Science Article

PIROXICAM-LOADED SELF-EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Background: A self-emulsifying drug delivery systems (SEDDS) is an oral lipid dosage form for improving the biopharmaceutical performance of hydrophobic drugs. SEDDS are able to self-emulsify rapidly in the gastro-intestinal fluids under the influence of gentle agitation provided by peristaltic and other movements of the gastro intestinal tract to produce ultrafine oil-in-water emulsion, thereby providing a large interfacial area for enhancement in both the rate and the extent of drug absorption.

Objective: This work aimed to formulate piroxicam, a poorly water-soluble drug into a self-emulsifying drug delivery system using a natural lipophile (N-L) (crude oil) from pressed sesame seeds and to compare it with using labrafac CC as the oil phase.

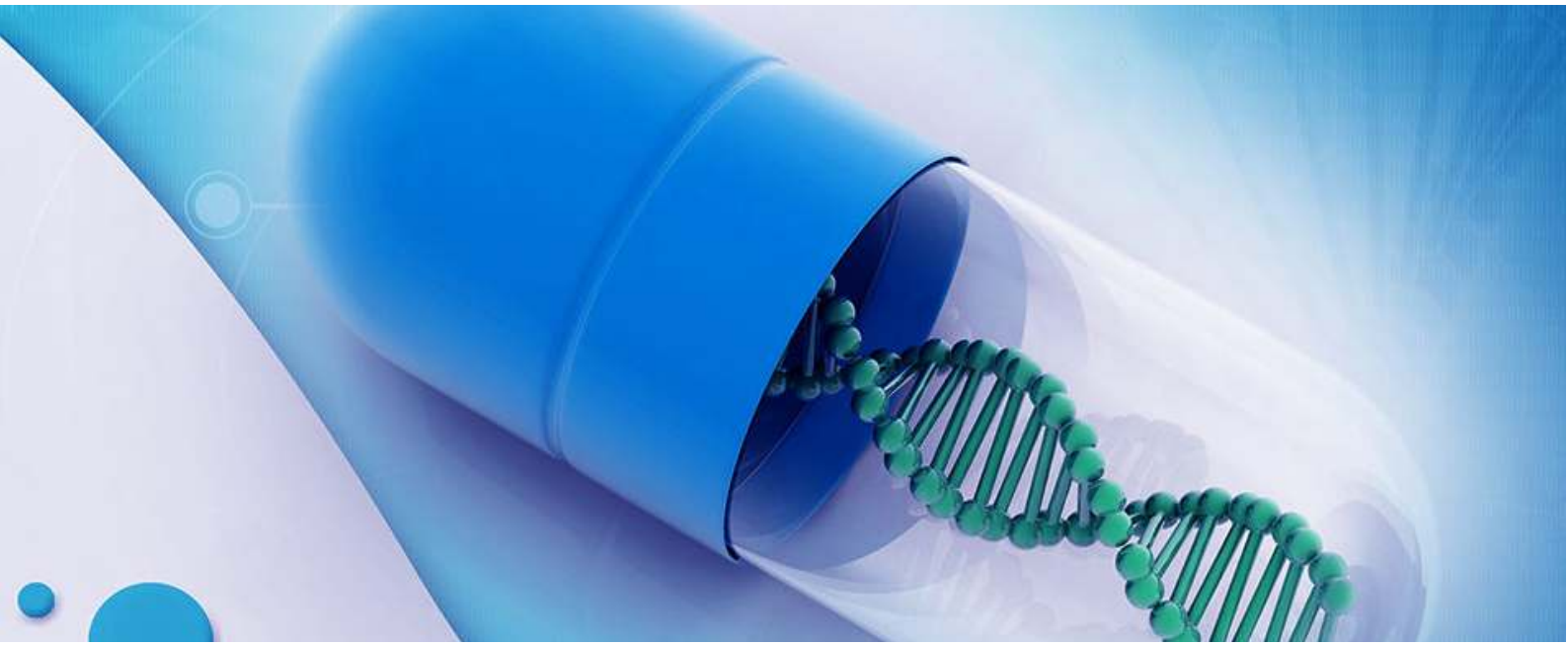
Methodology: Using a natural lipophile (N-L) and labrafac CC as the oil phase, Coliphor HS-15 or Cremophor EL as the surfactant and polyethylene glycol-400 as the co-surfactant, pseudo-ternary phase diagrams were generated following phase titration studies. The proportion of oil, surfactant and co-surfactant that can result in stable, maximum self-emulsification was selected, loaded with piroxicam and characterized with respect to percentage drug loading efficiency (%DLE), emulsification time, stability, infinite aqueous dilution, post-dilution drug precipitation, globule size and polydispersity index (PDI). The in vitro drug release rate of the optimal formulation was investigated using a polycarbonate dialysis membrane and it's in vivo anti-inflammatory activity was evaluated using carrageenan-induced paw edema in adult wistar rats.

