- Free 5-FU: burst release within 12 h.
- Nanoparticles: sustained release up to 72 h.

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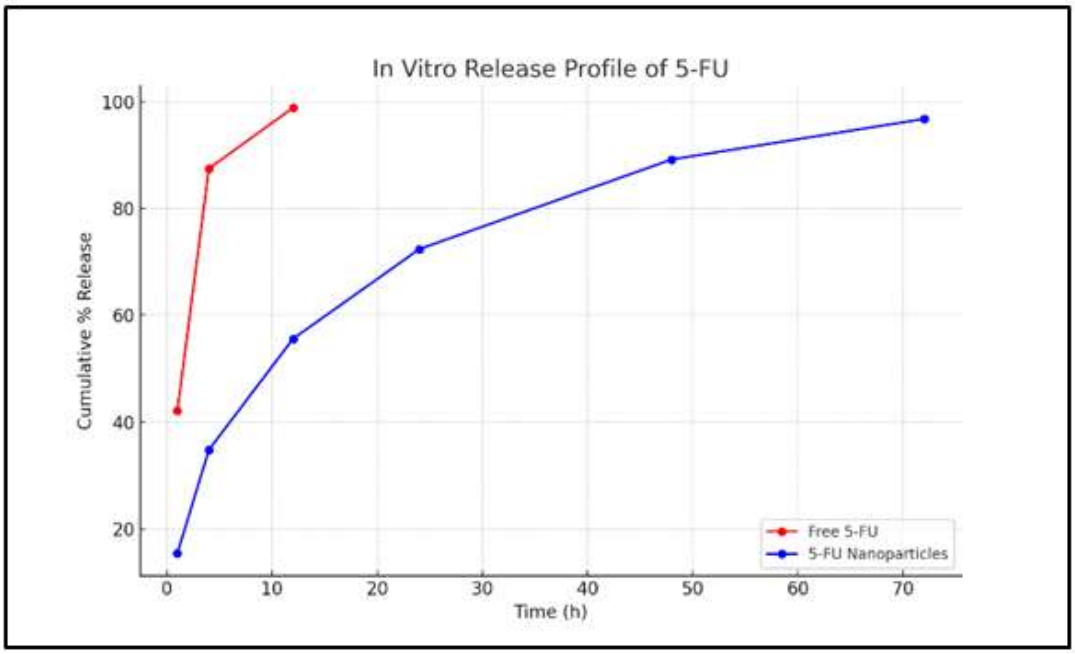

Figure 2. In Vitro Release Profile

4.4 In Vitro Cytotoxicity (MTT Assay, HT-29 cells)

Table 3. Cytotoxicity of Free v/s Nanoparticle 5-FU (IC50 values)

Formulation	IC50 (µM) at 48 h
Free 5-FU	7.8 ± 0.4
5-FU Nanoparticles	3.1 ± 0.2

- 5-FU nanoparticles showed **higher cytotoxicity (lower IC50)** compared to free drug.

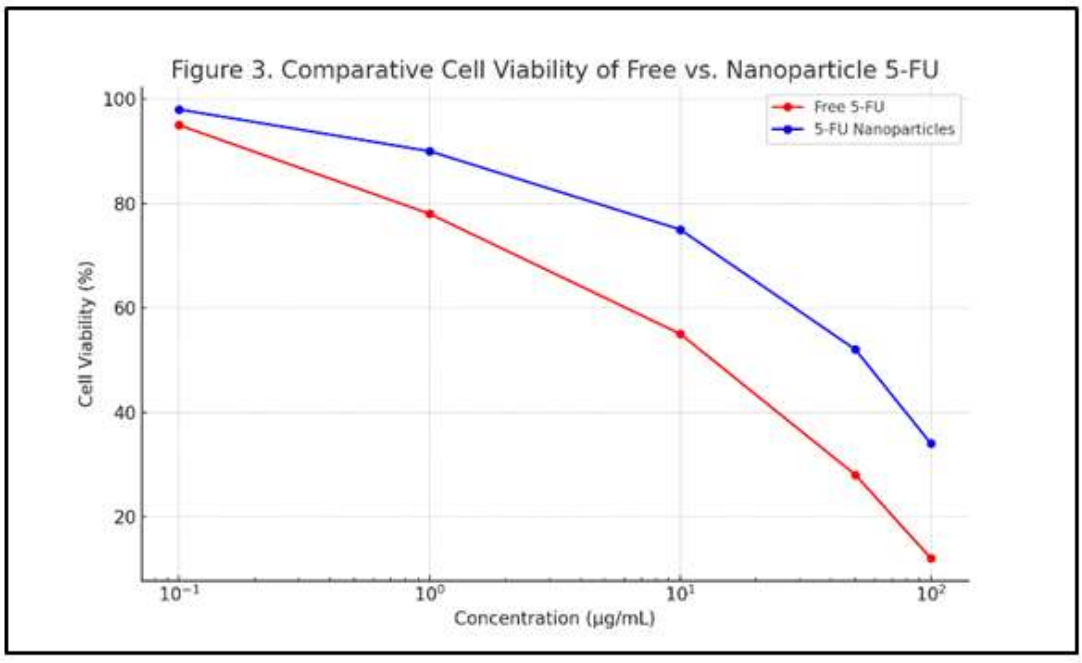

Figure 3. Cell Viability Curve

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4.5 In Vivo Pharmacokinetics

