IGBINEDION UNIVERSITY OKADA
JOURNAL OF PHARMACEUTICAL SCIENCES

https://pharmacy-journal.iuokada.edu.ng/ Volume 4, no. 1, pp. 014-027 (2025)

ISSN (online): 2992-5746 **ISSN (print): 2992-5339**

RESEARCH ARTICLE

SELF-EMULSIFYING PROPERTIES OF *MORINGA OLEIFERA* SEED OIL AND *CAMELUS* HOMOLIPID (CAMEL FAT) FOR THE DELIVERY OF 5-FLUOROURACIL (5-FU) IN THE MANAGEMENT OF BREAST CANCER

***Yinka J. OYENIYI, Isa O. ISMAIL**

Department of Pharmaceutics and Pharmaceutical Technology,
Faculty of Pharmaceutical Sciences,
Usmanu Danfodiyo University, Sokoto, Sokoto State, Nigeria
***Corresponding author's email**: oyeniyi.yinka@udusok.edu.ng, **Telephone:**+234 (0) 903 111 4106

ABSTRACT

Background and Aim: To formulate a self-emulsifying drug delivery system (SEDDS) based on *Moringa* seed oil (MSO) and its admixture with a homo-lipid from camel hump fat, *Camelus dromedarius* (CDH) for the delivery of 5-Fluorouracil for the management of breast cancer.

Method: MSO and CDH were extracted and characterised using standard methods, and utilized in the formulation of SEDDS (coded SDA1 to SDA4) loaded with 5-fluorouracil (5-FU). The properties of these were investigated with reference to isotropic test, droplet size determination, polydispersity index (PDI), zeta potential (ZP), emulsification time, absolute drug content, and percentage mortality against MCF-7 cell line. Granule formulations prepared through wet granulation technique were subjected to Carr's and Hausner's ratios analysis, encapsulated using hard gelatin shells, and subjected to relevant Pharmacopoeia quality control tests.

Results: MSO and CDH yielded 41 and 43% v/w, respectively with their oleic acid contents being MSO (72.5%) and CDH (39.2%). The saponification, crude fat, protein, carbohydrate, and ash values showed no significant differences from previously reported values. All formulations of 5-FU-loaded SEDDS were stable with no sign of precipitation or colour changes, gave mean emulsification times ≤ 40 minutes, and all droplet sizes were within the nano range (199 to 222.1 nm). The formulations were stable and polydisperse, as indicated by their PDI (< 0.5) and ZP (-40 mV) values. PDI, ZP and the IC_{50} were ranked as: SDA1≤ SDA4 ≤ SDA2 ≤ SDA3. Granules' flow parameters ($p \leq 0.05$) are ranked: SDA1≤ SDA4 ≤ SDA2 ≤ SDA3, except for the flow rate of granules having a reverse ranking: SDA1≥ SDA4 ≥ SDA2 ≥ SDA3. All formulations of 5-FU-loaded SEDDS capsules complied with United States Pharmacopeia requirements. SDA2 and SDA3 failed content uniformity test, which may be a direct consequence of the 5-FU SEDDS composition and the batch processing variables.

Conclusion: The *Moringa* seed oil and *C. dromedarius* homolipid were successively utilised in the formulation of SEDDS. Only SDA1 and SDA4 performances were pharmacopoeial compliant, and require further *in vivo* investigation and optimisation**.**

Key words: *Moringa* seed oil, camel fat (*Camelus dromedarius*), 5-fluorouracil, self-emulsifying drug delivery system

INTRODUCTION

Drugs with poor aqueous solubility will experience difficulties crossing the physiological membrane into the systemic circulation. Consequently, they are known to have poor oral bioavailability and delayed onset of action. Several attempts in the past aimed at solving the challenges include measures such as the preparation of the salt form of the drug, particle micronization, and solid dispersion, had yielded little or no success [1].

