Ind. J. Pharm. Edu. Res., 2026; 60(2):575-581.
https://www.ijper.org

Original Article

Exploring a Novel Approach: *In vitro* Cytotoxicity Study of Capecitabine Loaded Resealed Erythrocytes

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ABSTRACT

Background: Conventional chemotherapy with Capecitabine is often associated with systemic toxicity, poor tumour selectivity, and suboptimal drug concentrations at tumour sites, limiting its therapeutic efficacy. Advanced drug delivery strategies are needed to enhance drug bioavailability while minimizing adverse effects. **Objectives:** This study investigates resealed erythrocytes as a novel drug delivery system for Capecitabine, aiming to improve targeted drug release, therapeutic efficacy, and biocompatibility in hepatocellular carcinoma treatment. **Materials and Methods:** Capecitabine was encapsulated within erythrocyte membranes to formulate Capecitabine-loaded resealed erythrocytes. The *in vitro* anticancer efficacy of the formulation was evaluated using MTT cytotoxicity assay and DAPI staining-based apoptosis analysis in HepG2 cells. **Results:** The MTT assay demonstrated that Capecitabine-loaded resealed erythrocytes exhibited enhanced cytotoxicity, with a lower IC_{50} value (206.6 µg/mL) compared to plain Capecitabine (315.4 µg/mL). DAPI staining further confirmed increased apoptotic activity, characterized by chromatin condensation and nuclear fragmentation. These findings suggest that erythrocyte carriers provide sustained and targeted drug release, improving the anticancer efficacy of Capecitabine. **Conclusion:** The encapsulation of Capecitabine within resealed erythrocytes presents a promising targeted drug delivery strategy for cancer therapy. This approach has the potential to enhance drug retention, reduce systemic toxicity, and improve therapeutic outcomes, warranting further investigation in preclinical and clinical settings.

Keywords: Cancer, Cytotoxicity, Capecitabine, Resealed erythrocytes, MTT assay, Apoptosis.

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Received: 07-04-2025;
Revised: 16-06-2025;
Accepted: 21-08-2025.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is one of the most prevalent and aggressive liver malignancies, posing a significant challenge due to its poor prognosis and limited therapeutic options.[1] Conventional chemotherapy for HCC, including 5-Fluorouracil (5-FU), is often associated with systemic toxicity, rapid drug degradation, and poor tumour selectivity.[2] To address these limitations, resealed erythrocytes have emerged as a biocompatible, long-circulating, and targeted drug delivery system, capable of improving therapeutic efficacy while minimizing side effects.[3]

Capecitabine, a fluoro-pyrimidine carbamate prodrug of 5-FU, is widely used in HCC treatment due to its enhanced tumour selectivity and oral bioavailability.[4,5] However, its systemic administration leads to dose-limiting toxicities, necessitating a more controlled and targeted approach for drug delivery.[5,6] In this study, Capecitabine-loaded erythrocytes were developed to provide a sustained, targeted release of the drug at tumour sites, potentially improving anticancer efficacy while reducing adverse effects.

To ensure the integrity and efficacy of Capecitabine, its identity was confirmed using melting point determination, Fourier-Transform Infrared (FTIR) spectroscopy, maximum wavelength (λ_{max}) determination, and High-Performance Liquid Chromatography (HPLC) assay. The drug was then encapsulated within erythrocytes using two distinct techniques: the Preswell method and the Dilution method, with glutaraldehyde as a cross-linking agent. Comparative physicochemical and biological evaluations of both formulations were performed, leading to the selection of the Preswell technique for further *in vitro* and *in vivo* studies, owing to its superior encapsulation efficiency and stability.[7]

To evaluate the anticancer efficacy of Capecitabine-loaded erythrocytes, an MTT cytotoxicity assay was employed. The MTT assay is a well-established method that quantifies mitochondrial

DOI: 10.5530/ijper.20266766

activity in viable cells through the enzymatic conversion of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into purple formazan crystals.[7] The absorbance of formazan at 570 nm serves as a reliable indicator of cellular viability and drug-induced cytotoxicity.[7] Additionally, alternative metabolic assays, such as MTS, XTT, WST, and resazurin-based assays, were considered to complement the MTT findings, providing a comprehensive assessment of drug efficacy.[7]

Despite the advantages of cell-based cytotoxicity assays, significant intra-assay and inter-assay variability is often encountered.[8,9] Intra-assay variation arises from inconsistencies within a single experimental setup, whereas inter-assay variation refers to fluctuations between separate experiments conducted under different conditions.[10] These variations emphasize the necessity of robust experimental design, statistical validation, and appropriate controls to ensure reproducibility and reliability in drug efficacy studies.[8,10]

This study aims to establish Capecitabine-loaded resealed erythrocytes as a promising strategy for targeted HCC therapy, potentially enhancing treatment outcomes while mitigating systemic toxicity.

