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Development and Evaluation of Guar Gum and Ethyl Cellulose Nanoparticles for Targeted Delivery of Capecitabine in Colorectal Cancer

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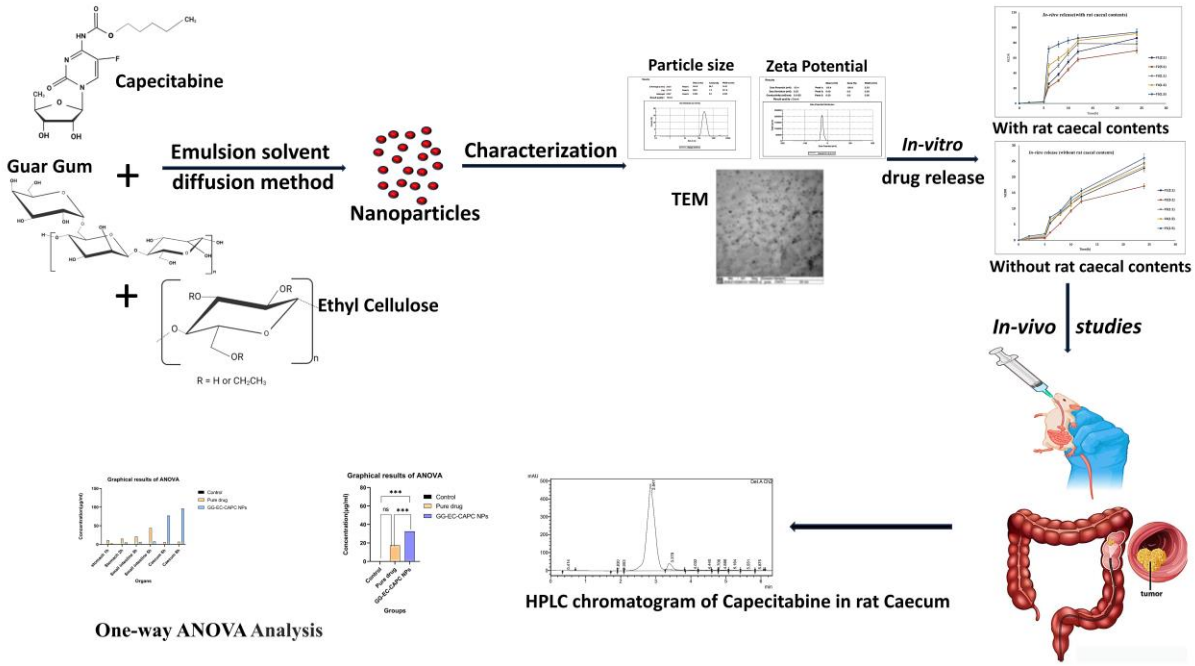
Abstract Currently, nanotechnology-mediated drug delivery systems are targeted towards cancer therapy. The guar gum and ethyl cellulose nanoparticle-based delivery system developed in this study demonstrates the potential of nanotechnology-mediated approaches for the targeted and sustained delivery of capecitabine in managing colorectal cancer. Guar gum and Ethyl cellulose have been selected as polymers to formulate NPs for colon targeting. Different batches of drug-loaded GG-EC NPs were prepared by the emulsion solvent diffusion method. The optimal batch exhibited a particle dimension of 235.6 ± 4.28 nm with a polydispersity index (PDI) of 0.153 and a zeta potential of -23.4 ± 3.12 millivolts. The *in vitro* drug release pattern demonstrated that the liberation of capecitabine was sustained for 24 hours. The mechanism of drug release from formulated NPs was followed with Non-Fickian mediated with diffusion-controlled. Animal studies determined the targeting efficiency of the ideal formulation. Results indicated that the concentration of capecitabine was higher than the standard drug. The distinctive characteristics of the polymers employed in the nanoparticle formulation facilitate specific drug discharge in the colon, diminishing systemic contact and amplifying remedial effectiveness.

Keywords Guar Gum, Ethyl Cellulose, Nanoparticle, Capecitabine, Colorectal Cancer

Graphical Abstract



1. Introduction

Cancer is a group of diseases characterized by the uncontrollable growth and division of abnormal cells. These aberrant cells destroy healthy body components. According to current cancer theory, normal cells transform into cancerous cells, resulting in abnormal cellular, molecular, and biochemical networking of normal cells [1].

Colorectal cancer (CRC) is positioned as the third most prevailing malignancy in males and the second most widespread carcinoma in females, encompassing an anticipated 1.9 million novel instances and 0.9 million fatalities on a global scale in the year 2020 [2]. The genomic study revealed identical rectum and colon cancers [3]. Over fifty percent of all occurrences and mortalities can be attributed to alterable risk elements such as tobacco use, an inadequate diet, heightened alcohol consumption, a sedentary lifestyle, and surplus body mass [4]. The signaling pathway mutation, which unnaturally increased signaling activity, was the most common cause of this disease, which emerged within the epithelial cells that envelope the colon or rectum of the gastrointestinal tract (GIT). The genetic mutation impacts the adenomatous polyposis coli (APC) gene within intestinal crypt stem cells, crucial for the generation of the adenomatous polyposis coli (APC) protein. This protein assumes a crucial function in the accumulation of the ß-catenin protein. In the absence of adenomatous polyposis coli (APC), ß-catenin accumulates to elevated levels and relocates into the nucleus, attaching to Deoxyribonucleic acid [5]. Practically every instance of colorectal carcinoma begins with the development of benign or noncancerous polyps [6].

Oral chemotherapeutic drugs like Capecitabine, Eniluracil, Emetifur, Tegafur, 9- Nitrocamptothecin, and 9- Aminocamptothecin can be used to treat CRC. The effectiveness of oral chemotherapeutic agents can increase patient comfort and acceptance while saving much money on treatment costs. An oral prodrug named capecitabine undergoes enzymatic transformation within the tumor to convert into active 5-fluorouracil, which hinders DNA synthesis and decelerates the growth of tumor tissue. It has a 0.85 h plasma half-life and a 40% oral bioavailability. For colorectal cancer, it is administered twice daily at a high dose of 1250 mg/m [7,8]. Serious undesirable consequences of such an elevated frequency and extreme dose encompass hand and foot syndrome, emesis, abdominal discomfort, febrility, and infection. Before it reaches the colon, capecitabine is significantly lost due to the environment in the upper gastrointestinal tract where it is broken down. The side effects are brought on by the drug's unintended release from the digestive system [9]. Therefore, to diminish adverse effects and frequency of dosing, the drug must be targeted to the colon and released under controlled conditions once it is used.

Many monosaccharide components are connected through glycosidic bonds to construct polysaccharides, elongated chains that can be either branched or unbranched. Natural polysaccharides are derived from natural sources and are gaining popularity as a material source because of their non-toxicity, biodegradability, biocompatibility, sustainability, safety, lower pricing, and availability [10]. Targeting the colon has been achieved in a variety of ways such as biodegradable polymers in a pH-dependent delivery system, an enzyme-triggered delivery system, and time-dependent delivery systems. Every delivery system has benefits and drawbacks. When compared to natural polymers (Guar gum, Xanthan gum, Alginate, Pectin, Chitosan, etc.), semi-synthetic polymers are quite expensive. Natural polymers are digested in the colon by bacteria such as *Bacteroides*, *Bifidobacteria*, and *Eubacteria* rather than in the stomach and small intestine [11]. Guar gum is a neutral polysaccharide derived from the seeds of the Leguminosae plant *Cyamopsis tetragonolobus*. It is made up of linear chains of (1→4)-β-D-mannopyranosyl units linked with α-D-galactopyranosyl units connected by (1→6) linkages[11]. Guar gum is reported to have stronger drug release-impeding properties and synergistically better gel characteristics when coupled with galactomannan gum [12].