Consequently, experts in the field are now employing self-emulsifying drug delivery systems (SEDDS) to confront the challenges. SEDDS is a unique composition of drugs, oil, surfactants, and co-surfactants. The system could easily form a micro or nanoemulsion whenever it comes in contact with the gastric fluid after oral administration. This allows the absorption of the drug through the lymphatic pathway thereby bypassing the first-pass metabolic effects of the liver and ultimately improving the oral bioavailability of the drug [2, 3].

SEDDS aims to improve the hydrophilicity/lipophilicity balance of drug molecules and has emerged as a credible alternative that successfully addresses challenges related to oral bioavailability of poorly water-soluble drugs [4]. SEDDS employed isotropic mixtures of oils, surfactants, solvents, and co-solvents/surfactants forming a micro/nanoemulsion system upon mild agitation thus significantly improving the solubility and absorption of the drug, and has become a vital strategy for increasing the oral bioavailability of drugs with poor aqueous solubility by enhancing the dissolution, transportation across the membrane, and bioavailability of orally administered insoluble drugs [5,6].

SEDDS are stable against intestinal enzymatic activity and, more importantly, they offer rapid permeation across the mucus barrier [6]. The ease of its preparation makes it highly suitable for industrial purposes, with large batches prepared within the shortest possible time and without any sophisticated technology [7,8].

In this investigation, we aim to evaluate the self-emulsifying properties of a mixture of *Moringa* seed oil (MSO) and *Camelus dromedarius* homolipid (CDH) for the novel delivery of 5-FU in breast cancer therapeutic management.

MATERIALS AND METHODS

Materials: Camel fat (*C. dromedarius*) was sourced from the Sokoto State abattoir, while *Moringa* seeds were acquired locally from the Sokoto Central Market in Sokoto State, Nigeria. The 5-FU powder was obtained from Sigma-Aldrich Chemie GmbH, Eschenstr. 5, 82024 Taufkirchen, Germany. All other reagents were of analytical grade and were used without further modification.

Extraction of *Moringa oleifera* seed oil: Dried powdered *Moringa* seed (100g) was extracted with n-hexane using a Soxhlet apparatus according to the Association of Official Analytical Chemists (AOAC 2003) standard method with little modification. The residual oil was cooled and weighed [8].

Extraction of homolipid from camel fat (Camelus dromedarius): Camel fat (*C. dromedarius*), 2 kg, was processed in the laboratory as follows:

Camel hump was minced, transferred into a pot containing small quantity of water boiled with frequent stirring until liquefaction. Mixture was filtered through a mesh strainer, filtrate cooled at 3 - 4°C to separate into a slab of solidified hump oil of a deep yellowish color on the top of water containing impurities. To further remove impurities, solidified hump oil was melted in two volumes of boiling water and filtered through a mesh strainer, and the fat, after cooling, was recovered by simple decantation of the lower aqueous layer [8] the fat, after cooling, was recovered by simple decantation of the lower aqueous layer [8].

***Proximate analysis*:** Percent concentrations of proteins, lipids, carbohydrates, crude fiber, moisture, and ash of both MSO and CHL were determined using standard procedures [8].

***FTIR analysis*:** To check for possible interactions (physical and chemical), the Fourier Transformed Infrared Spectrometer with $LiTaO_3$ (lithium tantalate) MIR detector (PerkinElmer FT 9700, 710 Bridgeport Ave, Shelton, CT 06484, USA) was used to scan constituents of each formulation using the instructional protocol [9].

***Formulation and encapsulation*:** SEDDS loaded with 5-FU were prepared according to the proportions stated in Table 1 and as described by Friedl *et al* [10]. In each case, weighed amounts of oil(s), surfactant, co-surfactant, and 5-FU were mixed with a homogenizer (type FSH-2A SerachTech, UK) operating at 1000 rpm. Each SEDDS formulation prepared was mixed with the appropriate diluent (Table 1) and screened through a sieve with an aperture size of 150 µm. The granules were dried using a hot air tray drier maintained at 45°C for 24 hours, after which they were transferred into an air-tight container and kept in a desiccator until needed.

