

Research Article

Self-Nanoemulsifying Drug Delivery Systems Based on Melon Oil and its Admixture with a Homolipid from *Bos indicus* for the Delivery of Indomethacin

Nicholas C Obitte¹, Kenneth C Ofokansi^{2*}, Ifeanyi T Nzekwe³, Charles O Esimone⁴ and Ifeanyi E Okoye³

¹Department of Pharmaceutical Technology, ²Department of Pharmaceutics, University of Nigeria, Nsukka,

³Department of Pharmaceutics and Pharmaceutical Technology, ⁴Department of Pharmaceutical Microbiology and Biotechnology, Nnamdi Azikiwe University, Awka, Nigeria.

Abstract

Purpose: To formulate self-nanoemulsifying drug delivery systems (SNEDDS) based on melon oil and its admixture with a homolipid from *Bos indicus* (cow fat) for the delivery of indomethacin, a hydrophobic anti-inflammatory agent.

Method: Melon oil and cow fat were extracted by standard methods and used in the formulation of SNEDDS based on either melon oil alone, or its admixture with cow fat by utilizing varying ratios of oil(s), surfactants and co-surfactants, with or without carboxyl, a glidant. The formulations were encapsulated in hard gelatin capsules and then evaluated using relevant parameters including isotropicity tests, dilution stability, precipitation propensity, emulsification time, absolute drug content, in vitro drug release, and anti-inflammatory activity in an animal model.

Results: Stable and negatively charged colloidal dispersions (zeta potential: -10.4 to -13.4 mV) in the nano size range (195 - 210 nm) were formed. Formulation of indomethacin as SNEDDS not only preserved the activity of the drug, but also guaranteed anti-inflammatory activity comparable to that of indomethacin injection. The inhibition produced by the drug-loaded SNEDDS and the positive control were identical for much of the 5 h test period, indicating a high degree of bioavailability of the administered SNEDDS formulation.

Conclusion: A 1:1 ratio of melon oil and cow fat could be used in the formulation and delivery of indomethacin-loaded SNEDDS with satisfactory properties and acceptable product performance. The anti-inflammatory activity of indomethacin was preserved in the formulation.

Keywords: Melon oil; Cow fat; Drug release; Indomethacin; Self-nanoemulsifying systems; Surfactants

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*Corresponding author: **E-mail:** kcofokansi@yahoo.com; **Tel:** +234-8131245821

INTRODUCTION

Self-emulsifying drug delivery system (SEDDS) is a strategy that has drawn wide research interest, basically due to its distinct capacity to solubilise and improve the bioavailability of poorly water-soluble drugs. This it does by ensuring aqueous solubility of the lipophilic drug. Aqueous solubility is an important molecular property required for successful drug development. This is because it strongly determines drug accessibility to biological membranes [1]. The importance of solubility in drug disposition is underscored by the fact that the optimal rate of passive drug transport across a biological membrane (the major pathway for absorption of drugs), not only depends on permeability but also solubility of the drug [1].

Conventional tablet formulations of lipid soluble drugs, especially those of class II in the biopharmaceutic classification system (BCS), eventually get solubilised with the aid of the emulsification process of bile salts. However, the rate at which this takes place is unpredictable due to inter- and intra-subject variations [2]; hence the unpredictable and variable bioavailability associated with such actives. This, amongst others, is the major disadvantage self-emulsifying formulations (SEOFs) seek to circumvent [3].

Peroral co-administration of poorly water-soluble drugs in lipid-based formulations such as SEOFs improves the bioavailability of such drugs with a predictable profile. Drug release from SEDDS has been reported to take place by interfacial transfer and vehicle degradation [4,5]. Drug release via interfacial transfer mechanism takes place when the drug diffuses from the formulation into the bulk medium or directly over the intestinal membrane while vehicle degradation involves mainly the lipase-catalysed lipolytic degradation of the SEDDS leading to drug release from the formulation [6].

