Nigerian Journal of Pharmaceutical Research
Vol. 8 No 1 pp. 162 - 173 (September 2010)

A NOVEL SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM BASED ON A HOMOLIPID FROM *CAPRA HIRCUS* FOR THE DELIVERY OF INDOMETHACIN

K. C. Ofokansi[1*], N. C. Obitte[2] and I. T. Nzekwe[3]
[1]*Department of Pharmaceutics, University of Nigeria, Nsukka, Enugu State, Nigeria*
[2]*Department of Pharmaceutical Technology, University of Nigeria, Nsukka, Enugu State, Nigeria.*
[3]*Department of Pharmaceutics and Pharmaceutical Technology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.*

[*]Corresponding author: E-mail: kcofokansi@yahoo.com; Phone: +234-81-31245821

Abstract
The dissolution of hydrophobic drugs, of which indomethacin is an example, in body fluids is a limiting step in its bioavailability. The objective of this study, therefore, was to improve the aqueous solubility of indomethacin through the development of self-nanoemulsifying drug delivery systems (SNEDDS) based on blends of a homolipid from *Capra hircus* with either oil bean seed oil or shea butter, which occur abundantly in most parts of sub-Saharan Africa. The oleaginous materials were extracted and purified by standard methods. After stability-indicating preformulation isotropicity tests, suitable quantities of lipid blends, surfactant blend (1:1 Tween 60 and Tween 80) and co-surfactant (Span 85) were mixed together in a beaker maintained at 50 ^{o}C to form a homogenous dispersion. The SNEDDS were assessed using the following parameters: isotropicity test, aqueous dilution stability and precipitation propensity, absolute drug content, emulsification time, *in vitro* release performance and anti-inflammatory activity. All the formulations of the SNEDDS exhibited low precipitation propensity and excellent stability on extensive aqueous dilution, as well as high anti-inflammatory activity in rats relative to the positive control. The absolute drug contents and emulsification times all fell within narrow limits. These results may indicate that blends of homolipid from *Capra hircus* with either oil bean seed oil or, particularly, shea butter could confer favourable properties with respect to drug release and anti-inflammatory activity on SNEDDS for the delivery of indomethacin.

Keywords Self-nanoemulfsifying drug delivery systems, indomethacin, *Capra hircus*, homolipid, shea butter, oil bean seed oil

INTRODUCTION

The dissolution of a hydrophobic drug in body fluids is a limiting step in drug bioavailability (Hang *et al*., 2006). Besides bioavailability, limited aqueous solubility may lead to other problems such as incompatibility and precipitation from solution due to effect (Aulton, 1990). Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility. The Biopharmaceutics Classification System (Amidon *et al*., 1995) classifies drugs into four categories depending

*Corresponding author
ISSN 0189-8434

on their solubility and permeability characteristics. According to this scheme, indomethacin belongs to the class II drugs whose solubility is too low to be consistent with complete absorption. For this class of compounds, defined as "low solubility/high permeability class," dissolution in the lumen environment is the rate-controlling step in the absorption process (Charman *et al*., 1992). Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs to increase their clinical efficacy. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles such as oils (Burcham *et al*., 1997), surfactant dispersions (Aungst *et al*., 1994) and self-emulsifying formulations (Aungst, 1993).

Poor aqueous solubility had threatened the development of many blockbuster drugs, for example, paclitaxel in cancer chemotherapy and also Saquinavir in acquired immune deficiency syndrome, necessitating a search for suitable solubilization technologies (Goldspiel, 1995; Mahar and Kim, 2006). Available strategies for improving poor aqueous solubility include co-solvency (Rubino and Yalkowsky, 1985), micellar solubilization (Gershanik and Benita, 2000), hydrotropic solubilization (Natesan *et al*., 2004), complexation (Bogdanova *et al*., 1998), and self-emulsifying drug delivery systems (SEDDS) (Kim and Khu, 2000). Approaches involving complexation and self-emulsifying drug delivery systems have been applied to indomethacin. Self-emulsifying drug delivery systems appear to be favoured because of short processing steps and also cost effectiveness due to reliance on cheap raw materials. It is also amenable to scale up. A SEDDS consists of a lipid mixed in a suitable ratio with a surfactant and co-surfactant which forms a micro-emulsion on contact with aqueous fluids under moderate agitation, such as is obtainable in the gastrointestinal tract. A SEDDS improves solubility, and also produces more reproducible plasma concentrations of drugs (Constantinides, 1995).

