ORIGINAL ARTICLE

# Solid self-emulsifying drug delivery system based on a homolipid and vegetable oil: A potential vehicle for the delivery of indomethacin a disadvantaged drug

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**Background:** The successful utility of some biocompatible natural excipients may be more advantageous over their synthetic counterparts in drug formulations. Indomethacin is a potent non-steroidal anti-inflammatory drug disadvantaged by adverse effects. **Aim:** Hence, the aim of this study was to formulate indomethacin-based solid self-emulsifying drug delivery system (SSEDDS) for possible improvement on aqueous solubility and anti-inflammatory property of indomethacin using two biocompatible lipid excipients. **Materials and Methods:** Indomethacin-loaded SSEDDS were formulated with *Bos indicus* (BI) fat or its blend with *Pentaclethra macrophylla* oil. The surfactant component constituted of Tween 65 and Tween 80 blend while Span 85 served as the co-surfactant. Carbosil® was incorporated in some of the formulations as a viscosity enhancer and stabilizer. The following *in vitro* properties of the formulations were studied: visual isotropicity test, droplet size, emulsification time, aqueous dilution and drug precipitation, drug content, and drug release studies respectively. The anti-inflammatory properties were also studied in Wistar rats. **Statistical Analysis:** Results were presented as the mean ± standard deviation. One-way analysis of variance was used to determine statistical significance using the Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS Inc. U.S.A). $P < 0.05$ was considered statistically significant. **Results:** All batches were isotropic before and after drug loading. Batches containing BI fat and PM oil blend exhibited faster emulsification time ($P < 0.05$) than those formulated with only BI fat. Carbosil® significantly ($P < 0.05$) increased the emulsification time. Faster drug release occurred in batches with oil blends. Higher significant ($P < 0.05$) anti-inflammatory effect was demonstrated by indomethacin self-emulsifying drug delivery system compared to the reference indomethacin powder. Therefore, BI fat and PM oil have proved useful lipid excipients in achieving improved solubility and increased anti-inflammatory activity of indomethacin.

**Key words:** Anti-inflammatory effect, *Bos indicus* fat, indomethacin, *Pentaclethra macrophylla* oil, solid self-emulsifying drug delivery system

## INTRODUCTION

The enhancement of the solubility of poorly soluble drugs to improve their oral bioavailability has constituted a palpable research concern. This is because low water solubility accounts for the poor oral absorption and inconsistent bioavailability of many hydrophobic or new drug entities. Some documented popular approaches to address this physicochemical hiccup include, oil or surfactant dispersions, cyclodextrins, liposomes, and self-emulsifying formulations.[1-4] Of all these, self-emulsifying drug delivery system (SEDDS) holds great promise. SEDDS is an isotropic mixture of oil, surfactant, and co-surfactant, which on gentle agitation in aqueous medium undergoes self-emulsification to produce oil-in-water or water-in-oil emulsions.[5,6] The emulsion droplets contain dissolved drug-excipient mixture, with the drug solution having no direct contact with the aqueous phase.

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SEDDS typically produces emulsion with droplet sizes of 100 nm and above. The advantages of SEDDS include, more consistent drug absorption, selective targeting of drug (s) toward specific absorption window in the gastrointestinal tract (GIT), protection of drug (s) from the gut environment, control of delivery profiles, ease of manufacture, reduced variability including food effects, enhanced oral bioavailability enabling dose reduction and high drug loading efficiency.[7]

Careful choice of surfactants and oils is crucial to guarantee drug solubilisation and formulation

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stability. Functionally, specialized synthetic oils and surfactants have been explored in the formulation of SEDDS. Nonetheless, biocompatible naturally-occurring vegetable and animal lipids have drawn investigative attention.[8] This present work sought to further investigate the utility potential of an edible oil of vegetable origin and animal lipid. If they are ascertained to possess acceptable excipient properties comparable to their synthetic counterparts, formulation preference may be given to them. This is because their nutritional values position them as essential household food items in especially African countries. Thus, in the pharmaceutical front, regulatory approval will be secured with minimal stringent considerations. It is interesting to note that whereas the animal lipid is often considered and discarded as waste it is being projected here as a useful formulation excipient.