Results: The optimized formulation consisted of 30 % oil, 56 % surfactant and 14 % co-surfactant, it gave an emulsification time of 6.0 s, had a % DLE of 91.1, a mean globule size of 32.0 nm, PDI of 0.175, released > 95.0 % of

the drug within 20 min while the pure drug showed only 13.8 % drug release over a period of 1 h and demonstrated significantly ($P < 0.05$) higher anti-inflammatory activity than the unformulated drug.

Conclusion: The developed SEDDS highlight the potential applications of the indigenous natural lipophile in the development of colloidal drug carriers for biopharmaceutical performance enhancement of piroxicam.

Keywords: sesame seeds, piroxicam, self-emulsifying, anti-inflammatory



1.0 INTRODUCTION

The oral route is the easiest, most convenient and major route of drug delivery for chronic treatment of many diseases.[1] In recent years, new chemical entities exhibit poor aqueous solubility which in turn presents a serious challenge to their successful formulation and marketing.[2] The oral delivery of such drugs is often associated with poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality.[3] Many formulation approaches are now employed to tackle the formulation challenges of poorly water-soluble drugs, either by means of improving the dissolution rate or via presenting and maintaining the drug in solution throughout its period in the gastrointestinal tract (GIT).

Self-emulsifying drug delivery systems (SEDDS) are one of the methods used to improve the oral bioavailability of hydrophobic drugs due to their capability of presenting and maintaining the drug in a dissolved state, in small droplets of oil, all over its transit through the gastrointestinal tract.[4] SEDDS are isotropic mixtures of natural or synthetic oils, solid or liquid surfactants and alternatively, one or more hydrophilic solvents or co-solvents/surfactants. These systems can form fine oil-in-water (o/w) emulsions or colloidal systems upon dilution in aqueous media such as GI fluids followed by mild agitation. Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification.[5] This property makes SEDDS suitable colloidal drug carriers for oral delivery of hydrophobic drugs with adequate solubility in oils or oil/surfactants blends.[3, 6] The digestion of lipid-based formulations, in the presence of endogenous materials (bile salts, phospholipids and cholesterol), induces a change in lipid composition and result in the formation of different colloidal

phases (micelles, vesicles, and liquid crystalline phases) in the intestinal lumen which plays a significant role in the solubilization capacity and consequently the absorption of co-administered drugs.[7, 8] The SEDDS mixture can be filled in either soft or hard gelatin capsules.

Piroxicam is an oxicam derivative and a non-steroidal anti-inflammatory drug (NSAID). It is practically insoluble in water. The drug is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis including juvenile idiopathic arthritis, in soft-tissue disorders, in acute gout, and postoperative pain but systemic usage in European Union countries is now restricted to chronic painful and inflammatory conditions.[9] The bioavailability enhancement characteristics of SEDDS presents a possibility for dose reduction which could have an effect in reducing piroxicam side effects like gastric ulceration. This work aimed to formulate piroxicam, a poorly water-soluble drug into a self-emulsifying drug delivery system using a natural lipophile (N-L) (crude oil) from pressed sesame seeds and to compare it with using labrafac CC as the oil phase.

2.0 MATERIALS AND METHODS

2.1 Materials

Piroxicam powder from (Sigma Aldrich, Germany), Coliphor HS-15 (poyoxyl-15-hydroxy stearate/macrogol-15-hydroxystearate) from BASF AG (Ludwigshafen, Germany), Cremophor EL (polyoxyl-35-castor oil) from BASF India Ltd, Tween 80 (polyoxyethylene-20-sorbitant mono-oleate) from India, labrafac CC (caprylic/capric glycerides) from Gattefosse, France, Polyethylene glycol-200 (PEG-200), PEG-400 and glycerol from BDH Chemicals Ltd, Poole England. Malvern Zetasizer ZS90 (M/s Malvern Instruments, Worcestershire, UK). Spectrophotometer (WWR UV-6300PC double beam, Switzerland). The natural lipophile was obtained from a batch processed in our laboratory. All other materials and chemicals used were of analytical reagent grade and were used as received.