In this study, the suitability of blends of homolipid from *Capra hircus* with either oil bean seed oil or shea butter, for the formulation and delivery of indomethacin-loaded SNEDDS is evaluated. All three lipids are in abundant supply in most parts of sub-Saharan Africa. Homolipid from *Capra hircus* has previously been evaluated as a lipid matrix for suppositories (Attama *et al*., 2000). It is expected that the formulations would deliver suitable and reproducible plasma concentrations of indomethacin. In addition, on oral administration, the incidence of gastrointestinal side effects due to poor aqueous solubility of indomethacin would be reduced since the systems form a micro/nano-emulsion with rapid gastric emptying time (Wakerly *et al*., 1985), and with a wide absorption surface for drug that minimizes prolonged local contact effects.

MATERIALS AND METHODS

Materials

Capra hircus homolipid was obtained from the Nsukka abattoir while oil bean seeds and raw shea butter were procured locally from Nsukka Main market, Enugu State, Nigeria. Other materials used were: indomethacin powder (Medrel Pharmaceuticals, PVT ltd, India); Tween 60, Tween 80 and Span 85

(Merck, Damstadt, Germany). All other reagents were analytical grade and were used without further modification.

Extraction of oils and fat
Oil bean seed oil (OBSO)

A quantity (1.5 kg) of the oil bean seeds was dehauled, dried, milled and the oil extracted with n-hexane by cold maceration. The oil was recovered under reduced pressure at a low temperature in a rotary evaporator.

***Capra hircus* homolipid**

About 1 kg of *Capra hircus* homolipid (goat fat) was processed in the laboratory by the process of rendering as reported previously (Attama *et al*., 2000). This was followed by straining using a porcelain cloth. After cooling, the homolipid was recovered by simple decantation of the lower aqueous layer.

Purification of oils

Activated charcoal, at a concentration of 2 % w/w, was employed in purifying each oil, by heating the dispersion of charcoal and oil/fat at 80 - 90 ^{o}C for 1 h, followed by vacuum filtration using a Buchner funnel.

Preformulation isotropicity test

Escalating ratios were used to prepare several batches of SNEDDS bases (without indomethacin). In each case, a 1: 1 blend of *Capra hircus* homolipid (CHH) with either oil was combined with a suitable quantity of surfactant (1: 1 ratio of Tween 60 and Tween 80) and co-surfactant (Span 85). Mixing was carried out at 45 ^{o}C for 15 min. The resulting oily formulation was stored at ambient conditions for 5 h and then visually inspected for evidence of phase separation (Pouton, 1985).

Drug loading

All batches which remained stable at the end of the preformulation isotropicity test were used in formulating the drug loaded-SNEDDS. Loading was done by mixing 400 mg of indomethacin with a suitable quantity of base, with or without carbosil, and stirring for 10 min over a water bath maintained at 50 ^{o}C to obtain a homogenous dispersion. The respective quantities utilized in preparing the SNEDDS of mass equivalent to 20 unit doses of 20 mg indomethacin are presented in Table 1.

Photon correlation spectroscopy (PCS)

Submicron particle size analysis was performed using a Zetasizer nano (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 the same instrument.

Postformulation isotropicity test

The drug-loaded SNEDDS were stored at ambient conditions for 72 h and again examined for signs of phase separation. All successful batches were encapsulated into 20 unit doses by enclosing a mass of product equivalent to 20 mg indomethacin in a 500 mg capacity hard gelatin capsule.