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) with prominent anti-inflammatory, analgesic and antipyretic properties similar to those of salicylates. It is a more potent inhibitor of cyclooxygenase than aspirin. It is hydrophobic but like other NSAIDs, it causes severe gastric ulceration.[9] Therefore, the objectives of this work were to formulate indomethacin solid self-emulsifying drug delivery system (SSEDDS) using vegetable oil/animal lipid for the purpose of improving aqueous solubility and anti-inflammatory activity of indomethacin. If anti-inflammatory activity is improved, in *in vivo* conditions dose reduction may retain acceptable therapeutic effect while diminishing adverse effects.

## MATERIALS AND METHODS

### Materials

Indomethacin (Merck, Germany), Span 85 (FLUKA AG Chemische Buchs, Engetragene Chemical Marke de Chemical Inc., USA), Tween® 80 (Sigma Aldrich, Seelze, Germany), *Pentaclethra macrophylla* (PM) seed (oil bean seed) was procured from Nsukka main market, Nigeria and appropriately identified before extraction of the oil. Tallow (*Bos indicus* (BI)) fat was obtained from Nsukka abattoir. All other reagents used were of analytical grade and were used as supplied.

### Extraction and Purification of Homolipid from BI and Oil from PM Seeds

About 1 kg of the fat was immersed in hot water maintained at 80-90°C for 45 min and extraction carried out according to reported protocols.[10,11] The seeds of PM were dried, milled and the oil extracted by cold maceration for 24 h using petroleum ether. The resultant oil was purified as described above.

### Proximate Analysis

BI fat and PM oil were evaluated for the quantitative presence of protein, lipid, carbohydrate, crude fibre, moisture and ash using standard procedures.[12,13]

#### *Pre-formulation isotropicity test*

Different batches of SSEDDS were prepared using PM oil or BI fat as the oil component, Tween 80 and 65 as the surfactants and Span 85 as the co-surfactant. Appropriate quantities of the constituents were introduced into a beaker and stirred over a water bath at 50°C for 10 min [Table 1]. Thereafter, it was stored for 24 h at ambient temperature and later visual examination was conducted for evidence of phase separation or loss of homogeneity. Only ratios, which remained isotropic without phase separation after this storage time were used for the formulation of drug-loaded SSEDDS.

#### *Drug solubility in the SSEDDS*

The experiment was carried out to determine the amount of indomethacin that could be dissolved in the SSEDDS formulations without precipitation, since the drug must be in solution. Increasing quantities of the drug 5, 10, 15 and 20 mg respectively were, added to 0.4 ml quantity of SSEDDS and stirred vigorously at 50°C for 30 min. The maximum drug quantity that dissolved in the SSEDDS formulations was noted and used for further studies.

#### *Formulation and encapsulation of SSEDDS*

Weighed amounts of fat/oil (s), surfactants, co-surfactant and indomethacin (20 mg), with or without Carbosil® (15 mg) were introduced into a 100 ml beaker over a water bath at 50°C. The mixture was stirred with a glass rod until the drug completely dissolved. Each formulation dose contained 370 mg of indomethacin-loaded or 385 mg of Carbosil®-containing indomethacin-loaded SSEDDS [Tables 2 and 3]. Subsequently, they were filled into hard gelatin capsules and stored for further use.

#### *Post-formulation isotropicity test*

The formulations were allowed to stand for 24 h and then visually examined for phase separation or drug precipitation to identify stable preparations.[11]

**Table 1: Composition of SEDDS for visual isotropicity test**

| Batch | O:S:C[a] | BIF[b]/BIF/PM[d] | Tween 65/80[c] | Span 85 (g) |
|---|---|---|---|---|
| 1 | 20:60:20 | 70 | 210 | 70 |
| 2 | 35:45:20 | 120 | 160 | 70 |
| 3 | 25:55:20 | 90 | 190 | 70 |
| 4 | 25:60:15 | 90 | 21 | 50 |
| 5 | 20:60:20 | 70 | 210 | 70 |
| 6 | 35:45:20 | 120 | 160 | 70 |
| 7 | 25:55:20 | 90 | 190 | 70 |
| 8 | 25:60:15 | 90 | 21 | 50 |

[a]Ratio of oil:Surfactant:Co-surfactant; [b]*Bos indicus* fat; [c]A 1:1 ratio blend of Tween 65 and Tween 80; [d]*Bos indicus* fat-*Pentaclethra macrophylla* oil blend; SEDDS – Self-emulsifying drug delivery system