MATERIALS AND METHODS

Materials

The human hepatocellular carcinoma cell line HepG2 was obtained from the National Centre for Cell Science (NCCS), Pune, India. Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Low Glucose, Cat No: 11965-092, Gibco, Invitrogen) supplemented with 10% Fetal Bovine Serum (FBS) (Cat No: 10270106, Gibco, Invitrogen) and 100 IU/mL penicillin and 100 µg/mL streptomycin (Krishgen Biosystems, Mumbai). To prevent microbial contamination, Antibiotic-Antimycotic Solution (100X) (Cat No: 15240062, Thermo Fisher Scientific) was used. All cell culture experiments were performed in 96-well flat-bottom plates (for cytotoxicity assays) and 24-well plates (for apoptosis studies). The incubator (New Brunswick Scientific CO_2 Incubator, Model CO281R) was maintained at 37°C with 5% CO_2 and 95% relative humidity.[11]

Synthesis of Capecitabine Loaded Resealed Erythrocytes

The whole 'O' blood samples were obtained from blood bank of Krishna Hospital, Karad, Maharashtra. It was centrifuged at 3000 rpm for 5 min at 4±1°C. The serum and buffy coats were removed by 3 times washing with phosphate buffer saline pH 7.4. The washed erythrocytes were diluted with PBS and stored at 4°C until use. The Capecitabine loaded erythrocytes were prepared by dilution technique and Preswell dilution technique as per the method described in our published work.[12]

MTT Assay

Cell Culture and Preparation

HepG2 cells were cultured in DMEM supplemented with FBS and antibiotics, as described above. Cells were maintained in a humidified incubator at 37°C with 5% CO_2. Upon reaching 60-70% confluency, they were trypsinized and seeded at a density of 5000 cells per well in 200 µL of DMEM in 96-well plates. The plates were incubated for 24 hr to allow cell attachment before drug treatment.

Cytotoxicity Assessment

The cytotoxic effect of Capecitabine-loaded resealed erythrocytes was evaluated using the MTT assay, which measures mitochondrial enzyme activity in viable cells. After 24 hr of incubation, cells were treated with varying concentrations of Capecitabine-loaded erythrocytes (160, 80, 40, 20, 10 and 5 µg/mL) and incubated for an additional 48 hr. The wells were then washed twice with PBS, followed by the addition of 20 µL of MTT solution (5 mg/mL in PBS) to each well. The plates were incubated at 37°C for 4 hr, allowing formazan crystal formation. After incubation, 100 µL of Dimethyl Sulfoxide (DMSO) was added to dissolve the formazan crystals, and the absorbance was measured at 570 nm using a microplate reader. The IC_{50} (half-maximal inhibitory concentration) was determined using GraphPad Prism (Version 5.1).[13,14]

$$\text{Surviving cells (\%)} = \frac{\text{Mean OD of test compound}}{\text{Mean OD of Negative control}} x100$$

DAPI Staining for Apoptosis Detection

Sample Preparation

Apoptotic cell death was assessed using DAPI (4′,6-diamidino-2-phenylindole) staining, a nuclear stain that binds selectively to DNA. HepG2 cells were seeded at a density of 2×10^5 to 1×10^6 cells per well in 24-well plates and allowed to adhere overnight. Cells were harvested, centrifuged, and resuspended in 1 mL of PBS at room temperature. Fixation was performed by slowly transferring the suspension into 4 mL of ice-cold absolute ethanol (-20°C) while vortexing at high speed. The fixed cells were stored at -20°C for 5-15 min, centrifuged, and rehydrated in 5 mL of PBS for 15 min.[15-17]

Counterstaining and Microscopy

The DAPI staining solution was prepared by diluting the stock solution to 3 µM in a buffer containing 100 mM Tris (pH 7.4), 150 mM NaCl, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$ and 0.1% Nonidet P-40. Cells were centrifuged, the supernatant was discarded, and 1 mL of DAPI solution was added to the pellet. The cell suspension was incubated at room temperature for 15 min.