Aqueous dilution stability test

One capsule from each batch was discharged into 100 ml of 0.1 N HCl. The resulting solution was transferred to a beaker and diluted with successive 100 ml volumes until the 1 litre mark was reached. The system was allowed to stand for 2 h, and then checked for drug precipitation or phase separation. From this diluted solution, 10 ml was

withdrawn, transferred into a test tube and securely covered. It was then allowed to stand for 24 h and visually inspected again for signs of drug precipitation

Absolute drug content

A calibration curve for indomethacin in alcohol was obtained by diluting a 2 mg % alcoholic solution of indomethacin serially with the solvent to obtain several dilute concentrations ranging between 0.1 mg% and 1 mg%. The absorbance of each concentration was determined at a predetermined wavelength of 232 nm using a spectrophotometer (Phoenix-220 DPC V model). For determination of the absolute drug content, a capsule from each batch was emptied into a 250 ml beaker and emulsified by the addition of about 90 ml of 0.1N HCl. The resulting solution was made up to 100 ml with 0.1 N HCl. A 0.1 ml volume was withdrawn and diluted to 10 ml with alcohol. The absorbance of the resulting solution was then determined with a spectrophotometer and the amount of indomethacin calculated from a calibration plot previously determined for indomethacin. Five replicate experiments were done and the mean of five determinations was taken to be the absolute drug content for each batch.

Determination of the emulsification time

One capsule from each batch was emptied into a 250 ml beaker containing 0.1 N HCl. The beaker was mounted on a magnetic stirrer hot plate assembly and stirred at 50 rpm at 37 ± 1 ^{o}C until complete emulsification had occurred, noted by constant turbidity. An average of triplicate determinations was taken as the emulsification time for each batch.

***In vitro* dissolution studies**

One capsule from each batch was introduced into the dissolution apparatus containing 900 ml of 0.1 N HCl. The apparatus was operated at 50 rpm at 37± 1 ^{o}C. At suitable time intervals, 5 ml samples were withdrawn from the resulting solution (and replaced with blank), filtered and the amount of indomethacin determined spectrophotometrically. The release medium was replaced after each withdrawal to maintain constant volume.

***In vivo* anti-inflammatory studies**

The animals for the study were maintained in accordance with the Federation of European Laboratory Animal Science Association and the European Community Council Directive of November 24, 1986 (86/609/EEC). Female Wistar rats (150-250 g) were housed in cages under controlled temperature and humidity and under a photoperiod schedule of 12 h light/12 h dark. They were fed a standard laboratory animal diet and tap water was provided *ad libitum*. The rats had free access to food and water prior to the commencement and throughout the duration of the experiment in order to mitigate the gastro-erosive side effects of the administered loaded drug. 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 4 animals, serving as negative control, received a volume (437 µl) of freshly distilled water equal to the volume of the administered injection. Groups 2 and 3 received, orally, 437 µl each of SNEDDS 3A and SNEDDS 2B respectively with the help of an intragastric tube. One hour

after initial drug administration in each case, 50 µl of the phlogistic agent was injected into the subplantar surface of the right hind paw. Oedema was assessed based on the difference between linear circumference (C_o) of the injected paw at time zero and the circumference (C_t) after time, t. Percentage inflammation (and hence inhibition) was calculated using the relationship:

$$Percentage\ inflammation = \frac{AI_t}{AI_c} \times 100 \quad \text{Eq. 1}$$

Where AI_t is the average inflammation at time, t, and AI_c is the average inflammation of control animals at the same interval. From the values obtained, percentage inhibition (100 % minus percentage inflammation) was calculated.

Statistical data analysis

Statistical analysis was performed using the SPSS statistical package. The means and standard errors for all values were calculated. For group comparisons, a one way analysis of variance (ANOVA) was used to determine statistically significant differences at p-values < 0.05.