**Table 2: Composition of indomethacin SEDDS containing BIF only**

| Batch | O:S:C[a] | BIF[b] | Tween 65/80[c] | Span 85 (g) | Carbosil® | Indomethacin (mg) |
|---|---|---|---|---|---|---|
| A1 | 20:60:20 | 70 | 210 | 70 | 15 | 20 |
| A2 | 35:45:20 | 120 | 160 | 70 | 15 | 20 |
| A3 | 25:55:20 | 90 | 190 | 70 | 15 | 20 |
| A4 | 25:60:15 | 90 | 21 | 50 | 15 | 20 |
| A5 | 20:60:20 | 70 | 210 | 70 | - | 20 |
| A6 | 35:45:20 | 120 | 160 | 70 | - | 20 |
| A7 | 25:55:20 | 90 | 190 | 70 | - | 20 |
| A8 | 25:60:15 | 90 | 21 | 50 | - | 20 |

[a]Ratio of oil: Surfactant: Co-surfactant; [b]*Bos indicus* fat; [c]A 1:1 ratio blend of Tween 65 and Tween 80; A1-A4 contain Carbosil®; A5-A8 contain no Carbosil®; SEDDS – Self-emulsifying drug delivery system; BIF – *Bos indicus* fat

**Table 3: Composition of indomethacin SEDDS containing a blend of BIF/PM**

| Batch | O:S:C[a] | BIF/PM[b] | Tween 65/80[c] | Span 85 (g) | Carbosil® | Indomethacin (mg) |
|---|---|---|---|---|---|---|
| B1 | 20:60:20 | 70 | 210 | 70 | 15 | 20 |
| B2 | 35:45:20 | 120 | 160 | 70 | 15 | 20 |
| B3 | 25:55:20 | 90 | 190 | 70 | 15 | 20 |
| B4 | 25:60:15 | 90 | 21 | 50 | 15 | 20 |
| B5 | 20:60:20 | 70 | 210 | 70 | - | 20 |
| B6 | 35:45:20 | 120 | 160 | 70 | - | 20 |
| B7 | 25:55:20 | 90 | 190 | 70 | - | 20 |
| B8 | 25:60:15 | 90 | 21 | 50 | - | 20 |

[a]Ratio of oil: Surfactant: Co-surfactant: [b]A 1:1 ratio of *Bos indicus* fat and *Pentaclethra macrophylla* oil blend; [c]A 1:1 ratio blend of Tween 65 and Tween 80; B1-B4 contain Carbosil®; B5-B8 contain no Carbosil®; SEDDS – Self-emulsifying drug delivery system; BIF/PM – *Bos indicus* fat/ *Pentaclethra macrophylla*

### *Emulsification time test*

A 100 ml quantity of 0.1 N HCl was introduced into a 250 ml beaker positioned on a hot plate and maintained at 37 ± 1°C. One capsule of SSEDDS was transferred into the beaker and the stirrer set at approximately 50 rpm. The time taken for the complete emulsification of the SSEDDS was visually observed.

### *Aqueous dilution test*

One capsule from each batch was discharged into 100 ml of 0.1 N HCl in a 1 l beaker at 37 ± 1°C. Incremental dilutions were made subsequently until 1 l volume was attained. It was allowed to stand for 5 h and then checked for drug precipitation or phase separation.

### *Post-dilution drug precipitation test*

The 1000 ml was further stored at ambient temperature for 24 h undisturbed and then inspected visually for signs of drug precipitation.

### *Refrigeration test*

Two capsules of the SSEDDS from each batch were wrapped in a polyethylene material and kept in the refrigerator for 24 h at 2°C. It was thereafter observed for drug precipitation or phase separation.