Table 1: Composition of 5-FU loaded SEDDS based on a blend of *Moringa* seed oil (MSO) and *Camelus dromedarius* (CDH)

Formulation	MSO (mL)	CDH (mL)	Tween 80 (mL)	Span 80 (mL)	5-FU (mg)	Solid Carrier
SDA1	20	30	10	30	100	Starch
SDA2	20	20	-	10	100	Lactose
SDA3	20	10	-	10	100	Lactose
SDA4	20	20	10	20	100	Starch

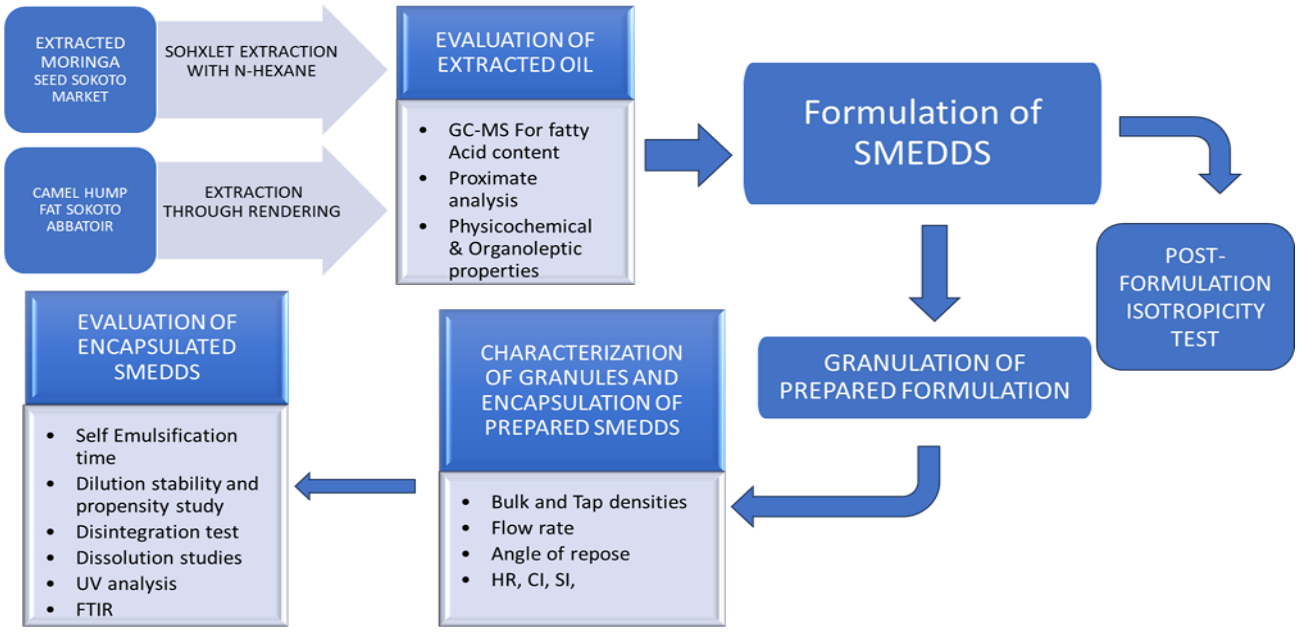

Figure 1: Schematic representation of the methods for self-emulsifying drug delivery system

Post-formulation isotropicity test: The formulations were allowed to stand for 24 h and then visually examined for phase separation to identify stable preparations [11].

Emulsification time: Distilled water (500 mL) water in a glass beaker mounted on a magnetic stirrer maintained at 37 OC was added to 1 mL of each formulation with mild agitation (50 rpm). The self-emulsification process was visually checked and recorded for the time taken for emulsification for each batch, as indicated by constant turbidity. The mean of triplicate determinations was taken as the emulsification time for each formulation [11].

Determination of the granules flow parameters: The flow characteristics of granule formulations were determined by standard Pharmacopoeial tests such as the angle of repose, Hausner's ratio, Carr's index, and the flow rate [12].

Absolute drug content: One capsule from each formulation was placed in 100 mL 0.1M HCl and emulsified under moderate agitation (50 rpm). After complete emulsification, the resultant solution was diluted 10-fold and the absorbance determined with a spectrophotometer at 266 nm. The amount of 5-FU present in each capsule was calculated from a calibration plot previously determined for 5-FU [13].