RESULTS AND DISCUSSION

Phase separation studies were initially carried out as a preliminary test for the efficiency of the self-nanoemulsification between the surfactant and the lipidic blends. The principal characteristic of self-emulsifying systems is their ability to form fine o/w microemulsions or nanoemulsions spontaneously upon mild agitation following dilution by aqueous phases. This is as a result of thermodynamic stability of self-emulsifying systems as opposed to the regular emulsions that are thermodynamically unstable. The formulated SNEDDS showed no detectable phase separation during the 1 h period and were subjected to subsequent studies. Incorporation of indomethacin did not affect the stability of the formulation throughout the course of the experiment. All batches of the formulated SNEDDS showed no evidence of phase separation during both the pre- and post-formulation isotropicity tests. This indicates a high level of stability of CHH based-SNEDDS. All batches remained isotropic after a ten-fold serial dilution. Following storage of the diluted solution for 24 h at ambient conditions, no evidence of drug precipitation was noticed. The development of self-emulsifying drug delivery systems had depended on the use of modified vegetable oils (Batherly, 2001), vegetable oils (Wakerly *et al*., 1985; Ofokansi *et al*., 2009) or semisynthetic medium chain triglycerides with amphiphilic nature. The SNEDDS formulated from blends of a homolipid from *Capra hircus* remained isotropic after drug loading. This uniform structure is necessary to avoid post formulation drug partitioning upon phase separation (Obitte *et al*., 2008). Based on this assessment alone, preference should be given to ratios with lower surfactant concentrations to avoid adverse effects due to use of surfactant in high concentration. All batches showed high stability on extensive dilution with aqueous fluid, as well as a low tendency to precipitate the loaded drug. This is due to the high thermodynamic stability of the resulting oil-in-water nano-emulsion. Stability from precipitation on dilution is a critical design parameter which depends on the solubility of drug in the various formulation components

(Charman *et al*., 1992), particularly in the oil. The capacity of the oil to dissolve and hold the hydrophobic drug is improved in the presence of surfactants, and hence the use of Span 85, a lipophile, as co-surfactant.

The mean diameter of the SNEDDS as measured by photon correlation spectroscopy was 214 nm for CHH/oil bean seed oil-based SNEDDS with a polydispersity index of 0.221 indicating a unimodal size distribution and 235 nm for CHH/shea butter-based SNEDDS with a polydispersity index of 0.314 indicating a bimodal size distribution as shown in Fig. 1 (a and c). Similarly, SNEDDS based on CHH/oil bean seed oil blends were found to have a zeta potential of -7.4 ± 0.2 mV while CHH/shea butter based SNEDDS were found to have a zeta potential of -6.4 ± 0.3 mV as shown in Fig 1(b and d). The absolute drug contents of all the batches tested are presented in Table 2. The samples all became completely emulsified within 4 min under the temperature and stirring conditions employed in the experiment. Carbosil-containing batches took slightly longer time to emulsify. The mean emulsification times for triplicate determinations are presented in Table 3. Particle sizes in such systems are generally of the order of nanometer size range (Charman *et al*., 1992; Devani *et al.*, 2004). Measurement of the droplet size could be done by photon correlation spectroscopy after extensive dilution (Shah *et al*., 1994). In general, the stability of a SNEDDS depends upon the particle size, emulsion droplet charge and droplet polarity. These influences are in turn governed by the nature (HLB, chain length and degree of unsaturation) and concentration of the surfactant employed. Admixtures of CHH and shea butter generally emulsified faster than equivalent oil bean seed oil-containing batches. Emulsification rate is an important parameter in emulsification efficiency (Pouton, 1985) and therefore product performance. In these cases, inclusion of carbosil increased the emulsification times beyond the 2 min time recommended for such systems (Khoo *et al*., 1998). Rapid self-emulsification occurs when the entropy change that favours dispersion of the SNEDDS is greater than the work requirement for increasing the surface area during dispersion (Reiss, 1975). Such free energy change should either be low but positive, or negative (Craig *et al*., 1993). The carbosil effect is explainable in terms of higher viscosities which inhibited diffusion and spreading/dispersion.