Improvement in the dissolution characteristics and, therefore, bioavailability of a

hydrophobic drug can be achieved by several solubilization technologies, including the use of self-emulsifying drug delivery systems (SEDDS). This refers to an isotropic mixture of oil and surfactants, which forms micelles or a microemulsion in the presence of water under gentle agitation. The system is thermodynamically unstable. The behavior of such systems can be modified by the use of oil and surfactants in different ratios, and by manipulating the polarity and charge of the dispersed globules. Benefits include enhanced solubility and dissolution behaviour [7,8] and a more reproducible plasma level - time profile [9]. The influence of such systems on the bioavailability of hydrophobic drugs has been explained in terms of drug solubilization in micellar systems [10] and ease of lymphatic absorption [11]. The formulation of liquid encapsulated self-emulsifying systems is a convenient way of delivering indomethacin, without the need for many processing steps. Preferred oily components are the medium chain triglycerides, which are however limited by low solvent capacity for surfactants or drugs. Semi-synthetic medium-chain triglycerides having amphiphilic behaviour may also be utilized, with better solvent effects.

The objective of this study was to investigate the suitability of melon oil, or its admixture with a homolipid from *Bos indicus*, for use as the oily component for indomethacin-loaded SNEDDS, using standard non-toxic surfactants. These materials are low-cost and readily available. It is expected that the resulting SNEDDS will show not just improved bioavailability but better tolerance due to non-toxicity of edible oils.

EXPERIMENTAL

Materials

Cow (*Bos indicus*) fat was obtained from Nsukka abattoir while melon seeds were procured locally from Nsukka main market, Enugu State, Nigeria. Indomethacin powder (Medrel Pharmaceuticals, Pvt Ltd, India),

Tween 65, Tween 80 and Span 85 (Merck, Darmstadt, Germany) were also used in the study. All other reagents were of analytical grade and used without further modification.

Extraction of melon oil

The melon seeds were dried, milled and then extracted by cold maceration for 24 h using petroleum ether (20 - 40 °C boiling point). The resulting oil was bleached by treating with activated charcoal at 80 - 90 °C for 1 h. Thereafter, the oil was recovered under vacuum and at low temperature using a rotavap.

Extraction of homolipid from cow fat

About 1 kg of cow fat was processed in the laboratory as reported previously [12]. Briefly, the cow fat was immersed in hot water maintained at 80 - 90 °C for 45 min. A porcelain cloth was used to strain off extraneous matter, and the fat, after cooling, was recovered by simple decantation of the lower aqueous layer.

Proximate analysis

Percent concentrations of proteins, lipid, carbohydrate, crude fibre, moisture and ash in melon oil and the homolipid from cow fat were determined using standard procedures [13].

Preformulation isotropic test

Different batches of SNEDDS were prepared based on escalating ratios of melon oil, cow fat, surfactants and co-surfactant. The preparation was achieved by simple mixing of weighed components in a beaker over a water bath at 45 – 50 °C for 15 min. After storage of the resulting dispersions at ambient conditions for 24 h, visual examination was conducted for evidence of phase separation. Only ratios which remained isotropic after this storage time were used in the formulation of SNEDDS.

Formulation and encapsulation

The preparation of SNEDDS batches was done according to the proportions depicted in Tables 1 and 2. In each case, weighed amounts of oil(s), surfactants, co-surfactant and indomethacin (20 mg), with or without carbosil (15 mg) were mixed manually with the aid of a stirring rod for 10 min in a beaker over a water bath at 50 °C. Carbosil, a glidant, is believed to promote dispersion behaviour. Encapsulation of the SNEDDSs from the different batches was carried out by transferring a mass containing exactly 20 mg of indomethacin into a 450 mg capacity hard gelatin capsule. Calculations for each batch of the indomethacin-loaded SNEDDS was done to give ten (10) capsules from which amounts containing exactly 20 mg indomethacin were weighed and encapsulated.

