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Original article

Sustainable Lipid-Based Drug Delivery: Development of Multiple Self-Emulsifying Systems for Hydrophilic Drugs Using Cashew Nut Oil

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Abstract

The oral delivery of hydrophilic drugs, such as 5-fluorouracil (5-FU), is often limited by poor permeability and rapid gastrointestinal degradation. Lipid-based self-emulsifying drug delivery systems (SEDDS) have shown promise in improving solubilization and oral bioavailability of lipophilic drugs; however, their application to hydrophilic molecules remains limited. This study aimed to develop multiple self-nanoemulsifying drug delivery systems (SNEDDS) for 5-FU using Cashew nut kernel oil (CKO) as a sustainable lipid excipient. A 2^3 full factorial design evaluated the effects of CKO extraction method, oil-to-surfactant ratio, and homogenization speed on droplet size, polydispersity index (PDI), zeta potential (ZP), entrapment efficiency (EE%), and the cumulative drug release. Primary w/o emulsions were converted to w/o/w SNEDDS and solidified using Aerosil® 200, then encapsulated in hard gelatin capsules. Formulations JXM4 and JXM8 exhibited optimal characteristics with small droplet sizes (105 nm), low PDI (0.22), highly negative ZP (≥ −43 mV), low viscosity (< 70 cps), near-complete EE (> 98%), excellent flowability, and rapid self-emulsification. *In vitro* release studies showed >98% cumulative drug release within 60 minutes, while cytotoxicity assays (MTT) demonstrate effective anticancer activity with decreasing IC_{50} values over 72 hours. Stability studies confirmed the preservation of physicochemical properties within acceptable limits over a 30-day period. These results indicate that optimized CKO-based SNEDDS can efficiently encapsulate hydrophilic drugs, providing a stable, sustainable, and orally administrable delivery platform. The study highlights the potential of regionally sourced lipids in enhancing the oral bioavailability of hydrophilic chemotherapeutics such as 5-FU and supports further *in vivo* investigations.

Keywords. 5-fluorouracil, Self-nanoemulsifying Drug Delivery System, Cashew Nut Oil, Hydrophilic Drug, Oral Bioavailability, Factorial Design

Introduction

Oral drug administration is widely preferred due to its convenience and high patient compliance; however, many drugs exhibit poor absorption via this route, especially class III biopharmaceutical agents, which have excellent aqueous solubility and yet are unable to cross the semipermeable lipid membrane into the systemic circulation [1]. Even though lipid-based drug delivery systems, particularly self-emulsifying drug delivery systems (SEDDS), provide a promising approach to enhance the oral bioavailability of drugs by forming fine emulsions in situ, thereby improving drug solubility, stability, and intestinal uptake [2], they are nevertheless, primarily suited for lipophilic drugs, and incorporating hydrophilic molecules such as 5-fluorouracil (5-FU) and metformin remains challenging because they tend to accumulate within the aqueous phase and escape entrapment [2,3].

5-FU is a cytotoxic anticancer agent of high therapeutic relevance, yet its oral delivery is limited by low permeability and rapid gastrointestinal degradation [3]. Several formulation strategies have attempted to overcome these limitations. For example, a multiple nanoemulsion system of 5-FU achieved droplet sizes of 50 nm and enhanced oral absorption compared to free 5-FU [4]. Similarly, chitosan-coated emulsions of 5-FU have demonstrated controlled release and improved permeation in topical and dermal applications [5]. Despite these efforts, oral lipid-based carriers specifically tailored for hydrophilic drugs such as 5-FU remain a challenge.

Other strategies employed recently include incorporating hydrophilic drugs into lipid-based carriers, such as Hydrophobic ion pairing (HIP), which increases drug lipophilicity by complexing charged drugs with counter-ions, promoting incorporation into lipid phases [5,6]. In another study, a complementary approach combines HIP with reverse micelle strategies to encapsulate hydrophilic molecules while preserving favorable droplet size and stability [7]. Although these formulation strategies were successfully applied to peptides and macromolecules, their application to small hydrophilic drugs such as 5-FU is still limited by complex stability, counterion toxicity, regulatory, and production process complexity and variability [8,9,10]. A self-nanoemulsifying drug delivery system (SNEDDS) represents a promising strategy to improve the oral delivery of 5-fluorouracil (5-FU), a hydrophilic anticancer agent with poor gastrointestinal permeability and rapid degradation.

Accordingly, this study aims to develop a cashew nut oil-based SNEDDS using multiple emulsion strategies (w/o/w) to achieve stable encapsulation and controlled release of 5-FU, thereby expanding the applicability of SNEDDS to hydrophilic drugs while promoting local and sustainable pharmaceutical development.