For flow cytometry-based detection, stained cells were analysed directly in suspension. For fluorescence microscopy, cells were

centrifuged, washed, and resuspended in PBS before being mounted on slides with a coverslip. Live cells appeared rounded with uniform blue fluorescence, whereas apoptotic cells displayed nuclear condensation, fragmentation, and increased fluorescence intensity.[16]

RESULTS

MTT Assay

The cytotoxic potential of Capecitabine-loaded resealed erythrocytes and plain Capecitabine was evaluated using the MTT assay on HepG2 cells. The assay is based on the reduction of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into formazan crystals by mitochondrial enzymes in metabolically active cells. The percentage of cell viability was determined to compare the cytotoxic effects of both formulations. A higher percentage of cell viability indicates lower cytotoxicity, whereas a decrease in viability reflects increased anticancer activity. The results showed a dose-dependent cytotoxic effect, with higher drug concentrations leading to reduced cell viability.

The IC_{50} value of Capecitabine-loaded resealed erythrocytes was 206.6 µg/mL, while that of plain Capecitabine was 315.4 µg/mL, indicating a greater cytotoxic effect of the resealed erythrocyte formulation (Table 1). The percentage of cell viability at different drug concentrations further supported this observation, as Capecitabine-loaded resealed erythrocytes demonstrated lower viability percentages compared to the plain drug at equivalent concentrations (Table 2, Figure 1).

The MTT assay results suggest that Capecitabine-loaded resealed erythrocytes exhibit enhanced cytotoxicity compared to plain Capecitabine, which may be attributed to improved drug delivery and intracellular uptake (Figure 1).

DAPI Staining for Apoptosis Detection

To further assess apoptotic cell death, DAPI staining was performed to visualize nuclear morphology following treatment with Capecitabine-loaded resealed erythrocytes and plain Capecitabine. Live cells exhibited uniformly rounded nuclei with evenly distributed dye (blue fluorescence), whereas apoptotic cells appeared as shrunken masses with chromatin condensation and nuclear fragmentation.

The control images showed predominantly viable cells, while both Capecitabine-loaded erythrocytes and plain Capecitabine-treated samples exhibited a mixture of live and apoptotic cells. However, cells treated with the Capecitabine-loaded resealed erythrocytes displayed a higher proportion of apoptotic cells, as indicated by brighter fluorescence intensity and increased nuclear fragmentation, compared to the plain drug-treated group (Figures 2-4).

DISCUSSION

Conventional chemotherapy often suffers from non-specific distribution, leading to systemic toxicity and adverse side effects.[18] Additionally, many chemotherapeutic agents, including Capecitabine, exhibit limited tumour selectivity and suboptimal pharmacokinetics, which can compromise therapeutic efficacy. To address these challenges, various drug delivery systems have been developed, each with distinct advantages and limitations.

Table 1: **IC_{50} values of Capecitabine Resealed Erythrocytes and Plain Capecitabine.**

Sample Code	IC_{50} Value (HepG2) (µg/mL)
Capecitabine Resealed Erythrocytes	206.6
Plain Capecitabine	315. 4