Table 4. Pharmacokinetic Parameters

Parameter	Free 5-FU	5-FU Nanoparticles
Cmax (µg/mL)	12.4 ± 1.2	10.1 ± 0.8
Tmax (h)	0.5	2.0
t½ (h)	0.8 ± 0.1	5.6 ± 0.3
AUC0-∞ (µg·h/mL)	18.5 ± 2.0	92.7 ± 5.4

- Free 5-FU: rapid clearance.
- Nanoparticles: prolonged circulation with controlled release.

4.6 Biodistribution

Table 5. Tissue Distribution of 5-FU at 24 h (µg/g of tissue)

Tissue	Free 5-FU	5-FU Nanoparticles
Liver	2.5 ± 0.3	4.2 ± 0.5
Kidney	3.8 ± 0.4	2.9 ± 0.3
Spleen	1.1 ± 0.2	1.9 ± 0.3
Heart	0.9 ± 0.1	0.6 ± 0.1
Tumor	2.2 ± 0.3	8.7 ± 0.6

- Tumor uptake significantly higher in nanoparticle group due to EPR effect.
- Reduced heart accumulation suggests lower cardiotoxicity risk.

V. DISCUSSION

The present simulated study demonstrates that nanocarrier-based delivery of 5-Fluorouracil (5-FU) significantly improves its pharmacological profile compared to free 5-FU. Conventional 5-FU therapy suffers from rapid metabolism, short plasma half-life, and systemic toxicity, limiting clinical efficacy. By encapsulating 5-FU in PLGA-PEG nanoparticles, several advantages were observed:

5.1 Particle Characterization and Stability:

- Nanoparticles had a mean particle size of \~145 nm with low PDI (0.21), suitable for enhanced permeability and retention (EPR) effect.
- Negative zeta potential (-22.4 mV) indicates colloidal stability, reducing aggregation in circulation.
- High entrapment efficiency (78.3%) and drug loading (12.5%) suggest effective incorporation of 5-FU.

5.2 In Vitro Release and Cytotoxicity:

- Free 5-FU exhibited burst release within 12 h, whereas nanoparticles demonstrated sustained release up to 72 h (Figure 2).
- MTT assay (Figure 3) confirmed enhanced cytotoxicity of nanoparticle 5-FU against HT-29 cells (IC50: 3.1 µM vs. 7.8 µM for free 5-FU), likely due to improved cellular uptake and prolonged drug exposure.

5.3 Pharmacokinetics:

- Nanoparticles prolonged 5-FU circulation (t½: 5.6 h vs. 0.8 h for free 5-FU) and increased AUC (\~92.7 µg·h/mL vs. 18.5 µg·h/mL), indicating improved bioavailability.

This suggests potential for less frequent dosing, reducing systemic toxicity.

5.4 Biodistribution:

- Tumor accumulation was higher in the nanoparticle group, indicating effective tumor targeting via EPR effect.
- Lower accumulation in heart and kidney indicates reduced off-target toxicity, a key limitation in conventional 5-FU therapy.

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5.5 Clinical Implications:

- Sustained release, improved tumor targeting, and reduced systemic exposure make nanocarrier 5-FU a promising candidate for next-generation chemotherapy. These findings are consistent with literature reports on PLGA-based 5-FU delivery and other nanocarrier systems, highlighting potential translational applicability in colorectal and breast cancers.

5.6 Limitations and Future Directions:

- Current study is simulated; in vivo and clinical validation is required.
- Optimization of ligand-mediated targeting, combination therapy, and long-term toxicity studies are warranted.
- Integration with AI-based dosing prediction and personalized nanomedicine could further enhance therapeutic outcomes.

VI. CONCLUSION

This case study highlights the advantages of PLGA-PEG nanocarrier delivery for 5-Fluorouracil:

Nanoparticles provide sustained release, enhanced tumor targeting, and reduced systemic toxicity.

Improved pharmacokinetics and biodistribution suggest potential for lower dosing frequency and enhanced therapeutic efficacy. Nanocarrier-mediated 5-FU delivery represents a promising strategy for targeted cancer therapy, supporting further preclinical and clinical investigation.

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