2.2 Solubility studies

The solubility of piroxicam in different oils and surfactants was determined. Briefly, an excess of piroxicam was added individually to the oils, surfactants and co-surfactants (5 g each) in screw-capped tubes. Mixtures were then shaken for 12 h in a water bath shaker maintained at 28 ± 2 °C. After 24 h, each sample was centrifuged at 5000 rpm for 10 min. The supernatant (1 mL) was diluted suitably and the amount of drug present was analyzed by spectrophotometric method (UV spectrophotometer - WWR UV-6300PC double beam, Switzerland) at λmax of 334 nm. The components were selected for further studies depending on the maximum drug solubility in the surfactants and co-surfactants.

2.3 Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagram was constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature using the water titration method of Tripathi et al.,[10] N-L, labrafac CC or a blend (1:1) of N-L and labrafac CC was the oil phase, coliphor HS-15 or cremophor EL was the surfactant and polyethylene glycol-400 was the co-surfactant. Series of SEDDS were prepared by combining varying mass ratios of oil to surfactant and co-surfactants mixture from 1:9 to 3:1, while the proportions of surfactant to co-surfactants was optimized by varying their mass ratio from 1:0, 1:1, 1:2, 1:3, 2:1, 3:1, to 4:1. To the resultant mixtures, water was added dropwise until the mixture becomes turbidity. The different phases exhibited by the system during the titration were also observed, that is, micro/nanoemulsion, microgel, emulsion and emulgel, respectively. An utterly transparent appearance of the liquid system was taken as the micro/nanoemulsion, while its semisolid gel-like consistency was taken up as the micro/nanogel. Likewise, a liquid with milky appearance was treated as an emulsion, while its semisolid form with gel-like consistency was taken as emulgel.[10] The amount of water at which transparency-to-turbidity transition occurs was recorded. The pseudo-ternary phase diagrams were plotted (using SigmaPlot 13.0 software) to demarcate the micro/nanoemulsification region. No attempts were made to identify the other areas in the phase diagrams. From the phase diagram, the appropriate percentage of oil, surfactant and co-surfactant were selected and used for the preparation of self-emulsifying formulation containing piroxicam.

2.4 Formulation of piroxicam SEDDS

Based on the stable batches obtained from the demarcated micro/nano-emulsifying region, the required volumes of the liquid excipients were converted to weights using their densities for easy measurement. The density of sesame oil was determined using a density bottle. The components were combined by initially weighing the oil, surfactant and co-surfactant into a glass vial and mixing at 50 °C in a water bath, and then piroxicam was dissolved in the mixture at 50 °C, followed by vortex-mixing to obtain a clear homogenous solution. The quantity of SEDDS required to dissolve the drug and keep it in solution completely was decided based on the solubility studies. Placebo formulations (blank SEDDS) were also prepared similarly without the addition of piroxicam. The resultants piroxicam-SEDDS were kept for three (3) months and observed for changes in organoleptic properties and drug precipitation. The compositions of the developed piroxicam-SEDDS are shown in Table 1.

Table 1: Prepared batches of piroxicam-SEDDS

	Composition (mg)			
Components	piroxicam-SEDDS-1 **(Batch A)**	piroxicam-SEDDS- 2 **(Batch B)**	piroxicam-SEDDS- 3 **(Batch C)**	piroxicam-SEDDS- 4 **(Batch D)**
Piroxicam	20	20	20	20
N- L	420	462	-	-
Labrafac CC	-	-	350	-
N- L+labrafac CC (1:1)	-	-	-	330
Coliphor HS- 15	742	700	-	-
Cremophor EL	-	-	840	616
PEG- 400	238	238	210	154
Total	1420	1420	1420	1120

2.4.1 Phase separation and drug precipitation

Two (2) ml samples of each of the formulation were diluted to 10 ml and 100 ml with distilled water respectively at room temperature (28 ± 2 °C), stored for a period of 24 h and observed afterward for phase separation and drug precipitation.[11, 12]

2.4.2 Assessment of emulsification time

One (1) ml samples of each of the formulation was introduced into a beaker containing 250 ml of distilled water, maintained at 37 ± 2 °C under continuous stirring at 50 rpm. The time required to obtain an entirely uniform cloudy/turbid dispersion was recorded as the emulsification time.