Postformulation isotropic test

The formulations were allowed to stand for 24 h and then visually examined for phase separation [14] to identify stable preparations.

Photon correlation spectroscopy (PCS)

Submicron particle size analysis of the SNEDDS was performed using a Zetasizer (ZEN 3600, Malvern Instruments, UK). Measurements were made at 25 °C at a scattering angle of 90°. The mean particle size and polydispersity index were determined in a single run while the zeta potential was similarly determined by phase analysis light scattering (PALS) using also a Zetasizer.

Dilution stability and precipitation propensity test

To test for dilution stability, one capsule from each batch was discharged into 100 ml of 0.1M HCl. The resulting solution was transferred to a beaker and diluted with successive 100 ml volumes until the 1 L mark was reached. The dilution was allowed to

Table 1: Composition of indomethacin-loaded SNEDDS based on melon oil only

Batch	Ratio* O: S: CS	Melon oil (g)	Tween 65 (g)	Tween 80 (g)	Span 85 g)	Carbosil (mg)	Indomethacin (mg)
1A	20:60:20	0.8	1.2	1.2	0.8	---	200
1B	20:60:20	0.8	1.2	1.2	0.8	150	200
2A	25:45:20	1.0	1.1	1.1	0.8	---	200
2B	25:45:20	1.0	1.1	1.1	0.8	150	200
3A	25:60:15	1.0	1.2	1.2	0.8	---	200
3B	25:60:15	1.0	1.2	1.2	0.8	150	200

* Ratio of oil blend: surfactant blend (Tween 65 and Tween 80): co-surfactant (Span 85)

Table 2: Composition of indomethacin-loaded SNEDDS based on a blend of melon oil and cow fat

Batch	Ratio* O: S: CS	Melon oil (g)	Cow fat (g)	Tween 65 (g)	Tween 80 (g)	Span 85(g)	Carbosil (mg)	Indomethacin (mg)
1C	20:60:20	0.40	0.40	1.2	1.2	0.8	---	200
1D	20:60:20	0.40	0.40	1.2	1.2	0.8	150	200
2C	35:45:20	0.70	0.70	0.9	0.9	0.8	---	200
2D	35:35:20	0.7	0.7	0.9	0.9	0.8	150	200
3C	25:55:20	0.5	0.5	1.1	1.1	0.8	---	200
3D	25:55:20	0.5	0.5	1.1	1.1	0.8	150	200
4C	25:60:15	0.5	0.5	1.2	1.2	0.6	---	200
4D	25:60:15	0.5	0.5	1.2	1.2	0.6	150	200

* Ratio of oil blend: surfactant blend (Tween 65 and Tween 80): co-surfactant (Span 85)

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 further placed in a test tube, corked and left undisturbed for 24 h, and then inspected visually for signs of drug precipitation.

Emulsification time

One capsule from each batch was emptied into a 100 ml beaker containing 0.1M HCl. The beaker was mounted on a magnetic stirrer hot plate assembly and stirred at 50 rpm and 37 ± 1 °C until complete emulsification occurred, as indicated by constant turbidity. A mean of triplicate determinations was taken as the emulsification time for each batch.

Absolute drug content

One capsule from each batch was placed in 100 ml of 0.1M HCl and emulsified under

moderate agitation. After complete emulsification, the resultant solution was diluted 10-fold and the absorbance was then determined with a spectrophotometer (UV-2102, Unico, USA) at 232 nm, using 0.1M HCl as blank. The amount of indomethacin present in each capsule was calculated from a calibration plot previously determined for indomethacin. Five replicate determinations were carried out and the mean taken to obtain the absolute drug content for each batch.

Drug dissolution studies

A capsule from each batch 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 900 ml of 0.1 N HCl. Mild agitation was provided at a speed of 50 rpm at 37 ± 0.5 °C. At predetermined time intervals, 5 ml volumes were withdrawn, filtered and assayed spectrophotometrically for

indomethacin after appropriate dilution. The release medium was replenished after each withdrawal to maintain constant volume.