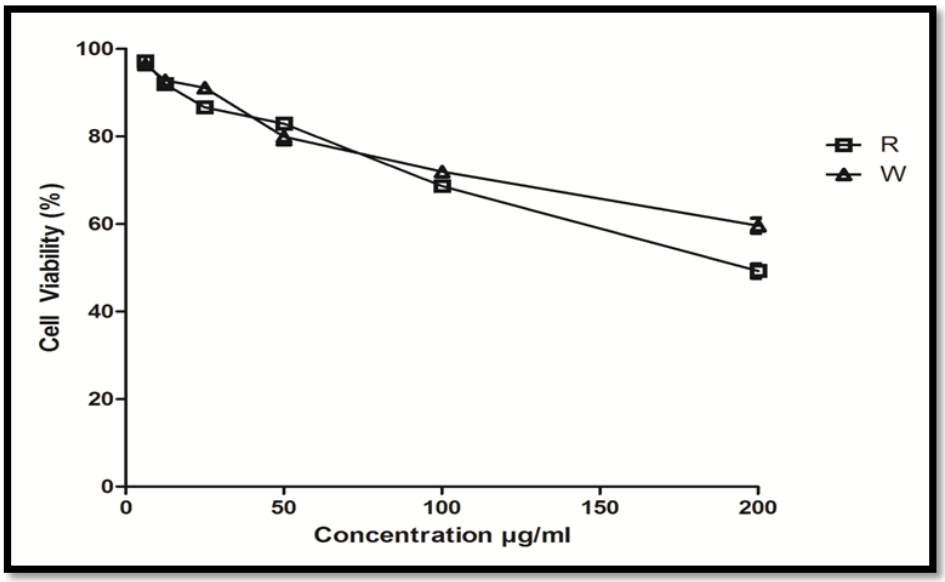

Figure 1: Graph of MTT assay. Where R is Capecitabine Resealed Erythrocytes and W is Plain Capecitabine.

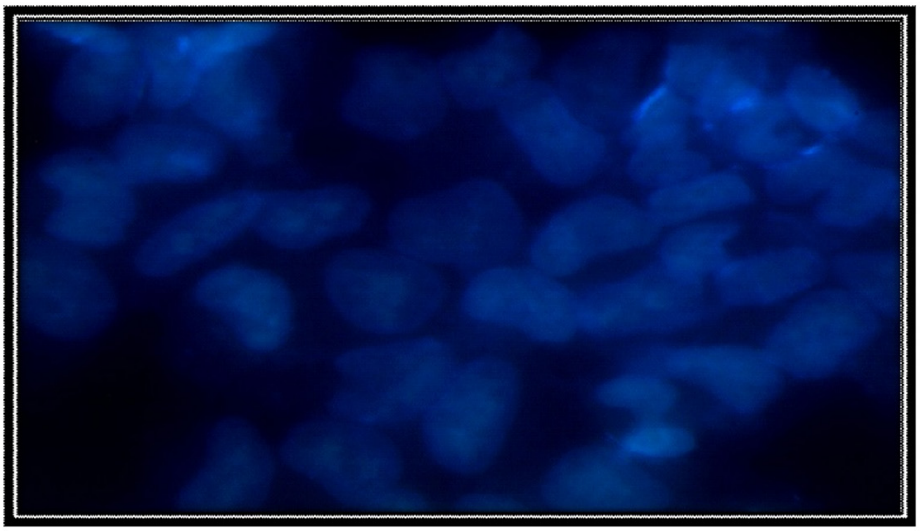

Figure 2a: Apoptosis image of control group.

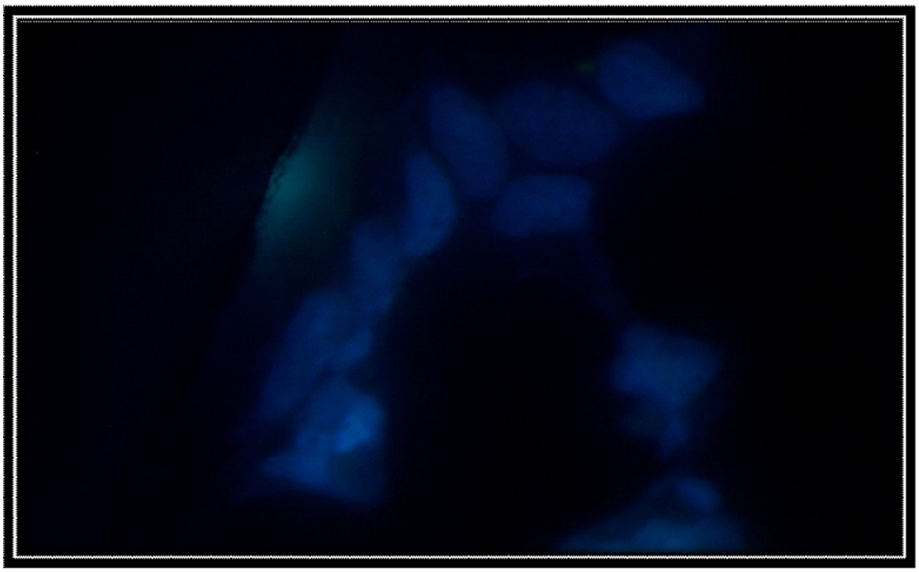

Figure 2b: Apoptosis study of control group.