2.4.3 Drug loading efficiency (DLE)

About 1 g of each formulation was dissolved in 100 mL of methanol and filtered via a Whatman filter paper No.42. The filtrate was then appropriately diluted and assayed for drug content by the spectrophotometric method at λmax of 334 nm for piroxicam and 334 nm.

2.4.4 Determination of globule size and polydispersity index

The globule size (Z) and polydispersity index (PDI) of each formulation were determined. An aliquot (1 mL) of each formulation was diluted 100-fold in distilled water, followed by gentle mixing. The resultant mixture was then subjected to globule size and polydispersity index analysis by dynamic light scattering technique using Malvern Zetasizer.

Based on the data obtained from the above evaluations, batch D (piroxicam-SEDDS-4) was selected (as a result of its possession of lower globule size, emulsification time and better polydispersity) as the optimized batch for further studies

2.4.5 Release rate determination

The USP paddle method was adopted in this study in determining the release rate of the optimized formulation and the unformulated drug. The dissolution medium consisted of 500 ml of freshly prepared medium (SGF pH 1.2 and SIF pH 7.5) maintained at 37 ± 2 °C. A polycarbonate dialysis membrane pretreated by soaking in the dissolution medium for 24 h before the commencement of the release experiment was used. A quantity of batch D equivalent to 20 mg of piroxicam or 20 mg of the unformulated piroxicam powder was transferred into the pretreated dialysis membrane containing 2 ml of the dissolution medium, securely tied with a thermo-resistant thread and then placed in the appropriate chamber of the release apparatus containing the dissolution medium. The paddle at 100 rpm provided agitation. Aliquot portions (5 mL) were withdrawn at predetermined intervals, namely 5, 10, 15, 20, 30, 40, 50 and 60 min, followed by replenishment with equal volumes of fresh dissolution medium. The withdrawn samples were filtered and assayed at λ_{max} of 334 nm using a UV spectrophotometer (WWR UV-6300PC double beam, Switzerland).

2.4.6 Stability studies

The stability of the formulation was investigated by obtaining the Fourier Transform Infrared Spectroscopy (FT-IR) spectra of freshly prepared formulation and after 6 weeks of storage at room temperature (28 ± 2 °C). The spectra were examined for shifting of peaks to either higher and lower frequencies or disappearance of some bands. The spectra were obtained over the range 650- 4,000 cm^{-1}.

2.4.7 Anti-inflammatory test

The protocol was approved by the Ahmadu Bello University Committee on Animal Use and Care (Approval number ABUCAUC/2018/017) and the work was carried out in the same premises. The anti-inflammatory activity assessment was carried out using the method described by Winter et al.,.[13] Adult Wistar rats of either sex (weighing between 180 to 200 g) randomly divided into 6 groups (n = 5 per group) as per the treatment mentioned, Group I (Positive control - no drug treatment), Group II (aqueous suspension equivalent to 0.4 mg/kg of piroxicam), Group III (batch D equivalent to 0.4 mg/kg of piroxicam), Group IV (0.4 mg/kg of blank-SEDDS-4) and Group V (a marketed formulation equivalent to 0.4 mg/kg of piroxicam). The rats used were allowed to acclimatize to their environment for 8 days before the start of the experiment. During the acclimatization period they were fed rat pellets (Vital feeds Limited, Ibadan, Nigeria) and water was given ad libitum. The housing provided had the following conditions: controlled lighting of 12:12 h of light: dark, temperature of 25 ± 2 °C and relative humidity of approximately 50 ± 5%. The rats were fasted and deprived of water for 12 h before the experiment to ensure uniform hydration and to minimize variability in edematous response.[13] The different groups of animal were administered the treatment at a dose of 0.4 mg/kg by oral gavage. Thirty minutes post-treatment, edema was induced by injection of 1% suspension of carrageenan in 0.9 % sterile saline solution into the sub-plantar tissue of the left hind paw of each rat. The paw diameter was measured with the aid of a Vernier caliper 0, 1, 2, 3, 4, 5 and 6 h after the injection of the carrageenan. The percentage inhibition of paw edema was calculated using equation (1).[14]

$$\% \, inhibition \, of \, paw \, oedema = \frac{Vc - Vt}{Vc} \, X \, 100$$

..... (1)

2.5 Statistical analysis

The data generated from the various determinations were analyzed using SPSS 20.0 software (SPSS, Chicago, IL, USA) and are presented as the mean ± standard deviation (SD). The differences between the data sets were determined using T-test and $p < 0.05$ was considered statistically significant.