Anti-inflammatory activity

The animal experimental protocols were approved by our institution's Animal Ethics Committee and were in compliance with the Federation of European Laboratory Animal Science Association and the European Community Council Directive of November 24, 1986 (86/609/EEC) [15]. Female Wistar rats (150 - 250 g) were housed in cages under controlled temperature and humidity (30 – 32 °C and 50 % relative humidity) and under a photoperiod schedule of 12 h light/12 h dark. They were fed standard laboratory animal diet and provided with tap water *ad libitum*. The rats had free access to food and water prior to the commencement of the test and throughout the duration of the experiment in order to mitigate the gastro-erosive side effects of the administered formulation. The animals were divided into four groups of five rats each. A 50 % aqueous dispersion of egg albumin was used as the phlogistic agent. Group 1 animals received, intraperitoneally, 0.357 mg of indomethacin injection per kg body weight of rat and served as the positive control while group 2 animals, serving as negative control, received a volume (437 µl) of freshly distilled water equal to the volume of the administered injection. Groups 3 and 4 received, orally, 437 µl each of SNEDDS 2A and SNEDDS 4C, respectively, with the aid of an intragastric tube. One hour after initial drug administration in each case, 50 µl of the phlogistic was injected into the subplantar surface of the right hind paw. Oedema was assessed based on the difference between linear circumference (C_0) of the injected paw at time zero and the circumference (C_t) after time, t . Percent inflammation (and hence inhibition) was calculated using the relationship:

$$\text{Inflammation (\%)} = AI_t/AI_c \times 100 \dots\dots\dots (1)$$

where AI_t is the mean inflammation at time, t , and AI_c is the mean inflammation of control animals at the same time. From the values obtained, percent inhibition (100 % minus percent inflammation) was calculated.

Statistical analysis

Statistical analysis was performed using SPSS statistical package. 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 $p \leq 0.05$.

RESULTS

The results of the proximate analysis of melon seed oil show that the oil is predominantly composed of fat (93.8 %) while ash and fiber were present in trace amounts. The amount of protein was 0.87 % while moisture constituted 0.2 % of the oil. All the batches tested were isotropic and none showed any evidence of phase separation. Additionally, all batches of the formulated SNEDDS retained their isotropicity after a ten-fold dilution. There were no signs of drug precipitation on visual inspection after dilution. The medium-term stability of the formulations was assessed by storing them at room temperature (28 °C) on a bench for four weeks. No phase separation or change in the integrity of the formulation was observed.

The mean emulsification time obtained for SNEDDS formulated with melon oil was 32 s while formulations containing an admixture of melon oil with the homolipid had a mean emulsification time of 36 s. The incorporation of carbosil into the melon oil-based formulation resulted in the prolongation of the time for complete emulsification to 288 s while formulations containing melon oil together with the homolipid from cow (*Bos indicus*) fat and carbosil had a mean emulsification time of 239 s. The inclusion of carbosil markedly affected the mean emulsification time.

The mean diameter of the SNEDDS as measured by photon correlation spectroscopy was 195 nm for melon oil-based SNEDDS and had a polydispersity index of 0.250, indicating a unimodal size distribution (narrow particle size distribution); mean diameter was 210 nm for the blend of melon oil and cow fat-based SNEDDS and had a polydispersity index of 0.273, depicting a bimodal size distribution (data not shown). Similarly, SNEDDS based on melon oil blends were had a zeta potential of -13.4 ± 0.2 mV while that of melon oil/cow fat-based SNEDDS was -10.7 ± 0.3 mV, as shown in Fig 1A and 1B.

The absolute drug contents of the formulated batches of SNEDDS did not show any remarkable deviation from the theoretical content and ranged between 18 and 23 mg of indomethacin.