The progression of remedial methodologies centered on NPs for cancer therapy has significantly amplified therapeutic modalities and lessened the adverse reactions of cytotoxic medications while enhancing their effectiveness, solubility, pharmacokinetics, and distribution within the body. Throughout the last five decades, numerous NPs of varied dimensions, configurations, and chemical structures have demonstrated remarkable proficiency in enveloping diverse anticancer drugs, encompassing siRNA, antibiotics, and chemotherapeutic agents. Leveraging the enhanced permeation and retention phenomenon facilitated by tumors' vascular and lymphatic drainage, these pioneering anticancer drug NPs passively infiltrate the tumor tissue, enabling extravasation and aggregation of NPs inside cancer cells, thereby amplifying therapeutic effectiveness [13,14].

The current research aims to use the naturally occurring polymer guar gum and synthetic polymer ethyl cellulose to treat colorectal cancer. The release of capecitabine from NPs that used biodegradable polymer as their primary component showed a minimal release in the upper GIT and utmost release in the colon.

2. Materials and Methods

2.1. Materials

Capecitabine was purchased from Vivian Life Sciences PVT. Ltd, Mumbai, India, Di-chloromethane, Distilled water, Ethylcellulose, Glutaraldehyde (25%), Guar gum, Polyvinyl alcohol, HPLC grade Acetonitrile, Methanol and HPLC Water were procured from Sigma Aldrich, USA.

2.2. Preparation of Guar Gum and Ethyl Cellulose NPs Containing Capecitabine (GG-EC-CAPC NPs)

Capecitabine-loaded guar gum and ethyl cellulose NPs were synthesized using the emulsion solvent diffusion technique with minor adjustments [15,16]. Briefly, 15 mg guar gum was weighed and dissolved in 10 ml 0.2% polyvinyl alcohol. 5 mg of the drug and 15 mg of ethyl cellulose were weighed and dissolved in 5 ml of dichloromethane. Subsequently, the drug-dichloromethane amalgam was slowly dripped into the guar gum solution via a syringe at a pace of 1 ml/min, all the while being continuously agitated (at a velocity of 500 revolutions per minute) at ambient temperature. The presence of turbidity in the solution suggested that NPs were forming. 100 µl of glutaraldehyde (1 ml in 100 ml of dilution) was added for cross-linking to stabilize the unstable particles. To ensure comprehensive cross-linking of all amino acid residues, the suspension was continuously stirred for 3 hours. Nanosuspension was centrifuged and supernatant liquid was removed [17]. The nanosuspensions acquired were subjected to freeze-drying and preserved for subsequent analysis. The schematic representation of the method is shown in Figure 1 and Table 1 displays the formula for preparation of capecitabine-loaded guar gum and ethyl cellulose NPs.

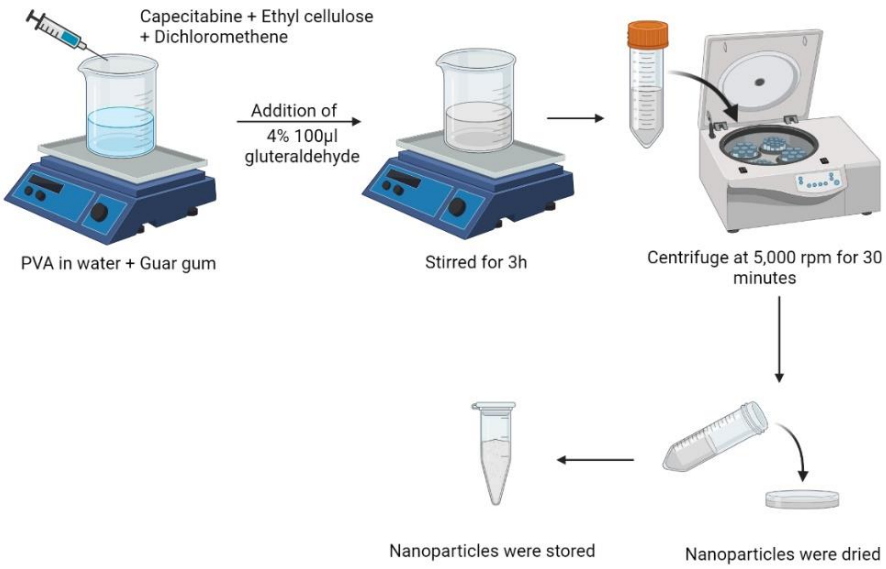


Figure 1. Graphical representation of the preparation of GG-EC-CAPC NPs

Table 1. Formula for preparation of GG-EC-CAPC NPs

Formulation code	Guar gum (mg)	Ethyl cellulose(mg)	Capecitabine (mg)
F1	20	10	5
F2	25	5	5
F3	15	15	5
F4	10	20	5
F5	5	25	5

3. Characterization of GG-EC-CAPC NPs

3.1. Determination of Process Yield and Drug Loading (%)

After drying, powdered NPs were produced. Eq. (1) was used to calculate the process yield.

$$Y\ (\%) = MNP/MT \times 100 \quad (1)$$

where MT is the mass of guar gum plus ethyl cellulose plus the mass of CAPC in the formulation, Y (%) is the process yield, and MNP is the mass of NPs recovered after drying [18].

The drug loading capability of GG-EC-CAPC NPs was evaluated by thoroughly extracting the drug from a specified quantity of NPs in pH 6.8 phosphate buffer, succeeded by centrifugation at 10,000 revolutions per minute for 10 min [19]. The concentration of the drug in the supernatant was determined utilizing a UV-visible spectrophotometer at a wavelength of 240 nm.

$$\%\ \text{Drug Loading} = \frac{\text{Actual drug content}}{\text{Weight of NPs taken}}\ \text{x}\ 100 \quad (2)$$

3.2. FT-IR Spectroscopy

To study interactions between the drug and polymers, FT-IR studies were carried out by IRSpirit-L, Shimadzu. The FTIR spectra between capecitabine and the excipients were recorded by KBr disks. Peaks of the pure drug and its combination with the polymer were obtained, and their compatibility was observed by studying various frequencies of the vibration modes [20].

3.3. Differential Scanning Calorimetry

Utilizing differential scanning calorimetry (DSC, Mettler 7, Germany) precise measurements were conducted. Samples weighing 1-2 mg were accurately weighed and enclosed in aluminum pan. The assessments were conducted across a temperature spectrum of 40-285 ℃ with a heating velocity of 10 ℃ per minute [21]. The baseline, temperature, and enthalpy of the Differential Scanning Calorimetry (DSC) were adjusted utilizing an empty pan as the benchmark. Throughout each DSC trial, nitrogen was streamed at a pace of 50 ml/min.

3.4. Dynamic Light Scattering

Malvern Zeta Nano S 90 (Malvern Instruments, Malvern, UK) analyses the colloidal particles' Brownian motion to determine the formulations' particle size using the dynamic light scattering (DLS) principle. It measures the polydispersity index (PDI) and hydrodynamic diameter. DLS measurements were made using particle emulsions diluted to 1 mg/ml in Millipore water. Samples were kept at 25 ℃ while measurements were made in triplicate at a 90 ° angle [21]. Malvern zeta potential (Nano Sight NS500) at 25 ℃ was used to estimate zeta potential based on electrophoretic mobility in an electrical field.

3.5. Determination of Surface Morphology

The morphology and the structure of NPs were observed and recorded using transmission electron microscopy (JEM 1230 electron microscope Jeol, Tokyo, Japan). A drop of diluted samples (GG-EC-CAPC NPs) was used on a copper-coated carbon grid and allowed to dry for about 15 min [20]. A filter paper removed excess dispersion and left the grid to air-dry. Afterward, the samples were examined through a high-resolution transmission electron microscope.