Capsules mean weight: According to the United States Pharmacopoeia 2022 protocol, randomly selected capsules (20) from each formulation were weighed individually, after which the deviation from the mean was calculated using Equation 1.

$$\{(Iw - Aw) / Aw\} \times 100\% \quad \text{.....eq 1}$$

where, Iw = individual weight of capsule;
Aw = average weight of capsule

Drug dissolution studies: A capsule from each formulation was enclosed in a dialyzing membrane (6 cm length x 3 cm width) which was tied at both ends and introduced into a dissolution apparatus containing 1000 ml 0.1 M HCl. Mild agitation was provided at a speed of 50 rpm at 37±0.5 °C. Ten mL volume of the media was withdrawn at predetermined intervals of 0, 5, 10, 15, 30, 45, 60 mins, filtered, and assayed spectrophotometrically (266 nm) for 5-FU. The release medium was replenished after each withdrawal to maintain constant volume [13, 14.15].

Drug stability and propensity studies: The stability of the formulation after dilution was investigated using a randomly selected capsule from each formulation. In a 1 L beaker containing100 ml 0.1M HCl, the content of the selected capsule was discharged and mixed thoroughly before diluting with successive 100 mL volumes until the 1 L mark was reached. The dilution was allowed to stand for 5 h and then checked for drug precipitation or phase separation. In testing for precipitation propensity, a 10 mL volume of this dilution was placed in a test tube, corked and left undisturbed for 24 h, and inspected visually for signs of drug precipitation continuously for an additional 24 h, and thereafter weekly for six weeks [13]

Capsules disintegration time test: Six capsules from each formulation were placed in each of the disintegration baskets. The baskets were then lowered into the medium containing 1 L 0.1M HCL and maintained at 37 °C. The baskets were repeatedly raised and dipped into the medium with the mean time taken for each capsule to break up into smaller pieces and the particles passed through the screen mesh at the bottom of the baskets into the disintegrating media completely was noted [16].

Friability test: The weight of twenty capsules randomly selected from each batch was noted (wI) before transferring the same into a Roche friabilator (TronTech, Canada) operated at 25 revolutions for 4 minutes. The final weight (wF) after 100 revolutions was also noted. The loss in weight for each capsule formulation was calculated from Equation II [16].

$$FR = \{(wI - wF) / Wi\} \times 100 \text{ ……...eq 2}$$

In vitro cytotoxicity assay: The 3-(4,5-dimethylthiazol-2,5-diphenyltetra zolium bromide (MTT) method was used to investigate the cytotoxicity of the formulations. MCF-7 cells were cultured in Dulbecco's modified eagle's medium (DMEM) without phenol red and supplemented with 10% fetal bovine serum. The cell culture medium was maintained at 37 °C in a humidified incubator containing 5% CO_2 atmosphere. Trypsinized confluent cell monolayers were grown (75–80%) and the cells in the exponentially growing phase were used for cytotoxicity experiments. Specifically, the cells were plated at a density of 5×103 cells/well (optimal seeding density) in 96 well plates and kept at 37 °C in 5% CO2 atmosphere in a CO2 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 the prepared 5-FU-loaded SEDDS formulations. After 48 hours, the MTT dye solution was added to each well, and the incubation was continued for an additional 4 hours. The medium in each well containing unbound MTT and dead cells was removed by suction.

The formazan crystals were solubilized with 100 µL of dimethyl sulfoxide, and the solution was vigorously mixed to dissolve the reacted dye. The absorbance of each well was determined by reading the optical density (OD) values at 266 nm using DMSO as a blank. A plot of cell viability against the concentration was constructed and the concentration required for a 50% inhibition of viability (IC50) was determined graphically [17, 18].

(%) Cell viability =
(OD (mean))/ (OD (control)) x 100 …... eq3

RESULTS

The results of the proximate analysis of the fat from *C. dromedarius* showed that it contained 86.7% crude fat and 4% protein with minimal moisture and carbohydrate contents 2.4%, while that of MSO are presented in Table 2.