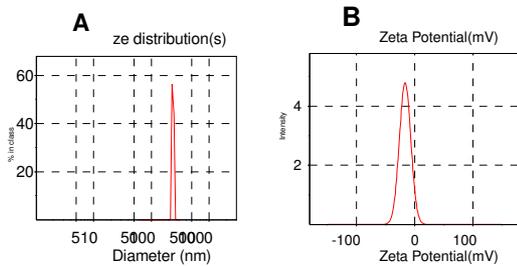


Fig 1: Particle size distribution and zeta potential of SNEDDS as measured by photon correlation spectroscopy. Mean size of melon oil-based SNEDDS (A) and zeta potential of melon oil-based SNEDDS (B) are shown

The release profiles of the formulated SNEDDS are depicted in Figs 2 and 3. In batch 3A, formulated from melon oil, surfactants and co-surfactants in the ratio 25: 60: 15, about 10 % of the incorporated drug was released after 10 min followed by a more rapid release of about 80 % in the next 20 min. Batches 1A and 2A recorded less than 2 % drug release within the first 20 min but showed a sudden rapid release of about 40 and 80 %, respectively, 30 min into the release experiment. All three batches containing melon oil, surfactants and co-surfactants in varying ratios showed complete

drug release at 50 min. SNEDDS formulated with an admixture of melon oil and the homolipid from cow fat showed a release pattern somewhat different from the melon oil only-based SNEDDS. With the exception of batch 2C containing oil: surfactant: co-surfactant ratio of 35:45:20 which showed a rapid release of up to 80 % within the first 20 min, drug release from the rest of the batches was marginal within the first 20 min but increased gradually thereafter attaining 100 % release at 60 min.

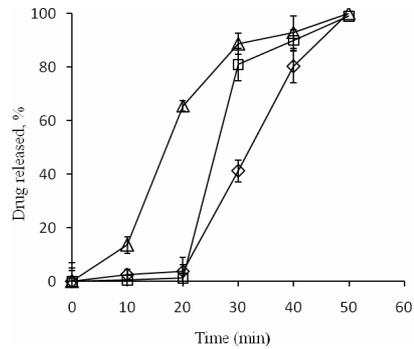


Fig 2: Release profile of indomethacin from melon oil only-based SNEDDS (\diamond = 1A, \square = 3A, \triangle = 4A)

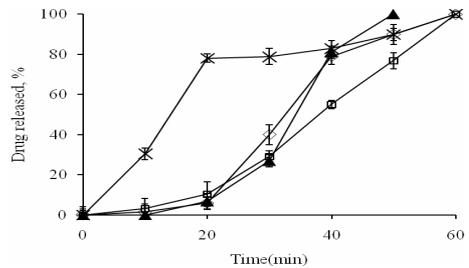


Fig 3: Release profile of indomethacin from SNEDDS based on melon oil and its admixture with cow fat and carboxyl (\diamond = 1B, \square = 2B, \triangle = 1C, \times = 2C)

The results of the anti-inflammatory activities of the administered SNEDDS are presented in Fig. 4 as a function of time. The formulations administered reduced the level of inflammation induced by the phlogistic but no significant difference ($p \leq 0.05$) in percent inhibition of inflammation was evident.