3.6. *In-vitro* Drug Release

To analyze the *in vitro* drug release for different formulations, the dialysis bag diffusion method was used [22]. Given that the typical gastric emptying time is around 2 hours, the NPs underwent drug discharge assessment over 2 hours in 0.1N HCl (100ml). Subsequently, considering the average transit time in the small intestine to be approximately 3 hours, the dissolution solution was substituted with pH 7.4 phosphate buffer (100ml), and drug liberation was monitored for 3 hours. The pH 6.8 phosphate buffer (100 ml) with and without (4% w/v) rat caecal contents was replaced for the dissolution medium after 5 hours. 100 rpm of stirring per minute was kept constant at room temperature [23]. At specified intervals, 5 milliliters of samples were withdrawn and substituted with a fresh dissolution medium of equivalent volume [8].

3.7. Kinetic Analysis of Drug Release of GG-EC-CAPC NPs

To comprehend the release mechanism and determine the best fit plot with the kinetic model, release kinetics studies were conducted [23,24]. The data acquired from the *in vitro* liberation investigations were matched with various kinetic frameworks, including the Higuchi model, the zero-order model, and the Korsmeyers-Peppas model.

3.8. Animal Study

The targeting effectiveness of GG-EC-CAPC NPs (with a drug-to-polymer ratio of 2:1) was assessed on Wistar albino rats. Following endorsement from the Institutional Animal Ethical Committee, fit adult male Wistar albino rats weighing 150–200g were procured from the animal facility (College of Pharmaceutical Sciences, Dayananda Sagar University, Bangalore). During the trial, the animals were housed in capacious cages on a 12:12-hour light-dark regimen. The rats were segregated into 3 cohorts, each comprising six individuals [25,26].

Group I received phosphate buffer saline, group II received the standard drug of capecitabine, while group III received GG-EC-CAPC NPs. The compositions were reconstituted in phosphate-buffered saline for the *in vivo* assessments. The nanoformulations was administered orally at a dose of 1.5 mg/kg of body weight [27]. The stomach, small intestine, large intestine, and caecum were quickly isolated, weighed, and preserved at -20 ℃. Every segment of the gastrointestinal tract was homogenized with pH 6.8 phosphate buffer to achieve a 20% w/v concentration before centrifugation for examination. The preparation of the samples involved a liquid-phase extraction procedure. 0.6 ml of acetonitrile (precipitating agent) was added to 0.1 ml of supernatant sample. For 5 minutes, the solutions were vortex-mixed. The mixture was subsequently centrifuged at 5000 revolutions per minute for 15 minutes. Through a 0.45 µl filter, the upper phase was separated [28] and preserved at -20 ℃ until analysis, and the drug content in the gastrointestinal segments was assessed utilizing the Shimadzu LC-20AT high-performance liquid chromatography (HPLC) [29,30] which is shown in Table 2. The sample was injected using a Hamilton syringe and the drug concentration was determined [13].

Table 2. HPLC Chromatographic conditions for capecitabine

Sl No.	Parameters	Results
1	Column	Luna 5u C18(2) 100H
2	Mobile phase	Acetonitrile: Methanol: Water (18:80:2)
3	Flow rate	1ml/min
4	Wavelength	240nm
5	Column temperature	25 ℃
6	Injection volume	20µl
7	Runtime	10 min
8	Diluent	Methanol
9	Elution	Isocratic
10	Needle wash	Methanol

3.9. Statistical Analysis

By employing GraphPad Prism version 9.3.1 software, one-way analysis of variance (ANOVA) combined with Tukey's test was employed to scrutinize the distinctions among the experimental clusters. Statistical significance was acknowledged [14] at p-values below 0.05. All tests

were executed in triplicate, and the outcomes were displayed as the mean value along with the standard deviation.

4. Results and Discussion

4.1. Characterization GG-EC-CAPC NPs

4.1.1. Determination of Process Yield and Drug Loading (%)

The process yield of a formulation depicts the efficiency of the formulation method used. The yield of GG-EC-CAPC NPs was observed to be in the range of 90% to 96%. The highest process yield and drug loading were achieved for formulation F1 and are shown in Table 3.

Table 3. Data of process yield and drug loading (%) for GG-EC-CAPC NPs

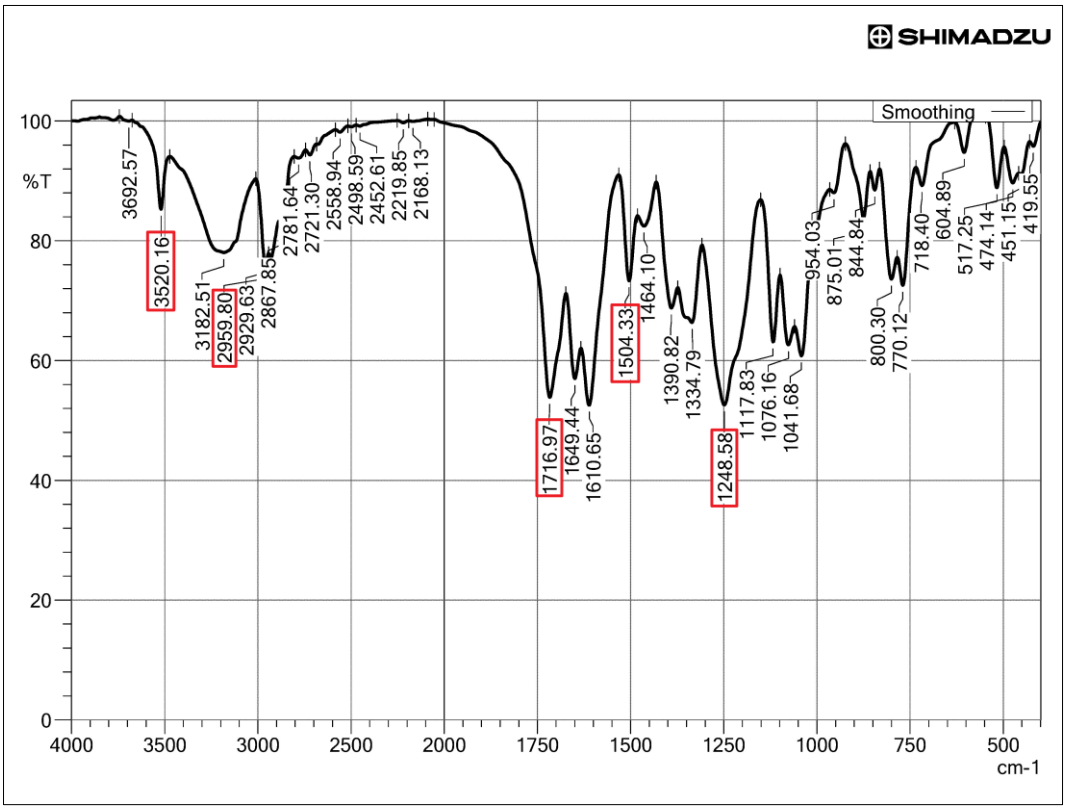
Formulation	% yield	Drug loading (%)
F1	**96 ±10.1**	**35.7 ±6.51**
F2	92 ±12.5	25.6 ±7.32
F3	94 ±09.4	16 ±4.76
F4	91 ±11.9	25.4 ±5.94
F5	90 ±12.8	23.9 ±2.31