The GC-MS results are presented in Figures 2a and b. The oleic acid content of MSO was 72.54 % while that of CDH was 29.2 %, the oleic acid contents of these lipid polymers were high enough to support the self-emulsification process. Also, the high proportion of the oleic acid in MSO and CHL is equally essential in the stability of the formulated SEDDS as they may offer synergy [19, 20].

Table 2: Fatty acid content (%) and profiling of *Moringa* seed oil and *Camelus dromedarius* homolipid

S/N	Parameters	MSO	CDH
1.	Percentage yield (%)	41.43	23.45
2.	Colour	Pale Yellow	Golden Yellow
3.	Odour	Mild Odour	Faint smoky smell
4.	Taste	Pungent Flavour	Slightly meaty taste
5	crude fat (%)	39.36	86.7
6	Protein (%)	2.22	2.46
7	Moisture Content (%)	0.56	0.84
8	Carbohydrate (%)	56.95	2.48
9	Oleic Acid Content (%)	72.50	39.20
10	Ash Content (%)	1.54	1.84

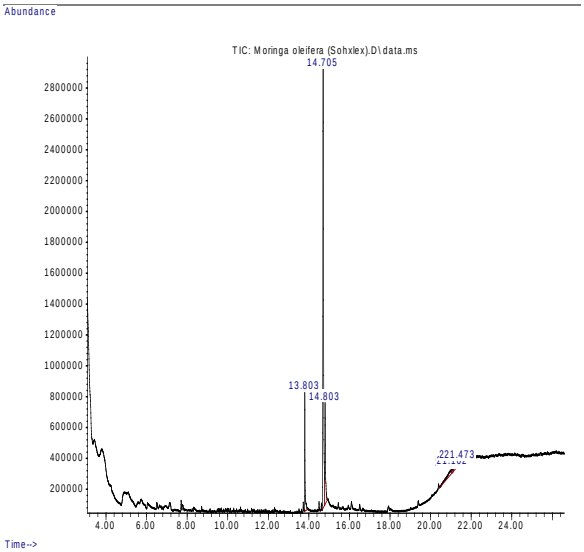

Figure 2a: GC-MS chromatogram of *Moringa oleifera* seed oil

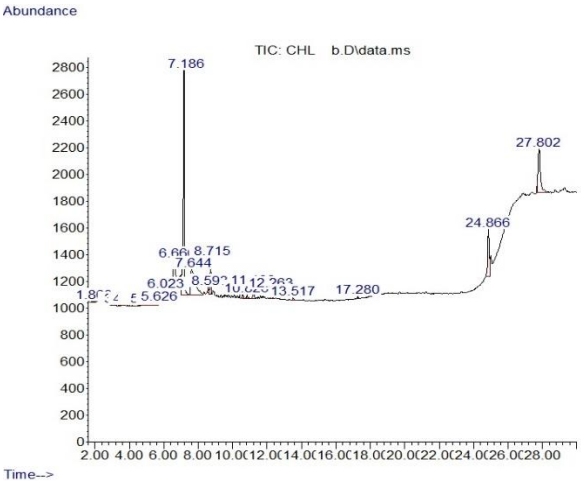

Figure 2b: GC-MS chromatogram of *Camelus dromedarius* homolipid

Table 3: Properties of 5 fluorouracil SEDDS formulations

Parameters	SDA1	SDA2	SDA3	SDA4
Mean Emulsification Time (S)	26.0±0.08	34.8±0.11	39.9±0.14	29.0±0.06
Absolute Drug Content (%)	99.8	68.9	68.3	96.9
Mean Diameter (nm)	199.0±0.04	220.0±0.13	222.1±0.14	200.2±0.03
Polydispersity Index (PDI)	0.25±0.05	0.46±0.25	0.48±0.22	0.28±0.15
Zeta potential (mV)	-24.5±0.25	-31.8±0.42	-2.9±0.45	-29.8±0.22
IC_{50} (µg/mL)	09.9±0.25	188.9±0.54	198.3±1.30	1.89±0.25

Isotropicity test results for the formulations were excellent as no phase separation was observed in any except that SDA2 and SDA3 lost their isotropicity after ten-fold dilutions. This may be due to the nature and concentration of the incorporated cosurfactants [21, 22, 23].