### *Loading efficiency*

A capsule of SSEDDS was emulsified in 100 ml of 0.1 N HCl at 37 ± 1°C and a 1 ml quantity withdrawn and made up to 10 ml using absolute ethanol. It was assayed in an ultraviolet (UV) spectrophotometer (Jenway 6305 Spectrophotometer, UK) for indomethacin content at a predetermined wavelength of 232 nm. Duplicate determinations were made. Loading efficiency was calculated as follows:

$$\text{Loading efficiency} = \frac{\text{Assayed amount per dose (mg)}}{\text{Amount incorporated per dose (mg)}} \times 100 \quad (1)$$

## Drug Release Studies

The United States Pharmacopoeia basket method was adopted in this study. The dissolution medium consisted of 900 ml of freshly prepared 0.1 N HCl maintained at 37 ± 1°C. One SSEDDS capsule was introduced into the basket chamber before the equipment was switched on to operate at a speed of 50 rpm. At predetermined time intervals 5 ml samples of the dissolution medium were withdrawn and assayed using the UV spectrophotometer (Jenway 6305 Spectrophotometer, UK) for indomethacin content at a predetermined wavelength of 232 nm. Furthermore, 5 ml of fresh 0.1 N HCl was used to refresh the dissolution medium. The experiment was run in duplicates.

### *Anti-inflammatory studies*

The anti-inflammatory activity of the indomethacin-loaded SSEDDS was carried out using the rat paw oedema test.[14] All experimental protocols were in accordance with the Animal Ethics Committee of the Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka. The phlogistic

agent employed in the study was fresh undiluted egg albumin.[14] Adult Wistar rats of either sex (180-200 g) were used for the study ($n = 6$). The rats were fasted and deprived of water for 12 h before the experiment.[15] Thirty minutes post-treatment; oedema was induced by injection of 0.1 ml fresh undiluted egg albumin into the sub-plantar region of the right hind paw of the rats. The volumes of distilled water displaced by treated right hind paw of the rats were measured using plethysmometer before and at 1, 2, 3, 4, 5 h after injection of egg albumin. Average oedema at every interval was assessed in terms of difference in volume displacement of injected paw ($V_t - V_o$). The percentage inhibition of oedema was calculated using the equation below:[16]

$$\%\text{oedema inhibition} = 1 - \frac{(a-x)}{(b-y)} \times 100 \quad (2)$$

where $a$ is the mean paw volume of treated rats after egg albumin injection; $x$, the mean paw volume of treated rats before egg albumin injection; $b$, the mean paw volume of control rats after egg albumin injection; and $y$ is the mean paw volume of control rats before egg albumin injection.

### *Droplet size, polydispersity index, and zeta potential*

The droplet size, zeta potential and polydispersity index (PDI) were determined using a zeta sizer (Zeta sizer 3000 h, Malvern Instruments, Worcestershire, UK).[8]

## Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 13 (SPSS Inc., U.S.A). Mean and standard error for all data were calculated. For batch comparisons, the Student's *t*-test was used to determine statistically significant differences at $P < 0.05$.

# RESULTS

## Proximate Analysis

BI fat showed moisture content of 0.02%, 0.078% of protein, 11.52% of carbohydrate, 87.5% of fats and trace amount of ash and fibre. PM oil contained 1.62% moisture, 88.8% fat, 1.05% protein, 8.58% carbohydrate and trace amounts of fibre and ash. Both showed high fat content.

### *Visual isotropicity test*

Pre-/post-formulation isotropicity test results showed that all batches were isotropic, implying, homogeneity, and absence of phase separation.

### *Emulsification time*

Emulsification time results [Table 4] showed that SSEDDS containing Carbosil® recorded significantly ($P < 0.05$) higher emulsification time values than those formulated without Carbosil®. Furthermore, SSEDDS containing blend of BI fat and PM oil exhibited significantly ($P < 0.05$) lower emulsification time than SSEDDS containing BI fat only.

### *Aqueous dilution*

The results of aqueous dilution studies are shown in Table 4. There was no evidence of phase separation or drug precipitation after a 1000 fold dilution. After 24 h, there was still no sign of drug precipitation; however, mild creaming was observed. This is predictive of potential GIT stability, at least within the intestinal transit time frame.