3.0 RESULTS

3.1 Pseudo-ternary phase diagram

Phase diagrams were constructed to obtain the proportion of components that can result in maximum micro/nanoemulsion existence. Fig.1 depicts the phase diagram from which the ratio of components used in formulating the optimized formulation was obtained. The circled area in the phase diagram depicts the self-emulsification region; it shows that a mixture of 27.5- 34 % of the oily phase with 66- 72.5 % surfactant mix is required to form stable micro/nano-emulsion effectively.

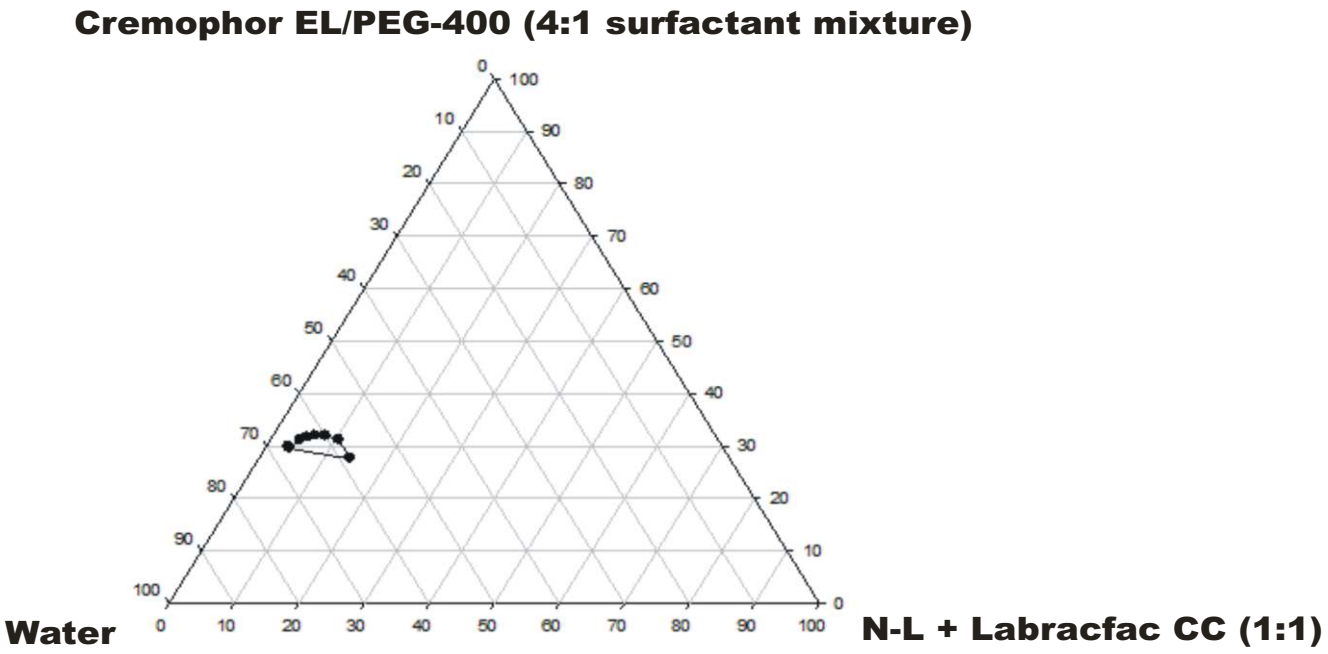


Figure 1: Pseudo-ternary phase diagram for cremophor EL/PEG-400 (4:1), N-L + labrafac CC and water

3.2 emulsification time, phase separation, drug precipitation, loading efficiency, globule size and polydispersity index

The quantity of unloaded SEDDS required to dissolve 20 mg of piroxicam and to keep it in solution was 1400 mg (for batch A and B) and 1100 mg for batch D. Upon storage for three (3) months, batch C exhibited drug precipitation and was therefore dropped. Batches A, B and D however, did not show drug precipitation or changes in organoleptic properties after storage for 3 months and no phase separation occurred in any of the three batches following aqueous dilution and storage for 24 h. The emulsification time for batch A, B and D was 7.0, 8.0 and 6.0 s while the percentage drug loading efficiency (%DLE) was 92.3±1.01, 94.5±0.46 and 91.1±1.11 % respectively. The results of mean globule size and polydispersity index (PDI) are shown in fig. 2 - 4. The mean globule size for batch A, B and D are 41.94, 45.34 and 32.00 while the PDI are 0.231, 0.235 and 0.175 respectively.