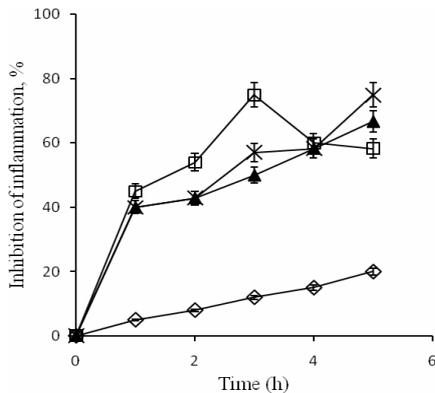


Fig. 4: Inhibition of egg-albumin induced inflammation due by indomethacin contained in self-emulsifying drug delivery systems (□ = PC, ◇ = Distilled water, ▲ = 2A, × = 4C). **Note:** PC + positive control (indomethacin injection); 2A = indomethacin in SNEDDS formulated from melon oil with surfactant blend (1: 1 of Tweens 60 and 80) and co-surfactant (Span 85) in the ratio of 25 :45: 20; 4C = indomethacin in SNEDDS formulated from a blend of melon oil and cow fat with surfactant blend (1: 1 of Tweens 60 and 80) and co-surfactant (Span 85) in the ratio of 25 : 45: 20, CHH and shea butter blend (1: 1) combined with surfactant blend (1: 1 of Tween 60 and 80) and co-surfactant (Span 85) in the ratio of 25 : 60: 15.

DISCUSSION

Melon oil is an edible oil consumed widely in Nigeria. The proximate analysis revealed a high content of fat, mostly triglycerides. Triglycerides have poor solvent properties but their solvent properties may be improved by blending with mono- and di-glycerides [3]. Semi-synthetic medium chain triglycerides with amphiphilic nature have also sometimes been preferred. Isotropic assessment of SNEDDS batches showed that all batches remained isotropic after drug loading. SEDDS are reputed for this high stability due to formation of thermodynamically inert microemulsions on contact with water under gentle agitation [16,17]. The solubility of hydrophobic drugs and therefore their bioavailability, is improved in such systems by selective dissolution/partitioning in the oily

component [5]. Particle sizes in such systems range in the order of 100 nm or less [7,18,19]. The preparations showed high stability on copious dilution. This low precipitation propensity is a valuable property of such systems, in that deposition of drug may not be expected to occur due to pH change, or dilution in the internal environment of the body. This should minimise dose dumping. However, extremely low propensity to deposit drug may limit efficacy, since activity is normally due to free drug, and not the reservoir fraction.

All non-carbosil containing batches showed rapid emulsification, achieving much faster emulsification times than the 2 min often recommended for such systems [20]. The inclusion of carbosil slowed down the emulsification times for carbosil-containing batches (batches B). This effect of carbosil is a direct consequence of its viscosity imparting effect. This can be remedied by the addition of short chain alcohols at concentrations not exceeding 5 %. The SNEDDS gave reproducible absolute drug contents not varying much between batches. This reproducibility is a common feature of SEDDS, due to uniform drug loading and dispersion. A comparable result (99.6 %) was obtained with loratadine self-emulsifying systems [21]. Drug release followed the trend of the emulsification time data, in that the batches with low emulsification time had rapid rates of drug release, each attaining more than 80 % drug release in 30 min.

Important parameters in drug release from SESs are droplet size and polarity, which in turn depend on the nature and concentration of surfactants and co-surfactant., as well as on the degree of unsaturation of the lipid. The release of drugs from SEDDS is also dependent on the degree of formation of liquid crystals at the interface. The loaded drug is expected to diffuse through the liquid crystal phase into the aqueous medium. This rapid diffusion is promoted by high polarity [22].

The formulations administered reduced the degree of inflammation induced by the phlogistic. Indomethacin inhibits inflammation by antagonizing the cyclo-oxygenase enzyme required for prostaglandin synthesis. In our present study, formulation of indomethacin as SNEDDS not only preserved the activity of the drug, but also maintained its anti-inflammatory activity at a level comparable to that of indomethacin injection. The inhibition produced by the positive control and the drug-loaded SNEDDS were identical for much of the 5 h test period indicating a high degree of bioavailability of the administered SNEDDS formulated in this study. The observed anti-inflammatory activity of indomethacin-loaded SNEDDS which was comparable with that of the positive control may be due to large absorption surface area brought about by emulsification.

CONCLUSION

A 1:1 ratio of melon oil and cow fat can be used in the formulation and delivery of indomethacin-loaded SNEDDS with favourable properties and acceptable product performance. The anti-inflammatory activity of indomethacin was preserved in such a formulation. The formulation was thermodynamically stable, showed rapid emulsification and had low propensity to deposit drug on moderate dilution.

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Obitte et al

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