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Materials and Methods

Materials

All the materials used for this investigation were of analytical grades, except for the cashew nut oil (CKO), which was extracted and characterized in our laboratory. 5-Fluorouracil (5-FU), the API, was obtained from Dalian Richfortune Chemicals, China. The surfactants and cosurfactants (Tween® 80 and PEG-400) were obtained from Vasudha Chemicals Pvt Ltd, India, while all other reagents, such as Aerosil® 200 (colloidal silicon dioxide), Acetonitrile, (KH_2PO_4), and orthophosphoric acid, were from Sigma-Aldrich, Germany. Milli-Q distilled water was used for all aqueous preparations.

Experimental Design (Three-Factor, Two-Level Factorial DoE)

The factorial experimental design approach affords efficient exploration of variable effects while minimizing experimental burden [11,12]. And for this reason, a 2^3 full factorial experimental design was employed for this investigation, as shown in (Table 1). Three independent variables were selected: the oil-to-surfactant ratio (CKO: surfactant mixture Low (40:60) vs. High (60:40)), the speed/time of homogenization (Low: 8,000 rpm, 3 min vs. High: 12,000 rpm, 5 min), and the method of CKO extraction (cold press and Soxhlet). This design generated eight experimental runs, enabling the evaluation of main effects and two-way interactions [13,14]. The response variables included droplet size (nm), polydispersity index (PDI), entrapment efficiency (EE%), and the percentage of cumulative drug release at 24 hours (% cumulative release). Statistical analysis was conducted using Design-Expert® software (version 13) with ANOVA at $\alpha = 0.05$.

Table 1. Factorial Design (2^3 Full Factorial)

Factor	Levels	Description
A: CKO Extraction	(−) Cold-press, (+) Soxhlet	Effect of the extraction method
B: Oil-to-Surfactant Ratio	(−) 40:60, (+) 60:40	Ratio of oil + oleic acid to surfactants
C: Speed/Time Homogenization	(−) 8,000 rpm /3 min, (+) 12,000 rpm /5 min	Energy input for droplet formation

Formulation Development

Primary Water-in-Oil (w/o) Emulsion

The internal aqueous phase was prepared by dissolving 20 mg of 5-FU in 0.50 g of distilled water. The external phase consisted of CKO and 1.0 g of Span 80, preheated to 35 °C, and maintained under constant homogenization at 12,000 rpm. To form a water-in-oil type emulsion, the aqueous phase was added dropwise to the external phase under constant agitation until a milky, consistent product was obtained [15].

Multiple Emulsion (w/o/w SNEDDS)

A secondary surfactant mixture (Tween 80: PEG-400, 3.0:0.5 g) was prepared in a 500mL beaker. The primary emulsion was added dropwise under stirring according to the batch formulation in (Table 2), which was immediately followed by nanosizing (by passing the samples twice through a high-pressure homogenizer at 300 bar). The weight of the obtained sample was noted for yield estimation [16].

Table 2. Batch formulary of 5 FU SNEDDS containing CKO

Formulations	Factor (A) Extraction Method	Factor (B) Oil/Surfactant ratio	Factor (C) Speed & Time	Combinations
JXM1	−1	−1	−1	$A_L B_L C_L$
JXM2	−1	−1	+1	$A_L B_L C_H$
JXM3	−1	+1	−1	$A_L B_H C_L$
JXM4	−1	+1	+1	$A_L B_H C_H$
JXM5	+1	−1	−1	$A_H B_L C_L$
JXM6	+1	−1	+1	$A_H B_L C_H$
JXM7	+1	+1	−1	$A_H B_H C_L$
JXM8	+1	+1	+1	$A_H B_H C_H$

Morphology

The morphology of the nano self-emulsifying drug delivery system (SNEDDS) was examined using transmission electron microscopy (TEM) to analyze droplet shape and surface features. Briefly, the formulations were diluted 100-fold with ultrapure water to ensure proper dispersion. A 3–5 µL sample of the diluted solution was carefully placed on a carbon-coated copper grid (200 mesh) that was previously rendered hydrophilic through glow discharge for 30 seconds. After a 30-second adsorption period, excess liquid was removed with filter paper, and the grid was negatively stained with 1% (w/v) phosphotungstic

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acid (PTA, pH 7.0) for 30 seconds to enhance contrast. The remaining stain was gently blotted off, and the grid was air-dried in a clean, dust-free environment at room temperature. Imaging was performed using a JEOL JEM-2100 transmission electron microscope (JEOL Ltd., Tokyo, Japan) operated at an accelerating voltage of 120 kV and equipped with a digital CCD camera to capture SNEDDS images [17,18].