**Table 4: Characteristics of indomethacin SSEDDS**

| Batch | O:S:C* | MET (min) | DS (nm) | ZP (mV) | PDI | LE (mg) | T50 (min) | T85 (min) |
|---|---|---|---|---|---|---|---|---|
| A1 | 20:60:20 | 10.38±0.23 | 288.1±1.0 | −7.3±0.8 | 0.299±0.04 | 91±0.05 | 63 | 75 |
| A2 | 35:45:20 | 9.15±0.17 | 174.7±4.0 | −8.7±1.9 | 0.248±0.05 | 106±0.07 | 80 | 94 |
| A3 | 25:55:20 | 9.43±0.11 | 200.6±3.0 | −8.8±1.3 | 0.223±0.02 | 106±0.03 | 35 | 60 |
| A4 | 25:60:15 | 9.56±0.12 | 189±5.0 | −9.6±0.7 | 0.296±0.04 | 99±0.10 | 53 | 70 |
| A5 | 20:60:20 | 3.19±0.09 | - | - | - | - | - | - |
| A6 | 35:45:20 | 2.39±0.07 | - | - | - | - | - | - |
| A7 | 25:55:20 | 3.07±0.12 | - | - | - | - | - | - |
| A8 | 25:60:15 | 3.20±0.11 | - | - | - | - | - | - |
| B1 | 20:60:20 | 7.32±0.19 | 256±3.0 | −5.5±0.5 | 0.320±0.01 | 98±0.05 | 37 | 45 |
| B2 | 35:45:20 | 5.41±0.07 | 265±3.0 | −6.9 | 0.296±0.03 | 99±0.05 | 28 | 47 |
| B3 | 25:55:20 | 6.13±0.27 | 258.3±1.0 | −6.2±0.6 | 0.311±0.06 | 104±0.03 | 27 | 42 |
| B4 | 25:60:15 | 6.22±0.20 | 183.9±2.0 | −6.5±0.2 | 0.312±0.05 | 104±0.09 | 37 | 43 |
| B5 | 20:60:20 | 2.08±0.04 | - | - | - | - | | |
| B6 | 35:45:20 | 3.13±0.07 | - | - | - | - | | |
| B7 | 25:55:20 | 1.06±0.12 | - | - | - | - | | |
| B8 | 25:60:15 | 2.23±0.11 | - | - | - | - | | |

*Ratio of oil: Surfactant: Co-surfactant; MET – Mean emulsification time; LE – Loading efficiency; SSEDDS – Solid self-emulsifying drug delivery system; PDI – Polydispersity index; A1-A8 contain *Bos indicus* fat; A1-A4 contain Carbosil®; A5-A8 contain no Carbosil®; B1-B8 contain *Bos indicus* fat and *Pentaclethra macrophylla* oil blend; B1-B4 contain Carbosil®; B5-B8 contain no Carbosil®; T50 is the time taken for 50% of drug to be released; T85 is the time taken for 85% of drug to be released

*Effect of refrigeration*

The results showed that the formulations lacked evident organoleptic change or apparent instability. This is an indication that storage at very low temperatures could be tolerated.

*Loading efficiency*

High drug loading efficiency [Table 4] of over 90% was recorded by the formulations.

### Drug Release Studies

The release profiles of indomethacin-loaded SSEDDS are shown in Figures 1 and 2 respectively while T50 and T85 values are recorded in Table 4. Formulations containing oil blends gave T50 and T85 values of 27-37 min and 42-47 min respectively; those containing only BI fat had values of 35-80 min and 60-94 min respectively.

*Anti-inflammatory properties*

The anti-inflammatory properties of indomethacin SSEDDS are shown in Figure 3. Batches (A4 and B4) SSEDDS exhibited significantly higher anti-inflammatory ($P < 0.05$) effects than the reference drug between the 4$^{th}$ and 5$^{th}$ h.

*Droplet size, zeta potential, and PDI*

Table 4 shows the values while [Figures 4-7] are graphical representations of the above parameters. The droplet size values were between 100 and 288 nm; zeta potential, −5 to − 9 mV and PDI, 0.2-0.3. SSEDDS containing oil blend recorded PDI values of mostly 0.3 while those with only BI fat 0.2. Higher PDI indicates greater size variation of the droplets.

## DISCUSSION

### Proximate Analysis

The nutritional richness of oils and their formulation usefulness underscore their nutraceutical potential in drug delivery. Furthermore, their physiological biocompatibility and little or no toxicity may minimize safety concerns and regulatory stringency. Although, the triglyceride content of oils are important in drug delivery they do not demonstrate as much solubilizing capacity as some synthetic oils do. Thus, the inclusion of suitable blends and/or surfactants and co-surfactants in their SEDDS formulations becomes necessary. In addition to promotion of absorption of fat soluble vitamins, alteration of drug metabolism and lymphatic drug transport are possible pharmaceutical functions of oils/fats.[17]

*Visual isotropicity test*

Drug crystallization and phase separation are two events that should not be seen in an isotropic formulation. All batches demonstrated isotropic stability. Prior to formulation the solid BI fat and Tween 65 respectively were separately warmed to achieve fluidity before admixing with other liquid excipients. Subsequently, encapsulation of the SEDDS in hard gelatin capsules was carried out. It was observed that on cooling solidification took place, which presented the SEDDS as solid preparations. This solid state immobilized dissolved molecular form of the drug and other liquid excipients without significant contribution of gravitational force on thermodynamic stability. In contrast, liquid SEDDS with dissolved molecular form of drug and excipients are subject to mobility and gravitational forces, which may affect the thermodynamic stability of meta-stable systems.