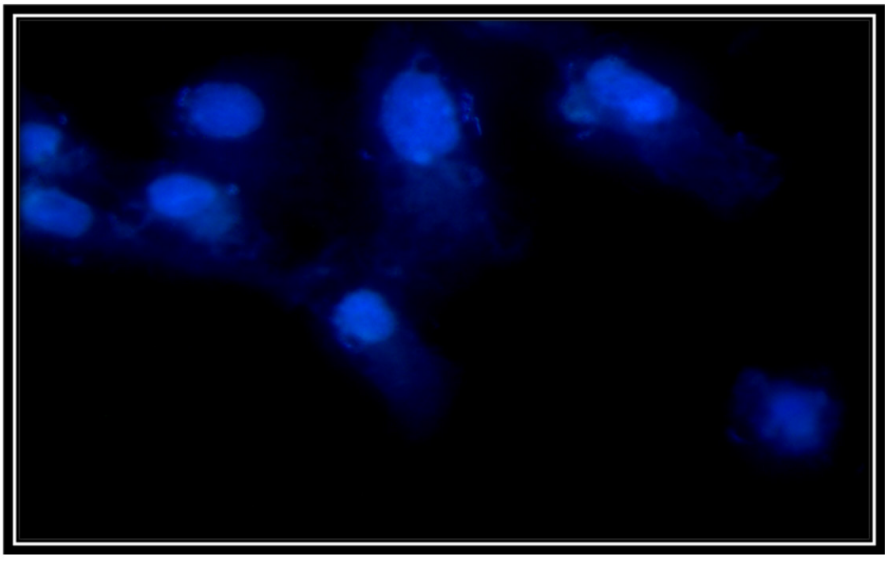

Figure 3a: Apoptosis study of Capecitabine resealed erythrocytes.

Nanocarriers such as nanoniosomes have been explored to enhance the delivery of chemotherapeutic agents.[19] For instance, Capecitabine-loaded nanoniosomes have demonstrated reduced cytotoxicity and higher efficacy compared to the free drug, attributed to improved drug encapsulation and controlled release profiles. However, these systems may face challenges like rapid clearance by the Mononuclear Phagocyte System (MPS) and potential immunogenicity, which can limit their clinical application.[20]

Utilizing erythrocytes as drug carriers offers several compelling advantages. Erythrocytes are inherently biocompatible and exhibit minimal immunogenicity, reducing the risk of adverse immune responses.[21] The natural lifespan of erythrocytes allows for prolonged circulation, facilitating sustained drug release and improved therapeutic outcomes.[22] Erythrocytes can encapsulate substantial amounts of therapeutic agents, providing a high payload capacity.[23]

In our study, the Capecitabine-loaded resealed erythrocytes demonstrated a lower IC_{50} value (206.6 µg/mL) compared to plain Capecitabine (315.4 µg/mL) in HepG2 cells, indicating enhanced cytotoxic efficacy. This improvement can be attributed to the prolonged circulation time and sustained drug release afforded by the erythrocyte carriers, which enhance drug bioavailability at the tumour site.

While erythrocyte-based systems offer significant benefits, they are not without challenges. The loading efficiency of drugs into erythrocytes can be variable, and the integrity of the erythrocyte membrane must be maintained to prevent premature drug release. Advancements in encapsulation techniques, such as hypotonic dialysis and membrane perturbation methods, are being explored to enhance drug loading and retention.[22]

In comparison to other delivery systems, the Capecitabine-loaded erythrocyte system offers a unique combination of biocompatibility, prolonged circulation, and high drug-loading capacity, positioning it as a promising alternative to conventional nanoparticle-based carriers. Future research should focus on optimizing loading techniques, ensuring membrane stability, and conducting comprehensive preclinical and clinical evaluations to fully realize the potential of erythrocyte-based drug delivery in cancer therapy.