All the formulations are equally self-emulsifying, with a mean emulsification time ranging from 26.0 to 39.9 seconds. A well-formulated SEDDS is expected to have a low emulsification time to facilitate and improve the drug molecule's faster absorption in the GIT compared to a non-SEDDS drug delivery system [24, 25]. The significant differences ($p \leq 0.05$) in these values imply a need to optimize the formulations in a future study. Self-emulsification time (SMT) is the time taken for the system to form a stable emulsion with little agitation. Values obtained range from 26 seconds to about 40 seconds, Table 3. SEDDS are expected to rapidly emulsify within 200 seconds upon exposure to gastric fluids [25].

The quantity of drug encapsulated per unit is expressed as the absolute drug content of the formulation. Values obtained from this investigation ranged from 68.9 - 99.8%, with a ranking order of SDA1 ≥ SDA4 ≥ SDA2 ≥ SDA3. This indicates that only SDA1 and SDA4 meet the pharmacopoeia requirement for the absolute drug content, which is 95 % of the stated amount for all pharmaceutical formulations. IC_{50} follows a reverse-ranking order of SDA1 ≤ SDA4 ≤ SDA2 ≤ SDA3. This corresponds to a high availability of 5FU for effective cell apoptosis, as expected [26, 27].

The PDI of the formulations ranged from 0.25 to 0.48 (Table 4) with a ranking order SDA1 ≤ SDA4 ≤ SDA2 ≤ SDA3. The differences in Polydispersity Index values are significant at $p \leq 0.05$. Polydispersity Index (PDI) is a

parameter that defines particle size distribution, which is expressed as a dimensionless number extrapolated from the autocorrelation function in photon correlation spectroscopy. SEDDS with PDI values below 0.3 are considered uniformly sized particle distribution formulations (homogeneous) and are more stable when compared to formulations with high PDI values, which are heterogeneous and less efficacious [28]. Interestingly the zeta potentials of all the formulations are negatively charged with a similar ranking order with PDI. The impact of zeta potential on the stability of dispersed particles in solution cannot be over-emphasized.

Zeta potential values below -30 mV or above +30 mV indicate stable nano-formulations [29, 30]. SDA1 and SDA4 were formulated with tween 80 as the co-surfactants. Both formulations are impressively homogeneous, and stable, able to withstand any form of aggregation or phase separation. The FTIR spectra of the formulations are presented in Figure 3. All the functional peaks of 5-FU were present in all the spectra with no shifting. This indicates that there were no physical nor chemical interactions between the excipients and the active medicaments [31,32]

The physical parameters of the various batches of 5FU-loaded SEDDS granules are presented in Table 4. There were significant differences in the values at $p = 0.05$. The bulk density of granules depends primarily on the size distribution of the granules, their morphology, and the tendency of the granules to adhere to one another allowing the granules to either pack in such a way as to enable many voids, resulting in granules of low bulk density or allow the smaller granules to sift between the larger ones, thereby forming high bulk density granules [32, 33]. Among the four formulations, SDA4 had the highest bulk density with a rank order of SDA4 ≥SDA2 ≥ SDA3 ≥ SDA1. Generally, a decrease in the volume of granules and reduced packing fraction was observed after tapping the granules resulting in a correspondingly higher value of tapped density [34].

Interestingly, the tapped density, Carr's index, and the angle of repose, all had similar ranking orders SDA3 ≥ SDA2 ≥ SDA4 ≥ SDA1 which is consistent with the reverse ranking for the flow rate of the granules SDA1 ≤ SDA4 ≤ SDA2 ≤SDA3. A uniform flow rate of granules is a critical requirement in the pharmaceutical formulation that guarantees uniform medication dosing. It is therefore essential to ensure that the flow rate of the granules is uniform to guarantee the success of the filling operation in pharmaceutical industries [35].