The release profiles of indomethacin from the formulated SNEDDS are shown in Figs. 2 and 3. Rapid emulsification regulates drug release. From the data shown, emulsification times did not vary widely, and this accounts for the observed release profiles of the different batches. Absolute drug contents of the batches varied between narrow limits (low standard deviation). This is a further indication of drug solubility in the SNEDDS base, otherwise sedimentation influences would have caused drug settling and marked variation in content between batches. This process yields uniform drug contents and is therefore amenable to scale up. The batches tended to delay the release of drug beyond 40 min. This could be an advantage in drugs with gastric mucosal toxicity such as indomethacin. However, the 40 min lag is too short, and it is likely that release of product would still occur in the stomach since most materials have residence times longer than 40 min in the stomach. But then, SNEDDS are known to have short residence times due to the

Table 1: Composition of batches of indomethacin-loaded SNEDDS

Batch*	Ratio of oil: surfactant: co-surfactant	Amount of oil blend (1:1) (g)	Amount of surfactant blend** (1:1) (g)	Amount of Span 85 (g)	Amount of indomethacin (mg)	Amount of carbosil (mg)
1A	20: 60: 20	1.4	4.2	1.4	400	--
1B	"	"	"	"	"	--
1C	"	"	"	"	"	300
1D	"	"	"	"	"	300
2A	35: 45: 20	2.45	3.15	"	"	--
2B	"	"	"	"	"	--
2C	"	"	"	"	"	300
2D	"	"	"	"	"	300
3A	25: 55: 20	1.75	3.8	"	"	--
3B	"	"	"	"	"	--
3C	"	"	"	"	"	300
3D	"	"	"	"	"	300
4A	25: 60 : 15	1.75	4.2	1.05	"	--
4B	"	"	"	"	"	--
4C	"	"	"	"	"	300
4D	"	"	"	"	"	300

*A contains CHH with oil bean seed oil, B contains CHH with shea butter, C contains CHH with oil bean seed oil and carbosil, D contains CHH with shea butter and carbosil. **A blend of 1: 1 ratio Tween 60 and Tween 80 was used for all batches

Table 2: Absolute drug contents of batches of indomethacin-loaded SNEDDS.

Batch*	Ratio of oil blend: surfactant blend: co-surfactant	Absolute drug content (mg)**
1A	20: 60: 20	17.20
1B	"	21.09
1C	"	19.98
1D	"	18.10
2A	35: 40: 20	18.08
2B	"	22.86
2C	"	23.95
2D	"	21.08
3A	25: 55: 20	20.12
3B	"	20.02
3C	"	21.08
3D	"	21.08
4A	25: 60: 15	21.12
4B	"	20.20
4C	"	23.19
4D	"	24.06

*A contains CHH with oil bean seed oil, B contains CHH with shea butter, C contains CHH with oil bean seed oil and carbosil, D contains CHH with shea butter and carbosil. **All batches were intended to deliver 20 mg of

*Corresponding author
ISSN 0189-8434

indomethacin

Table 3: Emulsification time of batches of indomethacin-loaded SNEDDS

Batch*	Ratio of oil blend: surfactant blend: co-surfactant**	Mean time ± S. E. M. (min)
1A	20: 60: 20	2.86 ± 0.24
1B	"	0.72 ± 0.15
1C	"	3.12 ± 0.25
1D	"	3.13 ± 0.25
2A	35: 45: 20	2.88 ± 0.12
2B	"	0.58 ± 0.05
2C	"	2.36 ± 0.21
2D	"	3.33 ± 0.33
3A	25: 55: 20	1.85 ± 0.14
3B	"	2.35 ± 0.18
3C	"	2.54 ± 0.22
3D	"	1.87 ± 0.15
4A	25: 60: 15	2.13 ± 0.20
4B	"	0.81 ± 0.04
4C	"	3.52 ± 0.30
4D	"	2.89 ± 0.21

*A contains CHH with oil bean seed oil, B contains CHH with shea butter, C contains CHH with oil bean seed oil and carbosil, D contains CHH with shea butter and carbosil. **All batches contain lipid (1: 1 blend of CHH with either oil bean seed oil or shea butter), surfactant (1:1 blend of Tween 60 and Tween 80) and Span 85 combined in the ratio shown above.