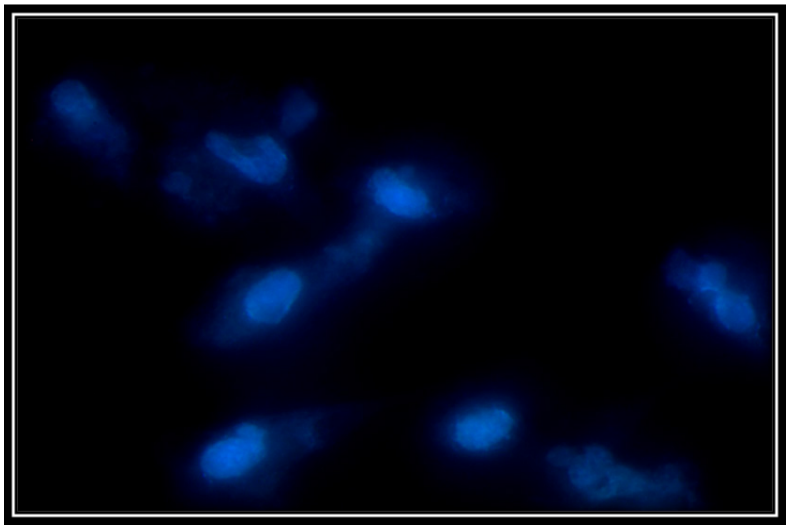

Figure 3b: Apoptosis study of Capecitabine resealed erythrocytes.

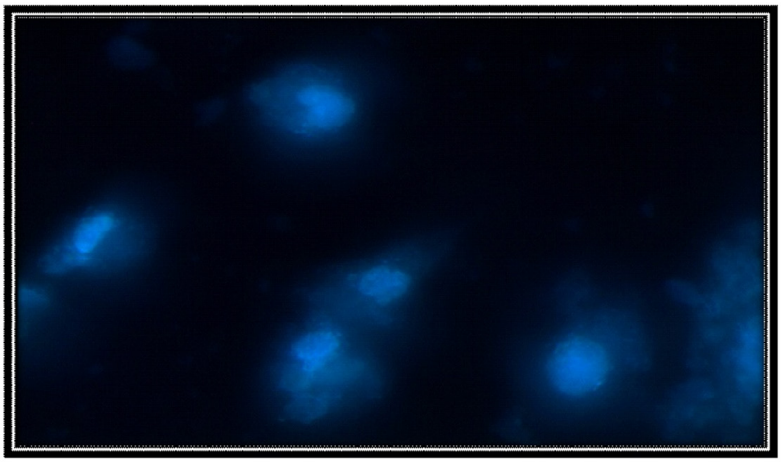

Figure 4a: Apoptosis study of Capecitabine.

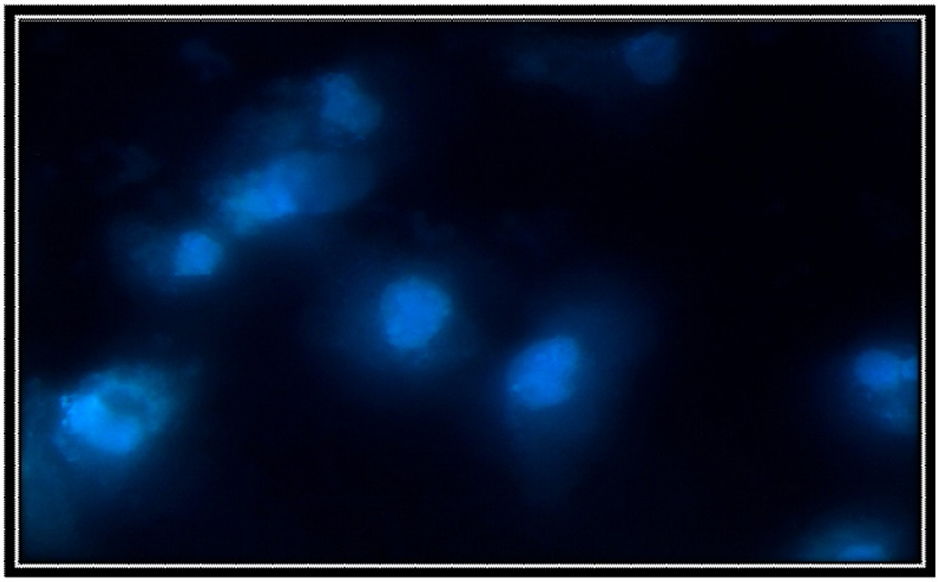

Figure 4b: Apoptosis study of Capecitabine.

Table 2: Percentage Cell Viability of Capecitabine Resealed Erythrocytes and Plain Capecitabine.