4.1.2. FT-IR Spectroscopy

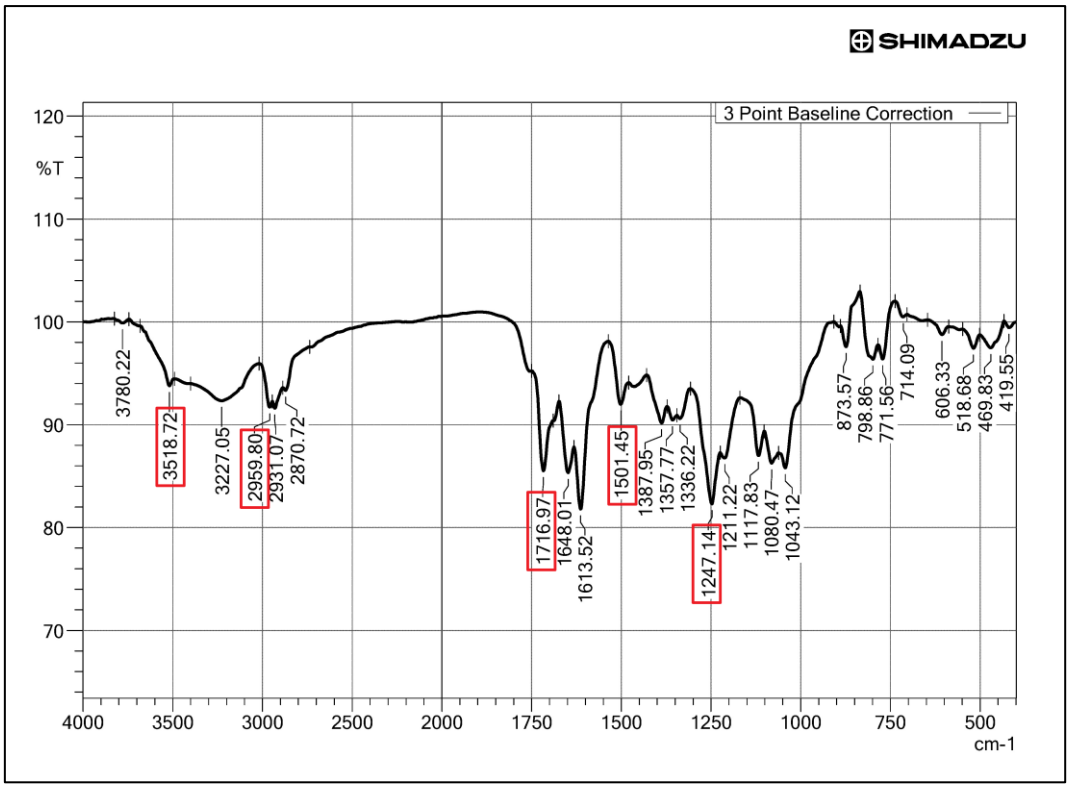
The drug capecitabine compatibility with the polymers ethyl cellulose and guar gum was investigated using FT-IR spectroscopy. Drug, physical mixture of drug and polymer, and GG-EC-CAPC NPs spectra were all recorded. All spectra were compared with each other to check whether any interaction was there or not between drug molecules and excipients (Figure 2). No major changes were observed in the functional group's peak for capecitabine in any spectra when linked with the spectrum of the physical mixture and GG-EC-CAPC NPs. Thus, it was deduced that no chemical interplay occurred among the drug and the excipients employed for the formulation advancement, indicating their compatibility with the drug.

4.1.3. Differential Scanning Calorimetry

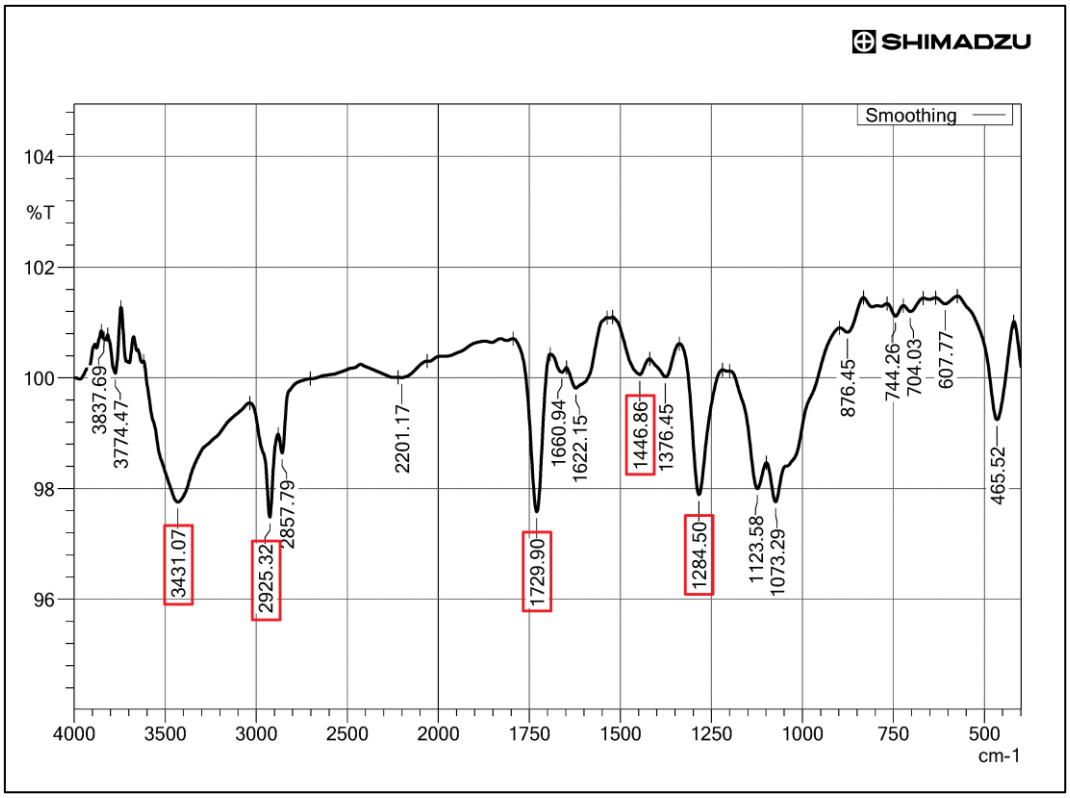
By comparing the DSC thermogram of GG-EC-CAPC NPs with the DSC thermogram of capecitabine, GG-EC-CAPC NPs were subjected to differential scanning calorimetry to confirm that capecitabine is compatible with excipients. A thermogram of the pure drug capecitabine shows an endothermic peak at 126.87 ℃. The thermogram of a GG-EC-CAPC NPs did not show any peaks which indicates the drug is distributed in the polymer matrix during the formulation. The comparisons are shown in Figure 3.