Determination of Droplet Size, PDI, and Zeta Potential
For each batch of obtained SNEDDS, a dilute dispersion (1:1000) was prepared and characterized for its mean droplet size, polydispersity index, and zeta potential by dynamic light scattering using a Zetasizer Nano ZSP (Malvern Instruments, Worcestershire, UK). All measurements were performed in triplicate at 37 °C [15,19].

Emulsification Time Test
20 mL of the test sample (SNEDDS) was added to 100 mL of stimulated gastric fluid maintained at physiological temperature ($37^{o}C$) on a magnetic stirrer operating at 100 rpm, and the time taken for a clear, homogeneous dispersion to form was recorded after three determinations [15].

Determination of Entrapment Efficiency (EE%)
The entrapment efficiencies of formulations were determined by the centrifugation method. A 1:1 dispersion of the sample was prepared and centrifuged at 1400 rpm for 30 min. After centrifugation, the supernatant liquid (containing the un-trapped drug) was decanted and analyzed using a UV spectrophotometer at 266 nm [18]. The absorbance entrapment efficiency (%EE) was calculated using equation 1;
EE% = (Total drug − Free drug) / Total drug) × 100. .....EQ I

Viscosity (cps)
Viscosity values for the formulations were determined at room temperature using a Brookfield viscometer (Brookfield Engineering Laboratories, Inc., U.S.A.).

Solidification by Adsorption, Characterization, and Encapsulation
A known quantity (200 mL) of the liquid SNEDDS formulated above was adsorbed onto 200g Aerosil®, yielding a free-flowing powder. This was then sieved through a 500 µm sieve mesh and then characterized for its flow properties (using density measurement, angle of repose, and Carr's index). Gelatin capsules (size 0 with a filling capacity of 300mg) were then filled with each capsule containing 0.6mg of 5-FU, after which the capsules were assessed (USP, 2020).

In-vitro Release
The *in-vitro* release profile of each capsule formulation was examined using the USP II paddle dissolution apparatus (Electrolab, TDT-08L), with 900 mL of simulated gastric fluid without enzymes as the dissolution medium, maintained at the physiological temperature of 37°C and a stirring speed of 50 rpm. Samples (5 mL) were taken at predefined intervals, filtered, and analyzed by HPLC. Sink conditions were preserved by replacing the withdrawn volumes [20,21].

MTT Assay
The cytotoxicity of each formulation was assessed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) MTT assay. Briefly, MCF-7 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) without phenol red and supplemented with 10% fetal bovine serum and 1% Penicillin + Streptomycin. The cell culture medium was maintained at 37°C in a humidified incubator containing 5% CO_2 atmosphere. Trypsinized confluent cell monolayers were grown to (75%–80%), and the cells in the exponentially growing phase were used for cytotoxicity experiments. Specifically, the cells were plated at a density of (5×10^3 cells/well) in 96-well plates, maintained at 37°C within 5% CO_2 atmosphere in a CO_2 incubator (Model MCO-15AC; Sanyo Electric Biomedical Co. Ltd., Osaka, Japan). After 12 hours of incubation, the medium in the wells was replaced with fresh medium containing prepared SNDDS formulations. The MTT dye solution was added to each well after 48 hours, and the incubation was continued for a specific period according to the experimental design. The medium in each well containing unbound MTT and dead cells was removed by suction. The formazan crystals were solubilized with 100 µL dimethyl sulfoxide, and the solution was vigorously mixed to dissolve the reactants. The reading of the resultant was done using an ELISA reader at 550 nm wavelength. A plot of cell viability against the concentration was constructed, and the concentration required for a 50% inhibition of viability (IC_{50}) was determined graphically [22,23].
Cell viability (%) = Mean OD/Control OD x 100% ..... (5)

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Accelerated Stability Studies

Samples from each formulation were stored at 40 °C/75% RH for 30 days. Samples were withdrawn at regular intervals and tested for drug content, droplet size, PDI, zeta potential, visual appearance, and peroxide/acid values of CKO [24].

Data Analysis

All results were expressed as mean ± SD (n=3). DoE outcomes were analyzed using ANOVA to determine the significance of factors and interaction effects. The desirability function was applied to identify the optimal formulation with the smallest droplet size, highest EE%, and sustained release [25].

Results

Table 3. Formulation Parameters of SNDDS after 24 Hrs.