Concentration (µg/mL)	% cell viability	
	Capecitabine Resealed Erythrocytes (R) (Mean±S.D.)	Plain Capecitabine (W) (Mean±S.D.)
5	96.385%	91.13%
10	92.765%	90.915%
20	91.06%	86.595%
40	79.895%	82.87%
80	71.915%	68.62%
160	59.575%	49.255%

CONCLUSION

This study highlights the potential of resealed erythrocytes as an effective drug delivery system for Capecitabine in cancer therapy. The encapsulation process yielded Capecitabine-loaded resealed erythrocytes with favourable physicochemical properties, demonstrating enhanced cytotoxicity and apoptosis induction in HepG2 cells compared to the free drug.

The MTT assay confirmed superior cytotoxic effects, with lower IC_{50} values for the resealed erythrocyte formulation, while DAPI staining revealed greater apoptotic activity, characterized by chromatin condensation and nuclear fragmentation. These findings indicate that Capecitabine-loaded resealed erythrocytes not only enhance anticancer efficacy but also function as a sustained-release formulation, potentially improving therapeutic outcomes while reducing systemic toxicity.

Overall, Capecitabine encapsulation within resealed erythrocytes represents a promising approach for targeted cancer therapy. However, further preclinical and clinical studies are warranted to validate its safety, efficacy, and translational potential in oncological applications.

ACKNOWLEDGEMENT

The authors would like to thank Hetero Drugs, Hyderabad, Telangana for providing Capecitabine as a free gift sample.

ABBREVIATIONS

HCC: Hepatocellular Carcinoma; **5-FU:** 5-Fluorouracil; **FTIR:** Fourier-Transform Infrared Spectroscopy; **λ_{max}:** Maximum Wavelength; **HPLC:** High-Performance Liquid Chromatography; **PBS:** Phosphate Buffered Saline; **DMEM:** Dulbecco's Modified Eagle Medium; **FBS:** Fetal Bovine Serum; **DMSO:** Dimethyl Sulfoxide; **MTT:** 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide; **DAPI:** 4′,6-Diamidino-2-Phenylindole; **IC_{50}:** Half-Maximal Inhibitory Concentration; **MTS:** 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; **XTT:** 2,3-Bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide; **WST:** Water-Soluble Tetrazolium; **MPS:** Mononuclear Phagocyte System; **NCCS:** National Centre for Cell Science.

FUNDING

The authors thankful to Krishna Vishwa Vidyapeeth (Deemed to be University) Karad forproviding necessary financial assistance for conducting this research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol was approved by Krishna Institute of Medical Sciences Animal Ethical Committee, Karad, Maharashtra, India (Reg. No. 255/PO/ReBi/S/2000/CPCSEA).

SUMMARY

Hepatocellular Carcinoma (HCC) is an aggressive liver cancer with poor prognosis and limited treatment options. Conventional chemotherapy (e.g., 5-Fluorouracil or Capecitabine) suffers from systemic toxicity and poor tumor selectivity. This study investigates the use of resealed erythrocytes (red blood cells) as a novel, targeted delivery system for Capecitabine, a prodrug of 5-FU, to improve its therapeutic efficacy against HCC. Capecitabine was encapsulated into erythrocytes using two techniques: Preswell and Dilution, with the Preswell method showing better efficiency. Drug identity was confirmed using melting point, FTIR, λmax, and HPLC. MTT assay was conducted on HepG2 (liver cancer) cells to assess cytotoxicity. DAPI staining was used to detect apoptosis. Capecitabine-loaded erythrocytes showed a significantly lower IC_{50} (206.6 µg/mL) compared to plain Capecitabine (315.4 µg/mL), indicating higher cytotoxicity. Apoptotic features, such as chromatin condensation and nuclear fragmentation, were more prominent in cells treated with the encapsulated form. Erythrocyte-based drug delivery showed better tumor targeting, prolonged circulation, and reduced systemic toxicity. Capecitabine-loaded resealed erythrocytes are a promising drug delivery system for targeted HCC treatment, combining sustained release, improved efficacy, and lower toxicity.

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Cite this article: Chivate AN, Chivate ND, Patil SS, Dhadde SB. Exploring a Novel Approach: *In vitro* Cytotoxicity Study of Capecitabine Loaded Resealed Erythrocytes. Indian J of Pharmaceutical Education and Research. 2026;60(2):575-81.