Batch D had a lower mean globule size, better polydispersity index and the fastest emulsification time, hence, was selected as the optimized batch for release rate, stability, and in vivo anti-inflammatory testing.

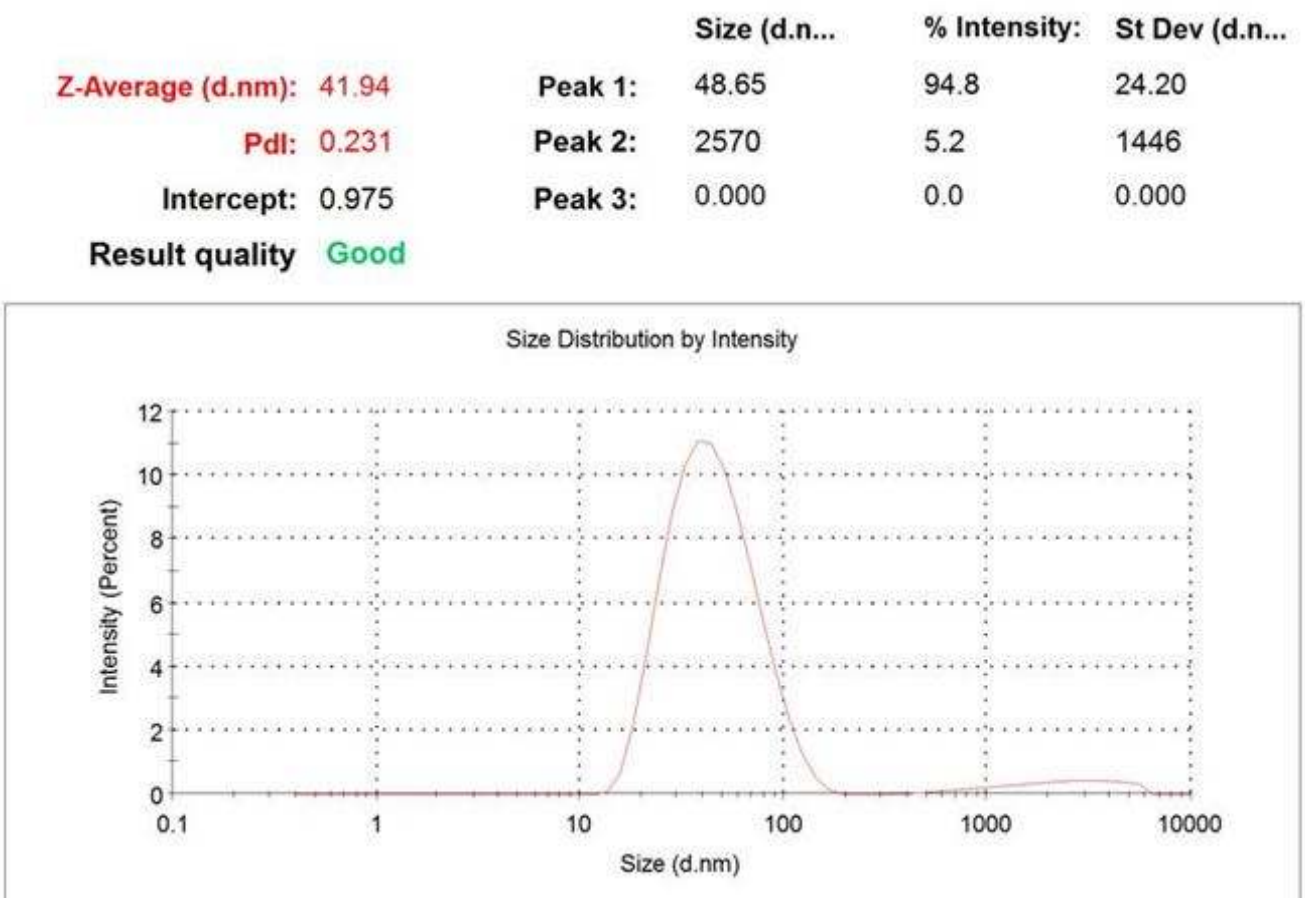


Figure 2: Graphical presentation of globule size (Z) and polydispersity index (PDI) of batch A

		Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 45.34	Peak 1:	57.84	97.2	35.49
PdI: 0.235	Peak 2:	3114	2.8	1392
Intercept: 0.887	Peak 3:	0.000	0.0	0.000
Result quality Good				

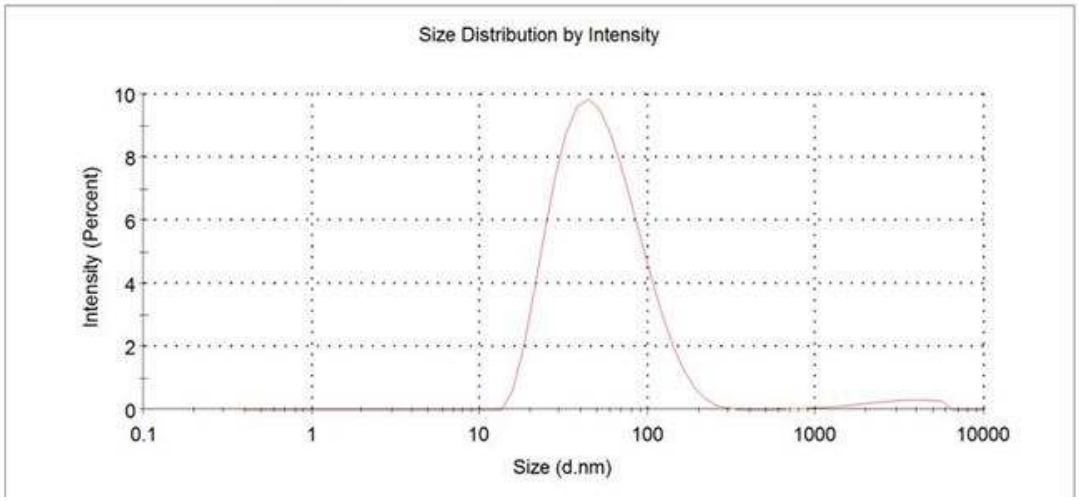


Figure 3: Graphical presentation of globule size (Z) and polydispersity index (PDI) of batch B

		Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 32.00	Peak 1:	36.37	98.4	15.21
PdI: 0.175	Peak 2:	4310	1.6	961.3
Intercept: 0.956	Peak 3:	0.000	0.0	0.000
Result quality Good				

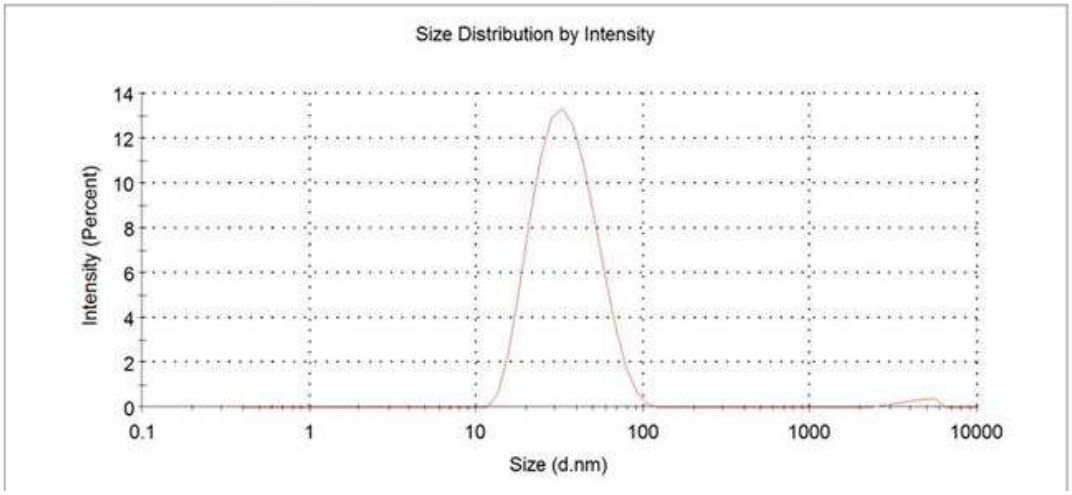


Figure 4: Graphical presentation of globule size (Z) and polydispersity index (PDI) of batch D

3.3 Release rate determination

The release profile of the unformulated piroxicam powder and batch D in different media are shown in fig. 5. The optimized batch showed marked improvement in the drug release rate compared to the unformulated piroxicam powder. The release rate of both the unformulated piroxicam powder and batch D was slightly higher in SIF than in SGF. In SIF, the unformulated piroxicam powder showed only 13.8 % release in 60 min while 98.3 % of the drug was released from batch D within 15 min.