Since pharmaceutical operations are in batches, the weights of the capsules are expected to be uniform per formulation to ensure uniform doses for the patients. Since this ideal situation is mostly unobtainable, all pharmacopeias specify maximum permissible weight variation limits. All SEDDS formulations complied with the United States Pharmacopoeia Convention requirements since the deviations from the mean for all the formulations were within the pharmacopeia specification of ± 5 % [36]. The release of the active drug from the solid oral dosage forms has been an important cause of bioavailability problems and as such new formulations must be designed in such a way as to facilitate a gradual and complete release of the drugs within the specified period [37].

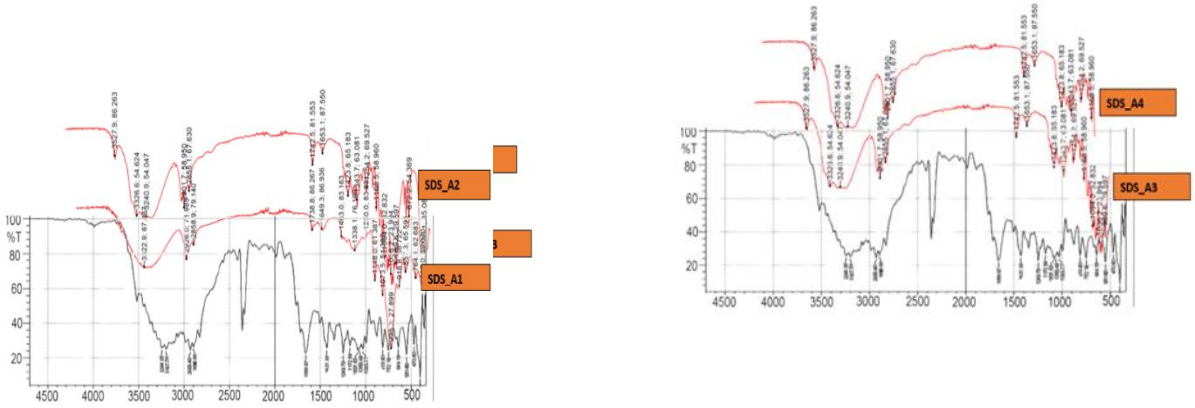

Figure 3: FTIR spectra of SEDDS formulations SDA1-A4 compared to 5-FU spectra

The disintegration time values ranged from 2.21 to 5.28 minutes, showing compliance with the Pharmacopoeia specification of 15 minutes [38,39]. Even though all the SEDDS formulations are in agreement with the pharmacopoeia requirement as it relates to disintegration time of the capsules, the differences are significant ($p \leq 0.05$), suggesting the need for product optimization. The USP 2022 [36] require 85 % of tablets and capsules contents to go into complete solution within 45 minutes which ensures efficient delivery of the drug to the receptor site.

While all the formulations complied with the official specifications on the disintegration time test, the same cannot be concluded for their dissolution profile, figure 4, since both SDA2 and SDA3 had values below the official expectations. This development is a direct consequence of the low absolute drug content of both SDA2 and SDA3, the nature of the surfactant employed, and the composition of the formulation.

This demonstrates the negative effects of the non-inclusion of co-surfactants in SEDDS design and formulation. Various authors [40, 41, 42] concluded that the nature and the concentration of excipient employed significantly affect the quality, stability, and therapeutics performance of diverse formulations [42]. Formulations that fail the absolute drug content test (assay) will equally fail the dissolution profile as in the case of non-conformity of SDA2 and SDA3 to USP specifications. Both SDA2 and SDA3 in-*vitro* cell mortality values were below 80 % this may be a direct consequence of their low absolute drug content and poor dissolution profiles, Figure 5. Consequently, SDA1 and SDA2 were selected for further studies especially optimizing the formulation.

CONCLUSION

This study demonstrated the potential of both the *Moringa* seed oil and *camel fat (C. dromedarius)* homolipid in the formulation of SEDDS, of which the selection of the excipient remains a critical hurdle that must be approached in a manner that will optimize the formulation.