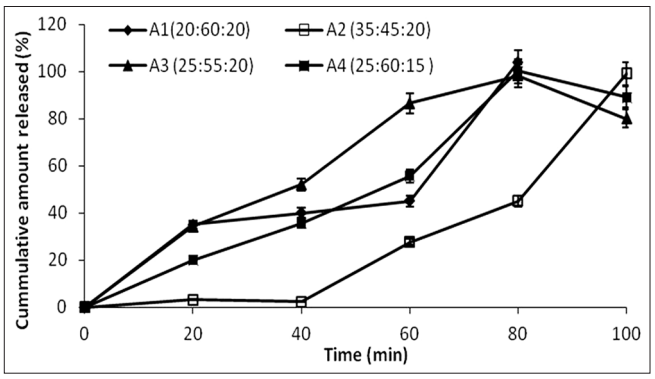


**Figure 1:** Release profile of indomethacin from solid self-emulsifying drug delivery system containing *Bos indicus* fat

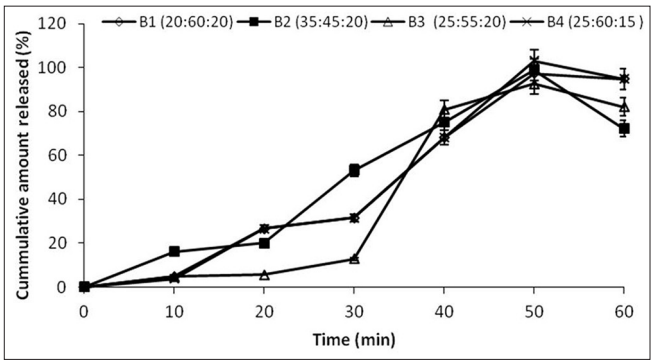


**Figure 2:** Release profile of indomethacin from solid self-emulsifying drug delivery system containing *Bos indicus* fat and *Pentaclethra macrophylla* oil blend

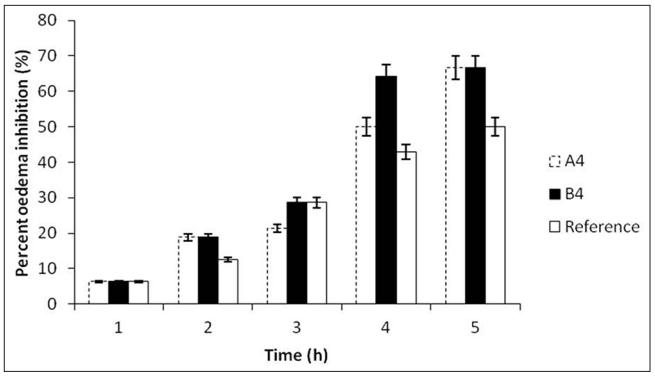


**Figure 3:** Anti-inflammatory properties of indomethacin-loaded solid self-emulsifying drug delivery system formulated with *Bos indicus* fat (A4) or blend of BI fat and *Pentacletra machrophylla* oil (B4)

### *Emulsification time*

Faster ($P < 0.05$) emulsification times of SSEDDS formulated with oil blends in comparison with those formulated with BI fat was probably due to the liquidity of the PM oil. The reduced consistency of the blend may have resulted to faster dispersion and consequently shorter emulsification time in aqueous phase. Carbosil®-containing batches recorded significantly ($P < 0.05$) longer emulsification times than those without it. This is attributable to gel formation outcome of interaction of Carbosil® and the oil.[8] Carbosil® disperses in oil to form smooth oleogel that has potential drug-retardation effect. Emulsification time is affected by such factors as viscosity, admixing of oils and free energy of the system,[8,18] It is obvious that the above three factors may have contributed to the emulsification time trend.