Formulations	DS (nm)	PDI	ZP (mV)	η (cps)	EE (%)
JXM1	190.46± 1.49	0.49	−24.96	169.08± 3.99	98.76
JXM2	136.44± 1.69	0.39	−22.89	168.19± 2.94	89.99
JXM3	189.69± 1.88	0.48	−23.07	160.65± 3.49	89.96
JXM4	105.84± 0.19	0.22	−43.08	66.67± 1.99	98.91
JXM5	168.69± 1.80	0.46	−25.97	120.65± 2.69	91.86
JXM6	134.25± 1.09	0.38	−22.96	89.34± 0.99	94.85
JXM7	108.02± 0.48	0.34	−27.99	64.67± 0.49	98.01
JXM8	105.08± 0.28	0.22	−43.69	59.67± 0.44	99.82

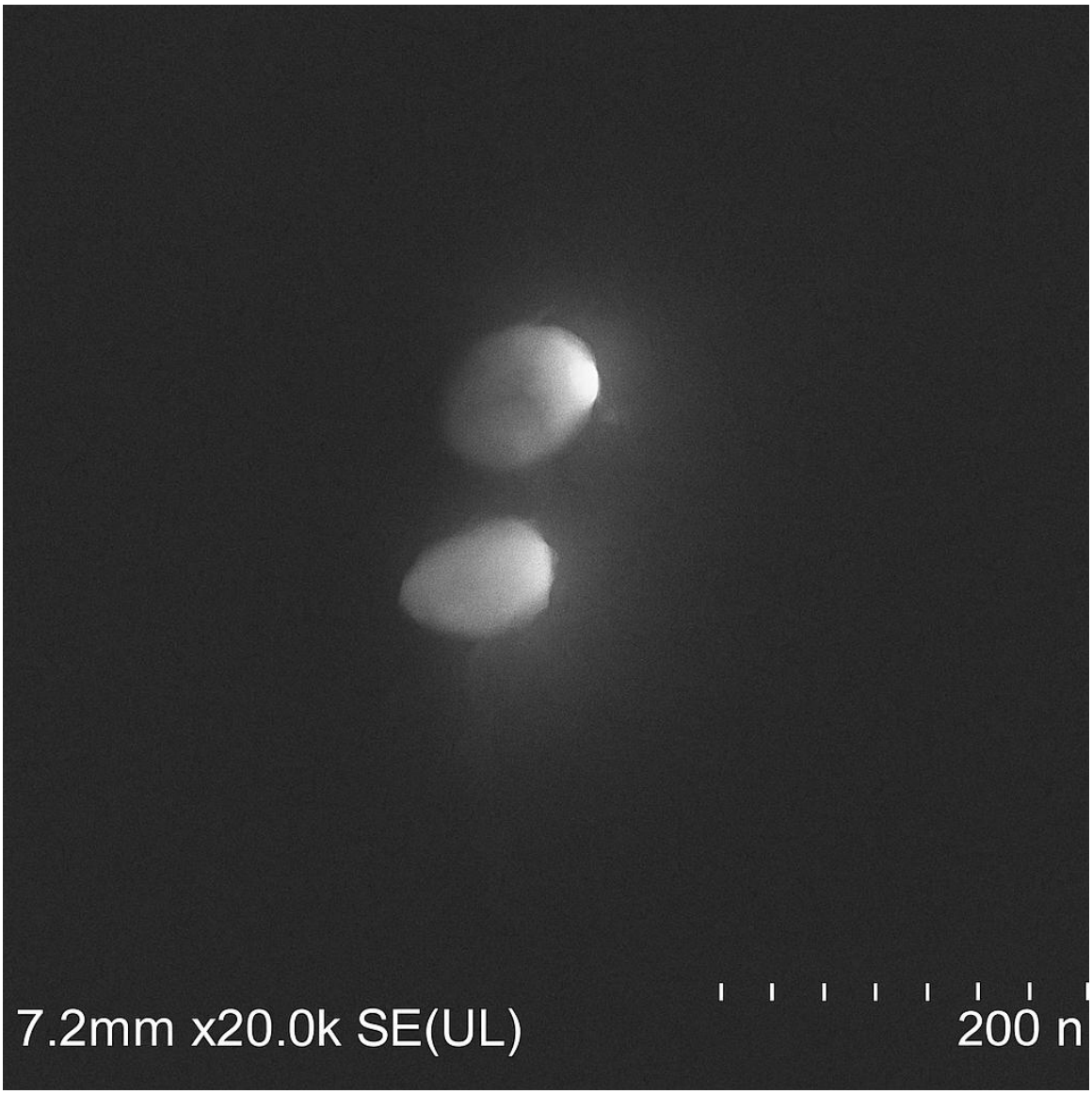

Figure 1: Morphology of CK_SNDDS

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The results of the various characterization parameters after 24 hours are presented in (Table 3). The droplet sizes (DS) of 5-FU SNDD formulations are all within nano sizes, ranging from 105 nm to 196 nm. The differences in DS values are significant ($p \leq 0.05$) with a ranking order of JXM8 ≤ JXM4 ≤ JXM7 ≤ JXM6 ≤ JXM2 ≤ JXM5 ≤ JXM3 ≤ JXM1. These observed differences highlight various interplays of homogenization energy, oil/surfactant ratio, and oil phase properties. Formulations produced under high shear force of homogenization were reported to have smaller DS compared to those formulations with low homogenization stress [26,27]. Likewise, the formation of a stable nanoemulsion is closely dependent on the concentrations of the surfactant and co-surfactant used. Increasing the surfactant-to-oil ratio effectively reduces interfacial tension, thereby facilitating the generation of nanoemulsions with smaller and more stable droplet sizes [28,29].