a) IR spectrum of capecitabine

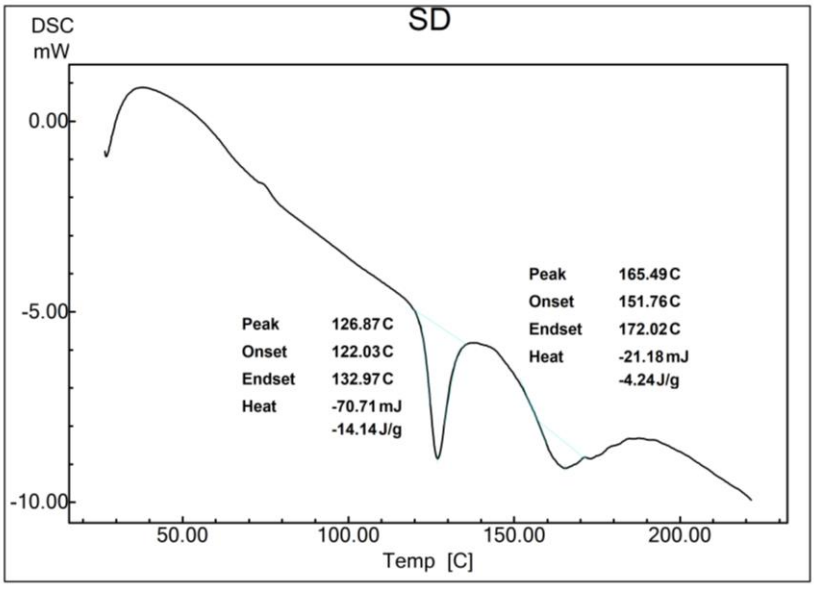


b) IR spectrum of Physical mixture of CAPC, EC and GG

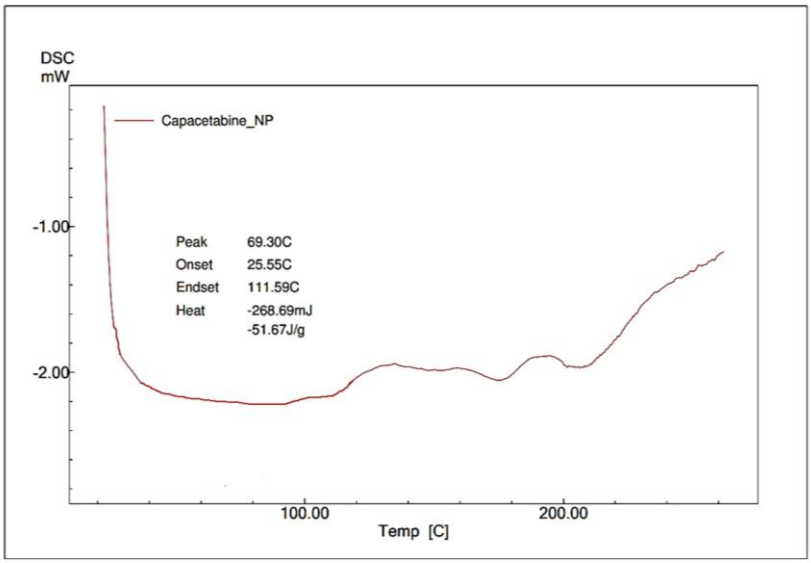


c) IR spectrum of GG-EC-CAPC NPs

Figure 2. FTIR Spectrum capecitabine, Physical mixture, and GG-EC-CAPC NPs



a) DSC thermogram of Capecitabine



b) DSC thermogram of GG-EC-CAPC NPs

Figure 3. DSC thermogram of Capecitabine (a), DSC thermogram of GG-EC-CAPC NPs (b)

4.1.4. Dynamic Light Scattering

The particle size of GG-EC-CAPC NPs (F1) was found to be 235.6 nm with a polydispersity index of 0.153. The process provides nano-sized particles with a low polydispersity index, indicating a monodisperse population of the particles. The prepared formulation (F1) was found to have a zeta potential of -23.4 mV (Figure 4), which suggests that the formulation is stable. Colloids having zeta potentials (negative or positive) between ±30 and ±40 mV are electrically stabilized [20].

4.1.5. Determination of Surface Morphology

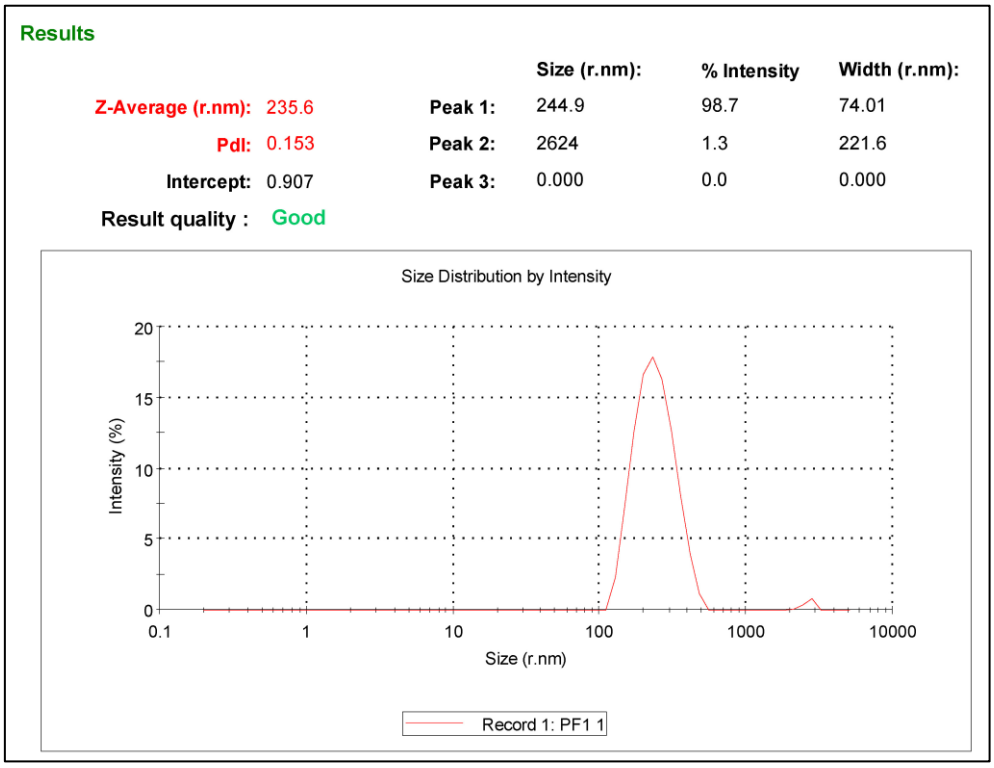
The surface topography of the GG-EC-CAPC NPs (F1) was investigated through TEM examinations. Figure 5 represents the surface morphology of GG-EC-CAPC NPs. The result revealed that the particles are almost in uniform size with spherical shape and the drug entrapment was also confirmed by TEM image.

4.1.6. *In-vitro* Drug Release

In vitro release studies of NPs loaded with capecitabine with different amounts of guar gum and ethyl cellulose have been carried out. *In vitro* release studies without rat caecal contents showed 22.8%, 17.1%, 24.4%, 23.3%, and 26.01 for F1, F2, F3, F4, and F5 correspondingly at the end of 24 h (Figure 6). This suggests that a negligible quantity

of the drug is liberated from the drug-laden guar gum and ethyl cellulose NPs in the stomach, small intestine, and colon in the absence of rat cecal contents.

Guar gum swells when it comes into contact with biological fluids, and the drug is released by diffusion. Unless the engorged guar gum disintegrates, additional hydration and expansion of the guar gum do not occur. The colonic bacterial enzymes would react with the swollen guar gum once it reached the colonic environment, releasing the drug it contained [15, 31].