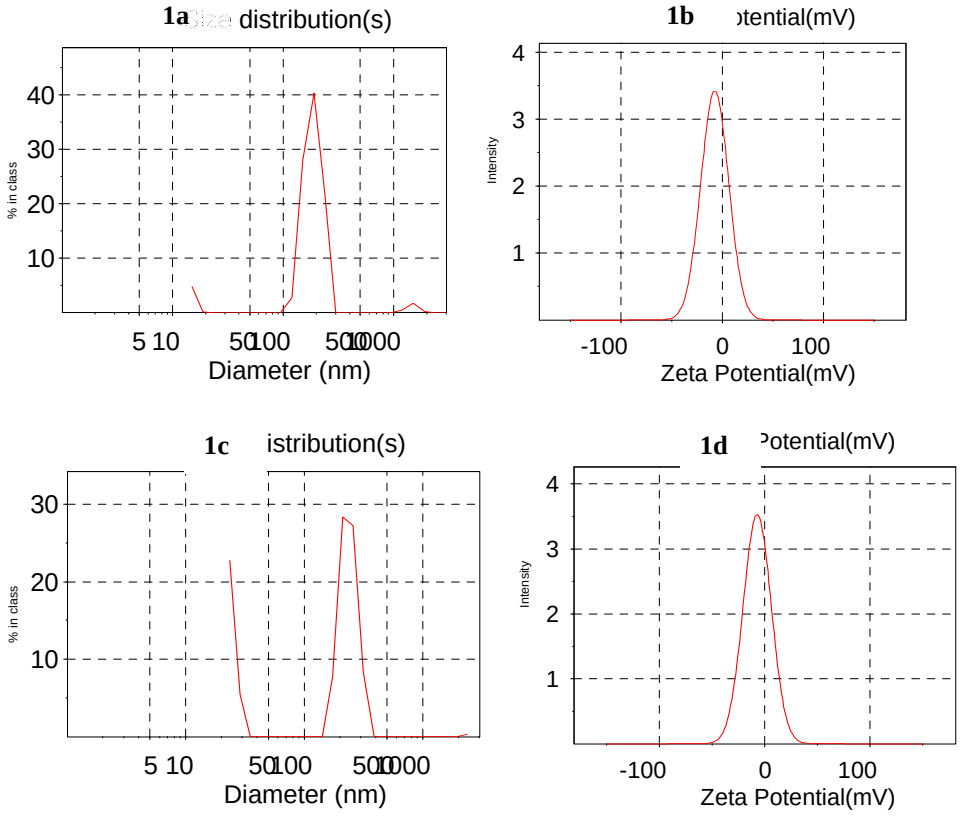

Figure 1**:** Particle size distribution and zeta potential of the SNEDDS as measured by photon correlation spectroscopy. Mean size of CHH/oil bean seed oil blend-based SNEDDS (1a), zeta potential of CHH/oil bean seed oil blend-based SNEDDS (1b), mean size of CHH/shea butter blend-based SNEDDS (1c), zeta potential of CHH/shea butter blend-based SNEDDS (1d).