The PDI values show significant differences at ($p \leq 0.05$); the values, which range from 0.22 to 0.49, indicate that JXM8 and JXM4 are monodispersed, while all other formulations are polydisperse. Both moderately dispersed and monodisperse nanoformulations are generally desirable due to their predictable drug delivery behaviors [30,31]. The values of ZP vary significantly ($p \leq 0.05$) among formulations. The zeta potential values obtained ranged between (- 22.06 to - 43.69 mV), suggesting that all formulations possess adequate electrostatic stability. Among them, JXM4 and JXM8 exhibited relatively higher negative surface charges, indicating improved colloidal stability compared to the other formulations (Table 3).

Table 4. Formulation Parameters of SNDDS after 7 days.

Formulations	DS (nm)	PDI	ZP (mV)	η(cps)	EE (%)
JXM1	200.46± 1.49	0.71	−24.34	189.08± 3.29	88.76
JXM2	200.44± 1.69	0.71	−22.44	188.19± 2.44	88.89
JXM3	199.69± 1.88	0.69	−22.87	160.65± 3.49	89.56
JXM4	105.84± 0.19	0.22	−43.08	66.67± 1.99	98.91
JXM5	189.69± 1.80	0.69	−25.87	120.65± 2.69	90.56
JXM6	150.25± 1.09	0.56	−22.06	89.34± 0.99	94.85
JXM7	119.04± 0.48	0.44	−27.89	64.67± 0.49	98.01
JXM8	105.08± 0.28	0.22	−43.69	59.67± 0.44	99.82

After 7 days (Table 4) and 30 days (Table 5), there were significant ($p \leq 0.05$) increases in DS, η, and PDI values for most formulations (JXM1–JXM3, JXM5, and JXM6). This may be due to Ostwald ripening effects. In this thermodynamically driven process, larger droplets grow at the expense of smaller ones, resulting in complete phase separation [32]. JXM4 and JXM8, however, maintained their DS, PDI for well over 30 days. This is desirable in nano-formulations and indicates excellent product stability [33,34].

Table 5. Formulation Parameters of SNDDS after 30 days.

Formulations	DS (nm)	PDI	ZP (mV)	η(cps)	EE (%)
JXM1	210.66± 1.49	0.59	−22.64	169.08± 3.99	98.76
JXM2	220.44± 0.69	0.55	−21.84	168.19± 2.94	89.99
JXM3	199.69± 0.88	0.69	−20.89	160.65± 3.49	89.96
JXM4	105.84± 0.19	0.22	−43.08	66.67± 1.99	98.91
JXM5	188.69± 1.95	0.58	−23.87	120.65± 2.69	91.86
JXM6	134.25± 1.09	0.51	−21.66	89.34± 0.99	95.05
JXM7	128.02± 0.48	0.44	−29.95	64.67± 0.49	98.01
JXM8	105.08± 0.28	0.22	−43.69	59.67± 0.44	99.82

Keys: DS=droplet size, PDI = Polydisperse Index, ZP = Zeta potential, and EE = Entrapment efficiency

The ZP values for formulations JXM1-JXM3, JXM5, and JXM6 equally vary with time, as shown in (Tables 4 and 5). The observed variations in these parameters were statistically significant ($p \leq 0.05$), indicating that the differences are attributable to the formulation variables under study [14]. Notably, JXM4 and JXM8 demonstrated markedly high negative zeta potential values (≥ –40 mV), which reflect enhanced electrostatic repulsion and, consequently, a reduced tendency for droplet aggregation [35]. Viscosity (η) values ranged from 59.67 ± 0.44 cps (JXM8) to 189.08 ± 3.29 cps (JXM1). Lower viscosities favor rapid self-emulsification and improved dispersion on administration, while higher viscosities slow emulsification but may support prolonged release [36]. Entrapment efficiency (EE) remained high across all formulations (88.76–99.82%), with JXM8 maintaining nearly complete entrapment (99.82%), confirming minimal drug leakage and good stability of the encapsulated phase [37]. The stability of these parameters over 30 days shows that all formulations stayed within acceptable limits for Nanoemulsion systems. Notably, formulations JXM4 and JXM8 exhibited the most favorable stability characteristics, demonstrated by features such as small droplet sizes (approximately 105 nm), low polydispersity indices (0.22), markedly negative zeta potentials (≤−43 mV),

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relatively low viscosities (≤70 cps), and high entrapment efficiencies exceeding 98%. These features suggest strong thermodynamic and kinetic stability, making the two formulations excellent candidates for further in vivo testing. Similar long-term stability trends have been reported for optimized SNDDS [38,39]. And considering all time points, JXM4 and JXM8 consistently outperformed other formulations across all characterization parameters. Their small droplet sizes, low PDIs, and highly negative ZP values demonstrate superior stability and predictability, while high EE values confirm efficient drug encapsulation.