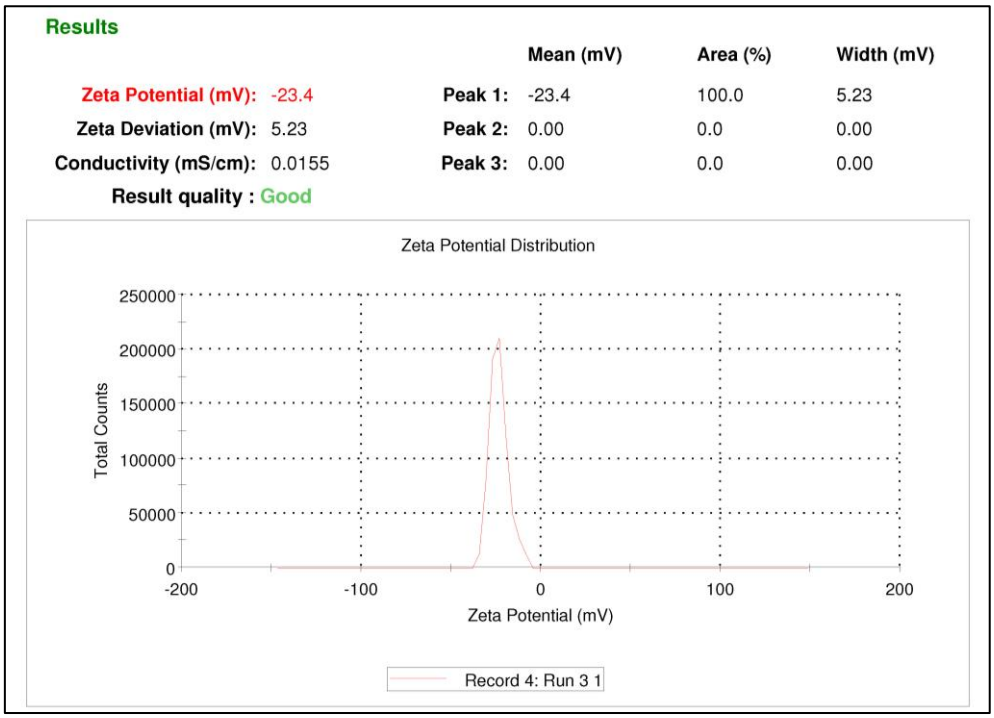


Figure 4. a) The particle size of GG-EC-CAPC NPs, b) Zeta potential of GG-EC-CAPC NPs

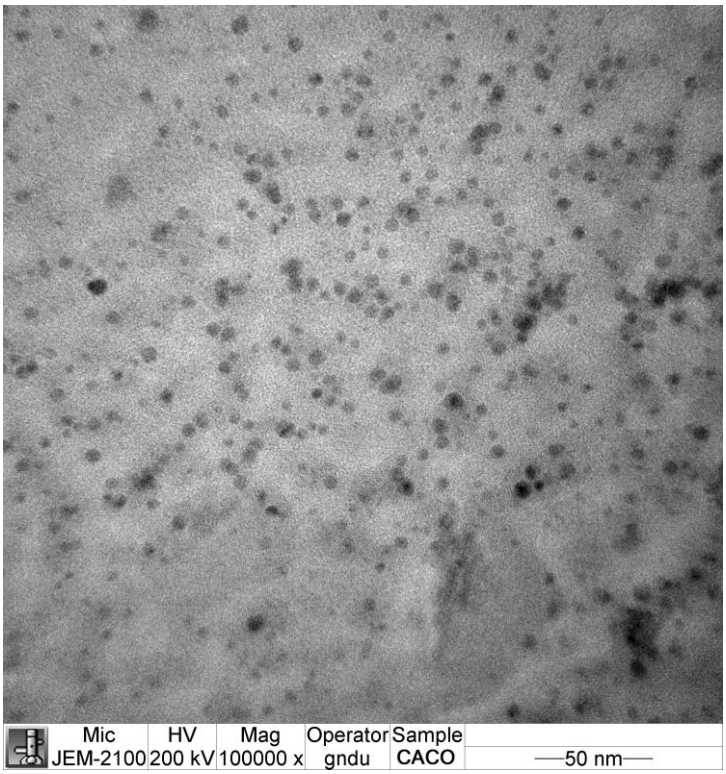


Figure 5. Transmission electron microphotograph of GG-EC-CAPC NPs

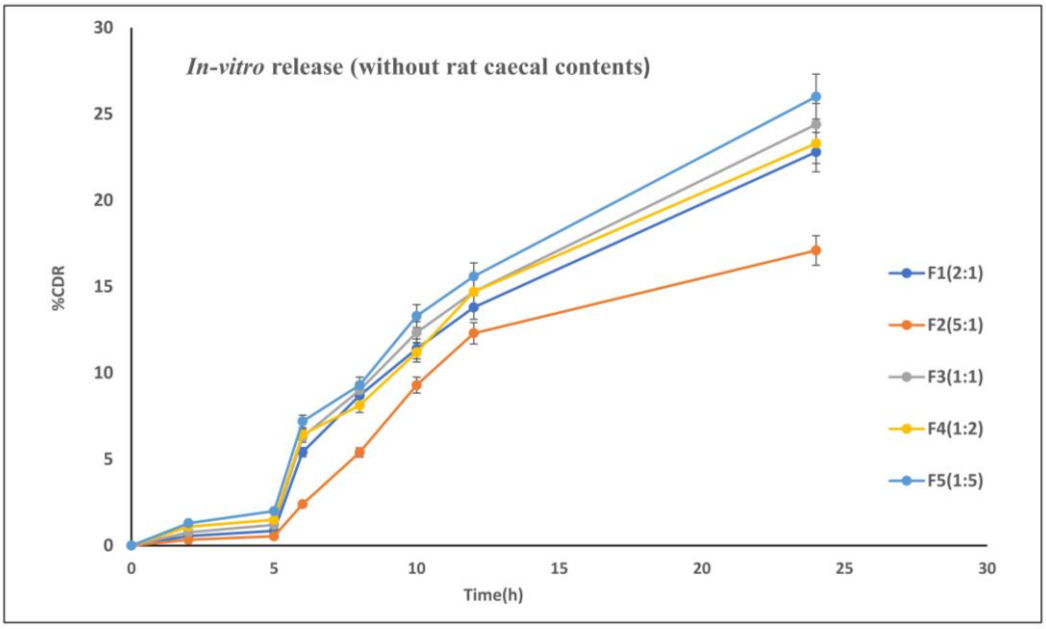


Figure 6. Cumulative percentage drug release profiles of GG-EC-CAPC NPs formulations without rat caecal content

In vitro release studies with rat caecal contents showed 86%, 69.65%, 78.51%, 92%, and 94% for F1, F2, F3, F4, and F5 respectively at the end of 24 hours (Figure 7). This indicated the maximum amount of drug is released from drug-loaded guar gum and ethyl cellulose NPs in the caecum without rat caecal contents.

Among the 5 formulations F3, F4, and F5 showed a burst release due to a minimal amount of guar gum and a maximal amount of ethyl cellulose in the formulation. As the guar gum concentration decreases and ethyl cellulose concentration increases drug release follows burst release. An increase in the concentration of guar gum and a decrease in ethyl cellulose concentration showed a decrease in drug release(F2). So highest drug release was found in F1 and it was considered as ideal formulation.

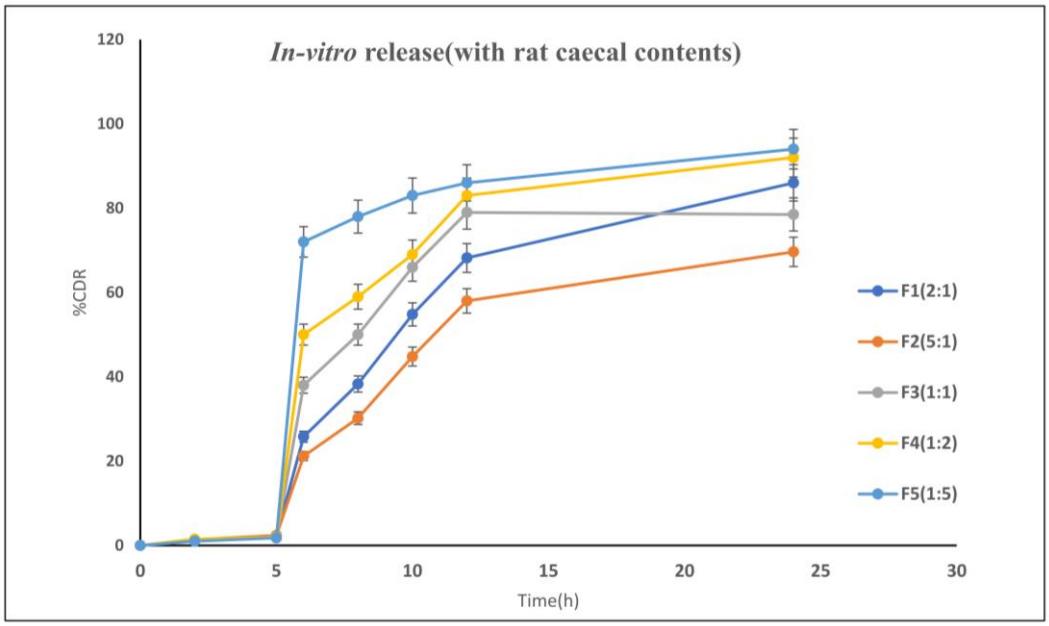


Figure 7. Cumulative percentage drug release profiles of GG-EC-CAPC NPs formulations using rat caecal content