Formulations	BD (g/mL)	TD (g/mL)	AR (o)	FR (g/s)	CI (%)	HR	MC (%)	SI (%)
SDA1	0.52±0.11	0.75±0.15	29.0±0.54	2.43±0.14	30.62	1.44	1.62	-18
SDA2	0.56±0.88	0.90±0.31	35.3±1.04	1.16±0.65	30.63	1.6	2.60	-20
SDA3	0.54±0.84	0.92±0.32	38.2±1.44	1.09±0.55	41.3	1.7	2.69	-60
SDA4	0.61±0.14	0.86±0.16	29.6±0.47	1.32±0.21	28.35	1.4	1.81	-58

BD = Bulk density, TD = Tapped density, AR = angle of repose, FR = flow rate, HR = Hausner ratio, MC = moisture content, SI = swelling index

Table 4: Physical properties of 5-fluorouracil-loaded SEDDS granules

Table 5: Physical properties of 5 fluorouracil-loaded SEDDS capsules

Parameters	SDA1	SDA2	SDA3	SDA4
MCW (mg)	600.00	602.65	608.82	600.01
FR (%)	0.00	0.01	0.01	0.01
DT (minutes)	2.21	4.68	5.28	2.29
D45 (minutes)	90.14	69.79	69,99	89.90
PM (%)	99.9	79.47	78.77	99.6

MCW = Mean capsule weight, FR = friability, DT = disintegration time, D45 = Amount in solution at 45 minutes, PM = percentage mortality

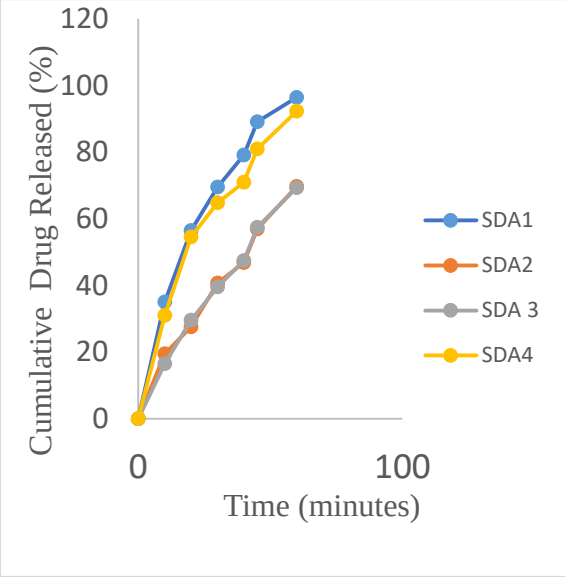

Figure 4: Dissolution profile of 5-fluorouracil SEDDS capsules

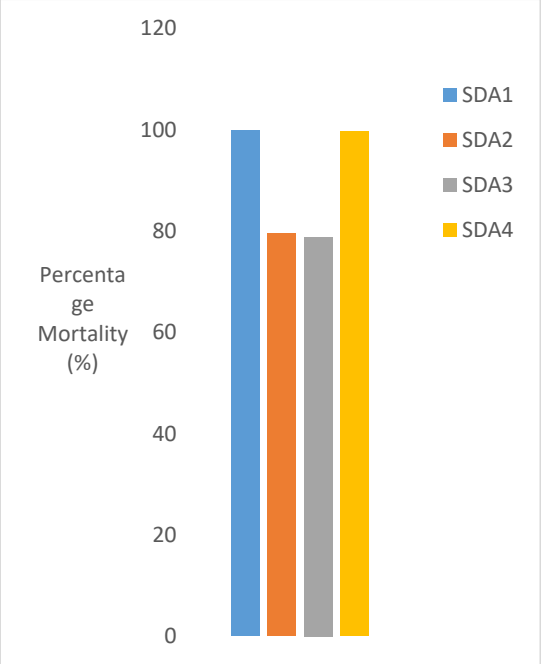

Figure 5: Percentage mortality

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