Table 6. Solidified SNDDS 5 FU Formulation Granules Flow Properties

Formulations	TD (gcm^{-3})	BD (gcm^{-3})	HR	CI (%)	AR (°)	ET (Min)
JXM1	0.84	0.62	1.35	26.10	28.94	3.02
JXM2	0.88	0.66	1.33	25.00	30.04	2.89
JXM3	0.81	0.62	1.31	24.69	25.66	3.01
JXM4	0.82	0.72	1.14	12.20	22.01	1.66
JXM5	0.89	0.64	1.39	28.09	29.46	2.66
JXM6	0.88	0.67	1.31	23.86	25.50	2.56
JXM7	0.88	0.70	1.26	20.45	25.09	1.89
JXM8	0.91	0.80	1.14	12.09	22.01	1.60

Keys: TD = Tapped density, BD = Bulk density, HR = Hausner ratio, AR = angle of repose, and ET = Emulsification time.

The flow properties of the solidified self-nanoemulsifying drug delivery system (SNDDS) granules of 5-fluorouracil (5-FU) presented in (Table 6), which revealed significant differences ($p \leq 0.05$) in bulk, tapped densities, Hausner ratios, Carr's indices, and angles of repose among formulations JXM1–JXM8. The bulk density (0.62–0.80 g/cm³) and tapped density (0.81–0.91 g/cm³) values indicated moderate to good packing characteristics of the granules. Formulations JXM4 and JXM8 demonstrated superior flowability (uniform flow necessary for solid dosage formulations) with low Hausner ratios (1.14) and Carr's indices around 12%, consistent with optimal powder flow behavior [40,41]. Conversely, formulations such as JXM1 and JXM5 exhibited higher Hausner ratios (>1.35) and Carr's indices (>25%), suggesting interparticulate friction and possible cohesiveness that may require optimization of excipient ratio or particle size distribution to enhance manufacturability. Hausner ratio values below 1.25 and Carr's index values less than 15% typically signify excellent flow and compressibility, attributes critical for uniform die filling during tablet compression [42,43].

Table 7. IC_{50} at different time intervals

Formulations	IC_{50} (24hrs) (µg/mL)	IC_{50} (48hrs) (µg/mL)	IC_{50} (72hrs) (µg/mL)
JXM1	14.89± 1.84	11.69 ±1.04	9.44 ± 2.94
JXM2	11.01± 1.93	9.96 ± 1.63	9.07 ± 2.43
JXM3	9.86 ± 2.83	8.68 ± 2.49	7.64 ± 1.43
JXM4	7.24 ± 1.67	4.18 ± 0.64	3.89 ± 2.79
JXM5	11.89 ± 2.99	10.06± 2.96	9.79 ± 2.86
JXM6	10.88 ± 2.26	9.88 ± 1.86	8.86 ± 2.45
JXM7	9.68 ± 2.55	7.87 ± 1.22	5.98 ± 1.49
JXM8	6.10 ± 1.34	4.05 ± 0.64	3.77 ± 0.94

The angle of repose and the emulsification time are further used to support the assessment of flow and dispersibility characteristics. JXM4 and JXM8 showed the lowest angles of repose (22.01°) and the fastest emulsification times (1.60–1.66 min), indicating better flow and rapid self-emulsification upon dilution compared to all other formulations. These findings suggest that improved flow parameters contribute positively to faster emulsification behavior, likely due to enhanced wettability and reduced aggregation among granules [44]. Overall, the data highlight the importance of optimizing solid carrier selection and processing parameters to achieve desirable flow and emulsification performance in solidified SNDDS formulations, aligning with current trends in enhancing the manufacturability and performance of nanoemulsified oral dosage systems [21,45].