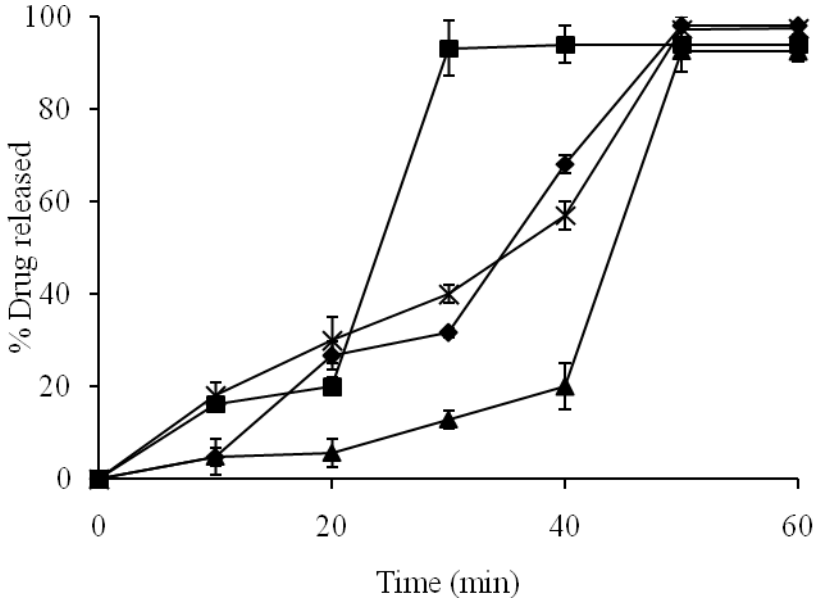

Figure 2**:** Release profiles of indomethacin-loaded self-emulsifying drug delivery systems based on CHH and oil bean seed oil blend (1: 1) combined in different ratios with a surfactant blend (1: 1 Tweens 60 and 80 blend) and co-surfactant (Span 85). —♦— (1A), —■— (2A), —▲— (3A), —×— (4A).

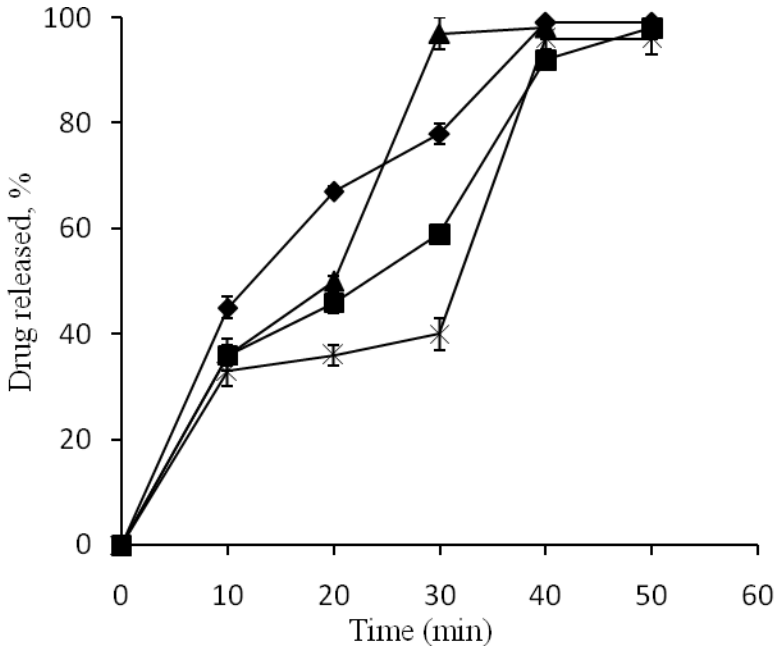

Figure 3: Release profiles of indomethacin-loaded self-emulsifying drug delivery systems based on CHH and shea butter blend (1: 1) combined in different ratios with a surfactant blend (1: 1 Tweens 60 and 80 blend) and co-surfactant (Span 85). —♦— (1B), —■— (2B), —▲— (3B), —×— (4B).