### *Aqueous dilution and phase separation*

The absence of phase separation and drug precipitation 5 h after dilution signalled intactness of drug solution and stability in the droplet. It also meant that the selected excipients and the ratios were optimal for reproducible and guaranteed stability in aqueous environment. This experiment enabled the prediction of the performance of SSEDDS droplets in the stomach and intestine bearing in mind the gastric transit time of 15-180 min and intestinal transit time of 3-4 h. A SEDDS preparation that witnesses drug precipitation within 1 or 2 h in aqueous phase may be incapable of ensuring the much expected bioavailability enhancement and consistency. The solid consistency of the SEDDS formulations in this work may have played a remarkable role as precipitation inhibitor. Precipitation inhibitors retard drug precipitation or leakage out of droplets.

### *Effect of refrigeration*

The refrigeration test results of, the SSEDDS indicates formulation stability. This means that the formulations could also be stored under cold temperature without possible phase separation or drug precipitation.

### *Loading efficiency*

Loading efficiency results showed high values of 91-106%. In polymeric nanoencapsulation involving organic solvents, high loading efficiency values are not easy to achieve. SEDDS are rather more amenable to high drug content values than polymeric nanoparticles are.

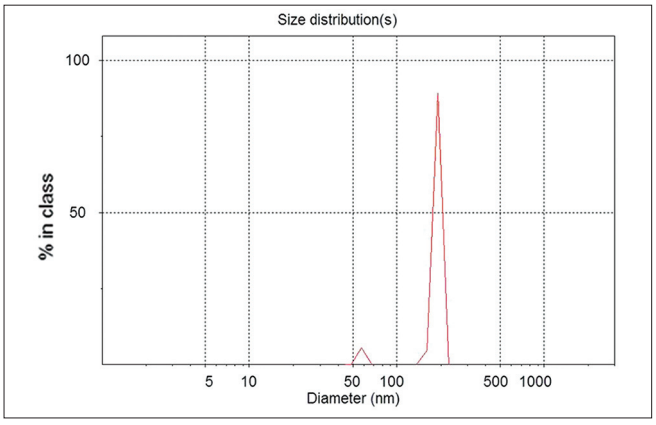


**Figure 4:** Droplet size distribution curve for 25:60:15 solid self-emulsifying drug delivery system containing *Bos indicus* fat

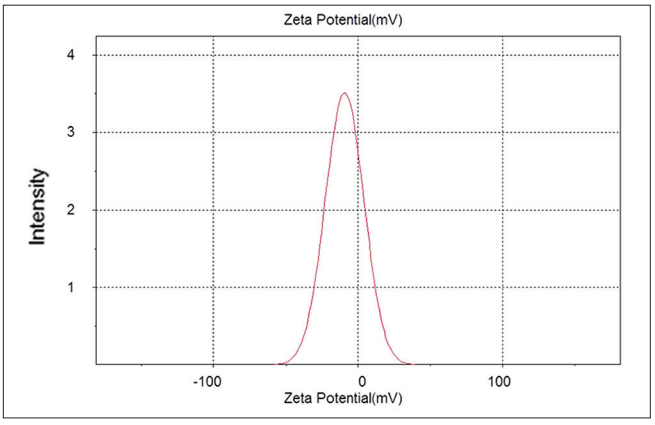


**Figure 5:** Zeta potential curve for 25:60:15 solid self-emulsifying drug delivery system containing *Bos indicus* fat

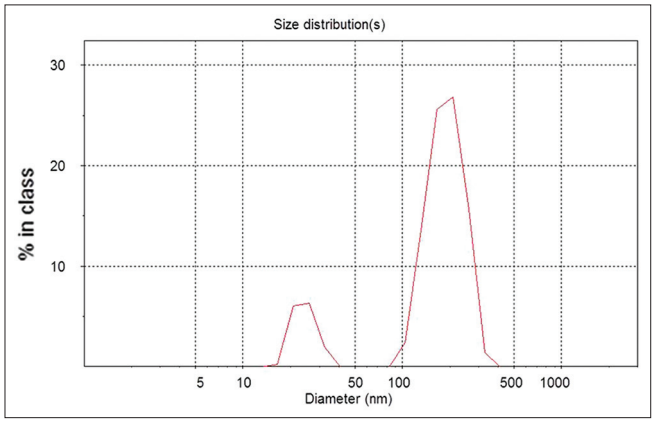


**Figure 6:** Droplet size distribution curve for 25:60:15 solid self-emulsifying drug delivery system containing *Bos indicus* fat and *Pentaclethra macrophylla* oil blend