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Table 8. Physical parameters of 5-FU SNDDS-loaded Capsules

PARAMETERS	JXM1	JXM2	JXM3	JXM4	JXM5	JXM6	JXM7	JXM8
MCW (mg)	600.00±2.89	602.65±2.7	604.32±2.09	600.01±0.89	603.82±2.20	600.02±1.09	599.88±2.99	599.98±0.89
FR (%)	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01
DT (minutes)	2.81 ±3.69	2.68 ±3.49	2.28 ±2.44	2.22 ±0.49	2.31 ±2.99	2.25 ±2.87	2.27 ±1.39	2.21 ±0.19
%CDR (60 Minutes)	72.44	77.03	84.67	98.77	72.98	75.05	86.02	98.99

Keys: MCW = Mean Capsule Weight, FR = Friability, DT = Disintegration Time, CDR = Cumulative Amount of drug released in solution at 60 minutes.

The physical characterization of the 5-FU SNDDS-loaded capsules (Table 8) indicates robust and pharmaceutically acceptable performance across batches JXM1–JXM8. Mean capsule weight (MCW) was tightly clustered (599.88 ± 2.99 to 604.32 ± 2.09 mg), demonstrating excellent dose uniformity consistent with expectations for well-optimized solid-dosage formulations and with reports that nanostructured lipid and self-nanoemulsifying systems can be formulated into weight-uniform solid dosage forms when excipient selection and fill processes are controlled [46]. The friability values of the 5-FU SNEDDS formulations ranged from 0.00 to 0.02%, which is substantially below the pharmacopeial threshold of ≤1.0% mass loss. This indicates that the formulations possess sufficient mechanical strength, making them suitable for routine handling and transportation [47,48]. There were, however, significant differences ($p \leq 0.05$) in disintegration times (DT) (2.21 ± 0.19 to 3.69 ± 0.19 min). DT values support rapid capsule breakup and drug availability for dissolution. Rapid *in-vitro* disintegration is a key desirable property for oral nanoparticle-loaded solid forms intended to maximize drug release in the upper GI tract or to allow subsequent controlled release behavior, depending on the formulation design [48]. The 60-minute cumulative drug release (CDR) (Figure 2) varied significantly ($p \leq 0.05$) among formulations (72.44% to 98.99%), with JXM4 and JXM8 achieving nearly complete release (99%), indicating that JXM4 and JXM8 formulations possess quality formulation attributes for possible pilot production and scale-up after a successful *in vivo* performance and clinical investigations.

The effect of high lipid/surfactant ratios and high homogenization energy may have favored JXM4 and JXM8, which significantly processed desirable quality formulation attributes as observed in this investigation [49,50]. Collectively, these data show that all batches meet routine physical quality requirements, while the observed differences in release profiles underscore the strong influence of SNDDS composition and solidification method on disintegration and release kinetics; JXM4 and JXM8 therefore merit further in-depth evaluation (e.g., *in vitro–in vivo* correlation, stability, and release mechanism studies) to confirm their potential for enhanced oral delivery of 5-fluorouracil.

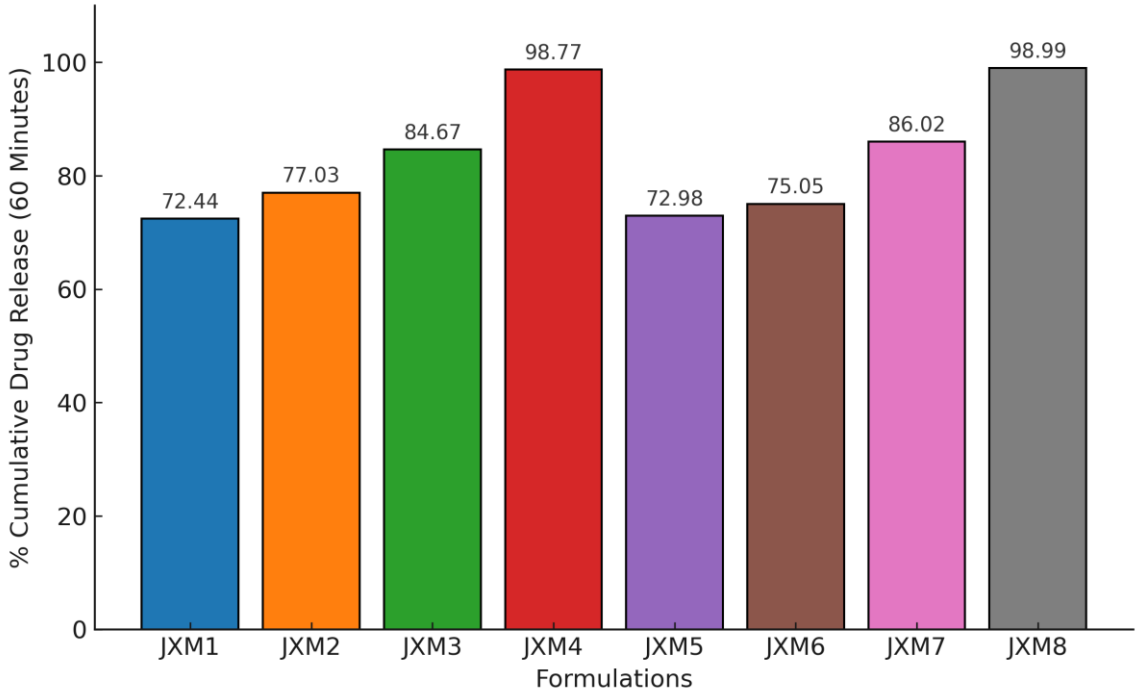

Figure 2. Percentage Cumulative Drug Released of 5-FU SNDDS (24 Hrs.)