4.1.7. Release Kinetics

To find out the release mechanism and determine the best fit plot with the kinetic model, release kinetics studies were conducted. The data from the *in vitro* release studies were fitted to a variety of kinetic models, including the Higuchi model, the Zero order model, and the Korsmeyers-Peppas model. The Higuchi model, which indicates the diffusion-controlled release of the drug, had the highest regression coefficient value, which was 0.813. The Korsmeyers-Peppas model's n value for the F1 formulation was 0.829, indicating that non-fiction mediated release was the drug release mechanism [32].

4.1.8. Animal Study

The concentration of capecitabine in the stomach, small intestine, and caecum after oral administration of standard capecitabine was found to be 15.20±0.90 µg/ml, 44.22±0.85 µg/ml, and 7.24±0.82 µg/ml, respectively. Figure 8 represents the HPLC chromatogram of standard capecitabine and Figure 9 (a,b,c) displays an HPLC chromatogram of the amount of capecitabine at various parts of the GI tract after oral administration of the standard drug. The concentration of capecitabine in the stomach, small intestine, and caecum after oral administration of GG-EC-CAPC NPs was found to be 5.17±0.99 µg/ml, 7.36±0.97 µg/ml and 96.47±0.98 µg/ml correspondingly (Table 4). Figure 9 (d,e,f) shows an HPLC chromatogram of the amount of capecitabine at various parts of the GI tract after oral administration of the GG-EC-CAPC NPs. The results of the animal studies indicated that the concentration of capecitabine in the target tissues, particularly the colon, was significantly higher for the nanoparticle formulation (96.47±0.98 µg/ml) compared to the standard drug (7.24±0.82 µg/ml). This enhanced tissue targeting and drug accumulation can be attributed to the unique properties of the GG-EC NPs and their ability to evade clearance mechanisms and preferentially accumulate in the tumor microenvironment. The results of animal studies concluded that GG-EC-CAPC NPs make it a more effective approach for delivering capecitabine to the colon, exploiting the enhanced permeation retention effect where NPs tend to accumulate more in tumor tissues due to their leaky vasculature and lymphatic drainage and potentially improving its therapeutic outcomes in cancer treatment [33].

4.1.9. Statistical Analysis

One-way analysis of variance was used to compare multiple groups (ANOVA). The mean value of each set of data is displayed, along with the standard deviation (mean ± SD) p-value was 0.001, which was less than 0.05, and considered that the animal study was statistically significant (Figure 10).

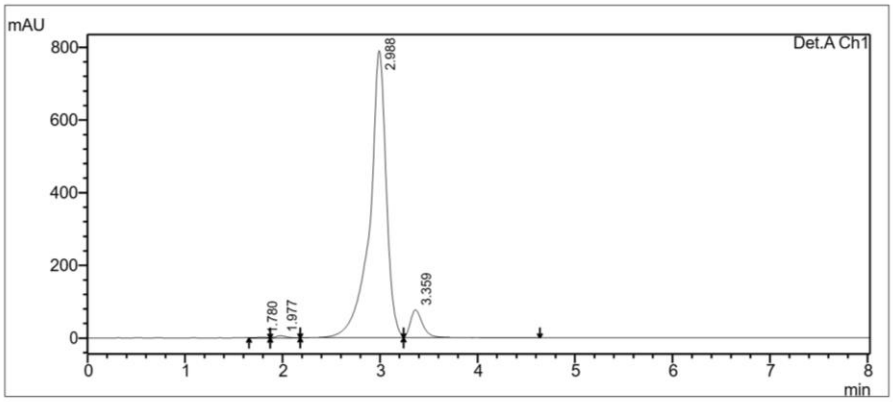
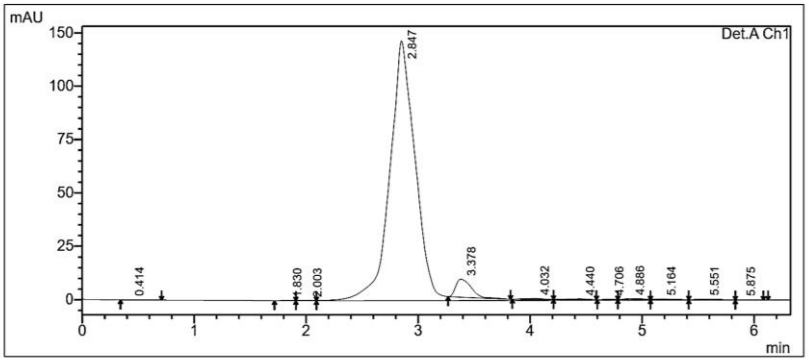
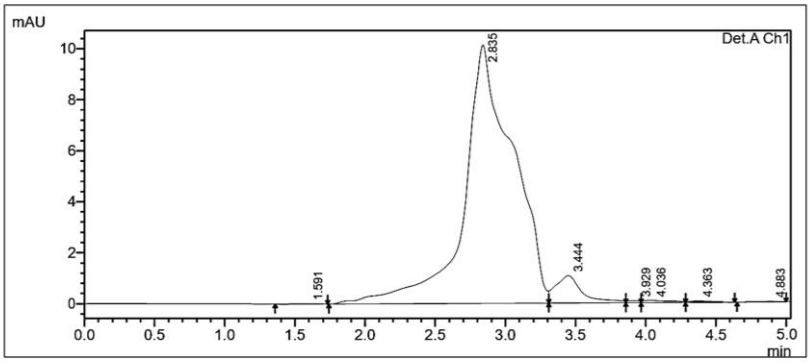
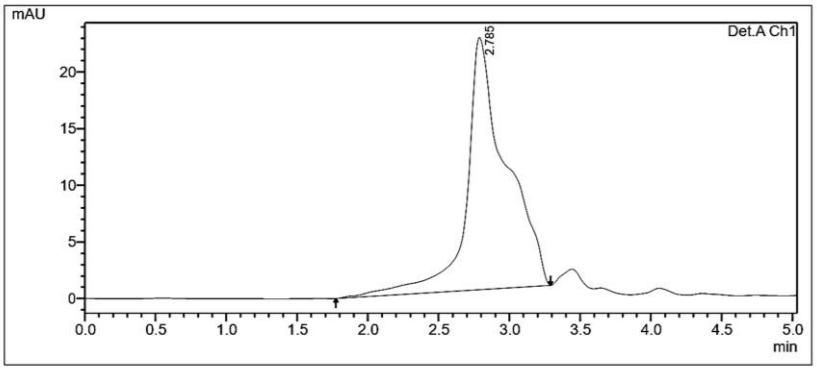


Figure 8. HPLC chromatogram of the standard drug (Capecitabine)