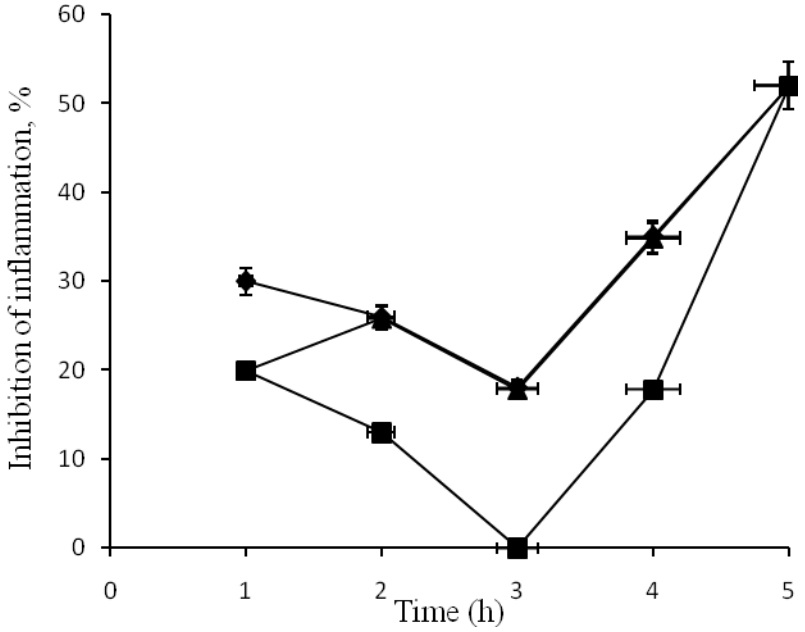

Figure 4: Inhibition of egg-albumin induced inflammation due by indomethacin contained in self-emulsifying drug delivery systems. —♦— (PC), —■— (3A), —▲— (2B). PC means positive control of indomethacin injection, 3A contains indomethacin in SNEDDS formulated from CHH and oil bean seed oil blend (1: 1) combined with surfactant blend (1: 1 of Tweens 60 and 80) and co-surfactant (Span 85) in the ratio of 25 : 55: 20 respectively, 2B contains indomethacin in SNEDDS formulated from 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 35 : 40: 20 respectively.

ultrafine particle size of the resulting micro/nano-emulsion which promotes gastric emptying (Pouton, 1985). Interestingly, a biphasic release phenomenon is seen in batches 1B, 2B and 3B where a rapid initial release of about 40 % of indomethacin occurred within the first 10 min, followed thereafter by a rapid drug release up to the 50th min, such that almost 100 % of the drug was released in 1 h. From our results, emulsification times failed to predict release performance either because the differences in the emulsification times were not significant in relation to the 10 min sampling time, or because drug release occurs via multi-factorial mechanisms, and does not consist only in emulsification time.

The anti-inflammatory activities of the samples administered are presented in Fig. 4 as a function of time. The formulations administered reduced the amount of inflammation due to the phlogistic. Indomethacin inhibits inflammation by antagonizing the cyclo-oxygense enzyme required for prostaglandin synthesis. In our present study, formulation of indomethacin as SNEDDS not only preserved the activity of the drug, but also guaranteed an anti-inflammatory activity comparable to that of indomethacin injection. The inhibition produced by the positive control and sample 2B were identical for much of the 5 h test period indicating a high degree of bioavailability of the administered SNEDDS formulated in this study especially for CHH/shea butter blend-based systems.

CONCLUSION

We conclude that a 1: 1 blend of homolipid from *Capra hircus* with

either oil bean seed oil or shea butter is a suitable base for development of SNEDDS for the delivery of indomethacin. The abundant supply of these materials is an advantage. Superior activity is evident in the use of shea butter. When its admixture with *Capra hircus* homolipid (1:1) is combined in the ratio of 35: 45: 20 (with surfactant blend and co-surfactant respectively), the resulting system produces comparably high inhibition of egg albumin-induced inflammation and exhibits biphasic drug release phenomenon, *in vitro*.

ACKNOWLEDGEMENT

Secretarial assistance of Mr. Patrick Asadu of the School of Postgraduate Studies is deeply acknowledged.

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