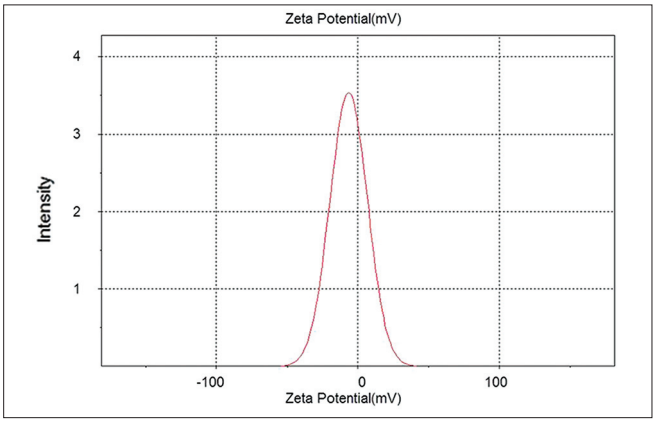


**Figure 7:** Zeta potential curve for 25:60:15 solid self-emulsifying drug delivery system containing *Bos indicus* fat and *Pentaclethra macrophylla* oil blend

*Release profile of indomethacin from SSEDDS*

The release of indomethacin [Figures 1 and 2] from the SSEDDS was gradual, demonstrating absence of possible burst effect. There was no consistent trend except that SSEDDS formulated with oil blend released drug faster than those with only BI fat; this being in tandem with the lower T50 and T85 values and faster emulsification time characteristics of these batches. The high consistency of BI and the gelling effect of Carbosil® may have contributed to the observed release trend. This release behaviour may reduce or preclude the possibility of time-based drug crystallization, which some SEDDS preparations suffer. Massive immediate release within 2 min may raise issues of toxic plasma drug levels due to fat absorption and bioavailability, especially for drugs with low safety margin.

*Droplet size, zeta potential, and PDI*

The droplet sizes did not show a consistent trend except that they were well within SEDDS range of above 100 nm.[19-21] However, the droplet size range of our formulations proved suitable for improved absorption of droplet-bound indomethacin. Negative zeta potential of oil-in-water emulsions is a common phenomenon, attributed to the fatty acid component of triglycerides.[22] PDI results depicted size variation within each batch. PDI runs on a scale of 0-1.0;[23] with lower values signifying tendency toward monodispersity. The values recorded by our formulations could be rated good as they were less than 0.4.

*Anti-inflammatory properties*

The formulations exhibited significantly ($P < 0.05$) higher anti-inflammatory effect than the reference drug (pure sample of indomethacin) at the 4$^{th}$ and 5$^{th}$ h. The *in vitro* results are consistent with and corroborate the anti-inflammatory results. The higher anti-inflammatory effect of indomethacin SSEDDS compared to the drug powder is therefore conclusive of enhanced absorption and optimal bioavailability. The long emulsification time and T85 of > 60 min for especially BI-containing SSEDDS are consistent with gradual drug release. This may explain the insignificant anti-inflammatory activity observed between the 1$^{st}$ and 3$^{rd}$ h, due to insufficient plasma and tissue concentrations *ab initio*. In addition, since the same dose resulted to higher anti-inflammatory activity when incorporated in SSEDDS unlike the drug powder, it is possible that further dose reduction of indomethacin in the SEDDS may drastically mitigate or completely preclude the dose-related adverse effects without compromising optimal anti-inflammatory activity.

## CONCLUSION

Indomethacin was successfully solubilised by the SSEDDS and remained as intact drug solution in the droplet as evidenced by isotropicity and aqueous dilution results. The anti-inflammatory effect of drug-loaded SSEDDS was higher than that of indomethacin powder. In conclusion, the use of BI fat or its blend with PM oil in SSEDDS formulations has proved beneficial in improving the *in vitro* and corresponding anti-inflammatory properties of indomethacin. This may suggest that dose reduction of indomethacin loaded in SEDDS may reduce or avert its dose-related adverse effects without compromising therapeutic efficacy.

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