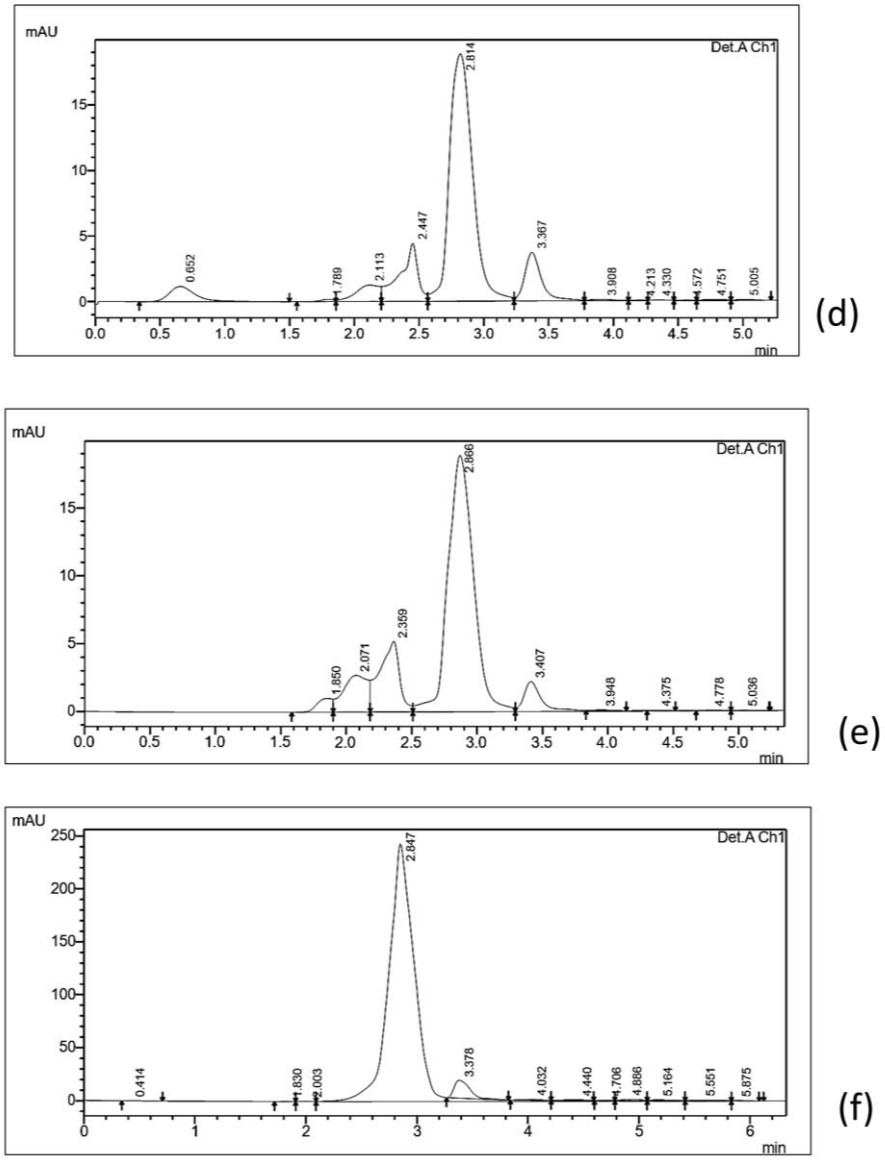


Figure 9. HPLC chromatogram of capecitabine concentration from rat's ((a) stomach b) small intestine, (c) caecum received standard capecitabine and rat's (d) the stomach e) in the small intestine, f) in the caecum received GG-EC-CAPC NPs

Table 4. Capecitabine concentration in organs after oral administration of standard capecitabine and GG-EC-CAPC

Sl. No.	Organs	Standard capecitabine (µg/ml)	GG-EC-CAPC NPs (µg/ml)
1	Stomach	15.20 ±0.90	5.17 ±0.99
2	Small intestine	44.22 ±0.85	7.36 ±0.97
3	Caecum	7.24 ±0.82	96.47 ±0.98

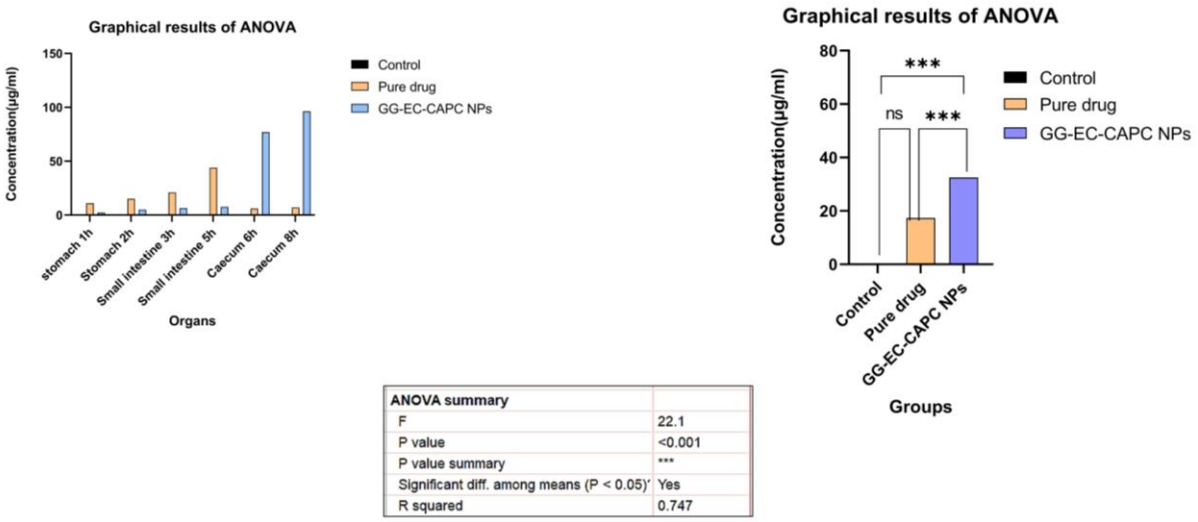


Figure 10. Statistical data by one way ANOVA Analysis

5. Conclusions

In the current investigation, efforts were made to develop NPs encapsulating capecitabine within guar gum and ethyl cellulose polymer. The emulsion solvent diffusion method was employed to fabricate GG-EC-CAPC NPs exhibited an average diameter of 235.6 nm with a PDI of 0.153, and a zeta potential of -23.4 mV was recorded. Among the different nanoparticle batches, Formulation (F1) was identified as the optimal formulation based on its drug loading capacity, particle size, and *in vitro* drug release profiles with and without caecal content. This suggested that the unique properties of the polymers used in the nanoparticle formulation allow for selective drug release by colonic enzymes in the colon, minimizing systemic exposure and enhancing therapeutic efficacy. The animal study results showed that the NPs increased the caecum concentration of capecitabine compared to standard drug (7.24 ±0.82µg/ml) and drug bound with NPs (96.47± 0.98 µg/ml). The nanoparticle system provides a prolonged and controlled release of capecitabine, which can help maintain therapeutic drug concentrations in the colon. The promising results from this study warrant further preclinical and clinical investigations to explore the full potential of the GG-EC NPs platform for the management of colorectal cancer.

Declaration

The authors declare that this manuscript is original and has not been submitted elsewhere for publication. The content of this manuscript is the sole work of the authors listed. The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethical Approval

Animal studies were carried out on healthy adult Wistar albino rats after appropriate animal ethical committees by the IAEC of the College of Pharmaceutical Sciences, Dayananda Sagar University, DSU/M.Pharm/IAEC/83/2021-2022.

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Author's Contribution

J. Josephine Leno Jenita contributed to the conception and design of the study. Pasupathy A and Seema S Rathore performed the experiments. Wilson B analyzed the data. Josephine Leno Jenita and Seema S Rathore wrote the first draft of the manuscript. All authors have read and approved the final manuscript.

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