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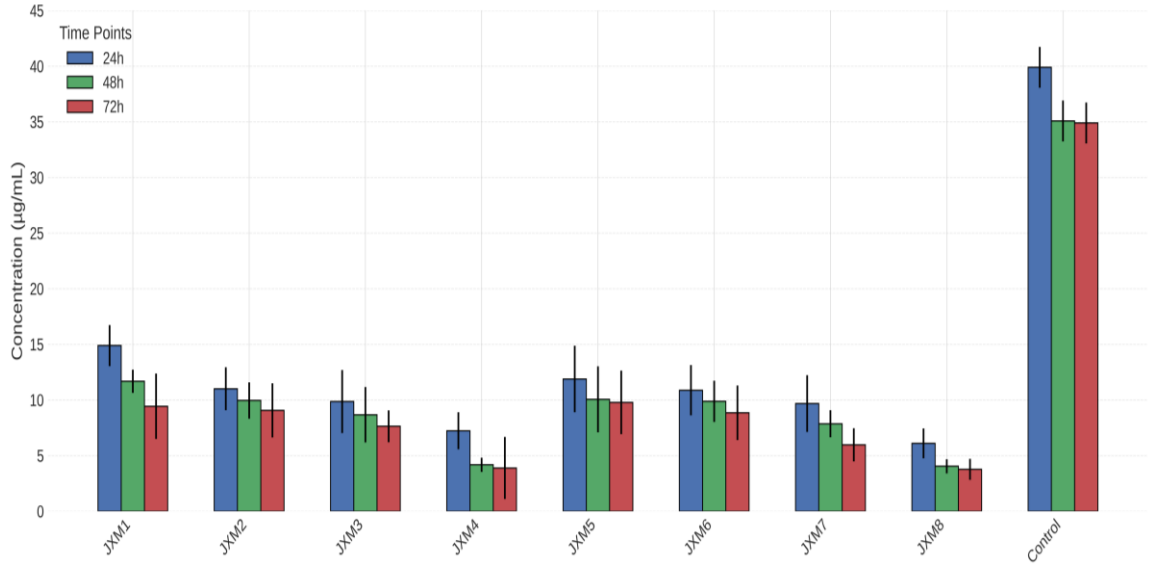

Figure 3. IC_{50} of 5-FU SNDDS Formulation After Different Treatment Periods (mean ± SD).

Figure 3 shows how the half-maximal inhibitory concentration (IC_{50}) values of the 5-FU SNDDS formulations change over different treatment periods (mean ± SD). A clear reduction in IC_{50} over time was observed, with values significantly decreasing ($p \leq 0.05$) as exposure time increased. The observed statistically significant enhancement in cytotoxicity with prolonged treatment duration indicates that the SNDDS formulation facilitates increased cellular uptake and sustained intracellular release of 5-FU. The progressive reduction in IC_{50} values at extended incubation periods further confirms the improved therapeutic efficacy of the nano-formulated system relative to shorter exposures. This trend is consistent with previous reports demonstrating that nanoparticle-based 5-FU delivery systems enable controlled release and enhanced bioavailability, thereby achieving superior anticancer performance compared to conventional 5-FU dispersions [49–50]. Collectively, the significant ($p \leq 0.05$) increase in cytotoxic potency over time underscores the potential of the developed formulation as a sustained and effective platform for prolonged delivery of the chemotherapeutic agent.

Conclusion

This investigation highlights the potential of cashew nut oil as a drug delivery vehicle in pharmaceutical formulations (especially as a self-emulsifying nano-drug delivery system), dedicated to improving the systemic bioavailability of the drug by facilitating the transport of drugs across the various lipid barriers within the gastrointestinal tract. Formulations JXM4 and JXM8 both show brilliant performances at higher oil/surfactant ratios and homogenization speeds, implying that the homogenization speed and the oil/surfactant ratio must be critically optimized for a successful SNDDS formulation. And as such, JXM4 and JXM8 will be subjected to thorough optimization and *in vivo* studies aimed at repositioning 5-FU as an orally administrable chemotherapeutic agent.

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