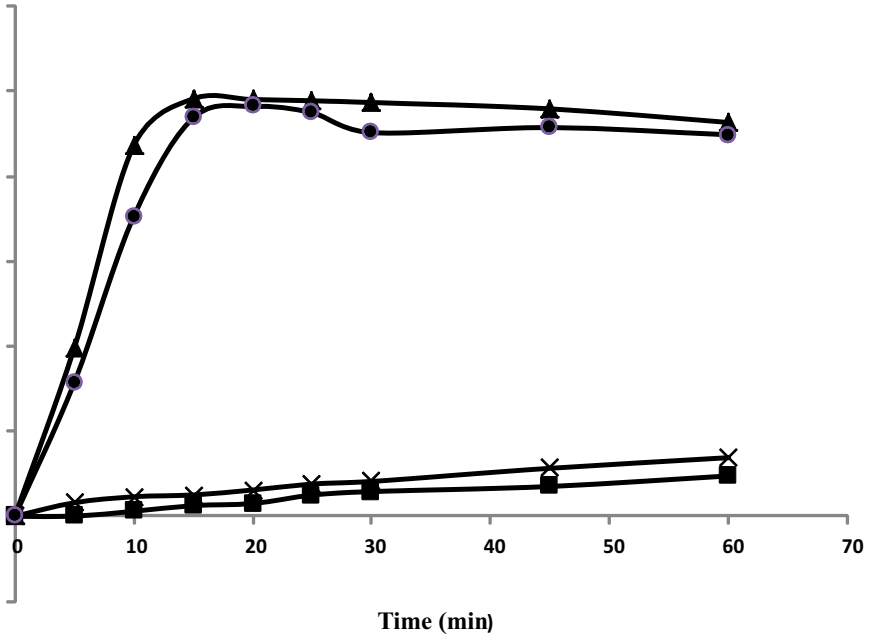


Figure 5: Release profile of: (■) unformulated piroxicam powder in SGF, (X) unformulated piroxicam powder in SIF, (●) batch D in SGF and (▲) batch D in SIF

Stability studies

The superimposed FT-IR spectra of day one (1) and six weeks (6) old batch D are presented in Fig. 6. The characteristic FT-IR peaks occurred at occurred at 2000-1667 cm-1 indicating aromatic overtones 1600-1430 cm-1 due to C=O stretching, 2500-3000 cm-1 indicating OH stretching, 1600-1430 cm-1 indicating C=N stretching and the O=S=O functional group occurred at 1415-1300 cm-1 and 1200-1120 cm-1

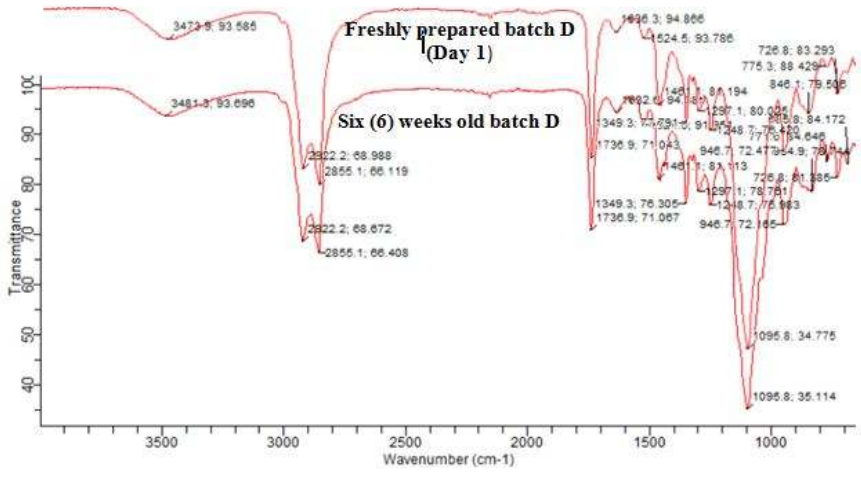


Figure 6: FT-IR spectra of freshly prepared (day one) and six weeks (6) old batch D, superimposed for comparison

3.4 Anti-Inflammatory studies

Induction of acute inflammation resulted in a prominent increase in paw thickness, beginning 1 h after intra-plantar injection of carrageenan and reaching a peak of inflammation after 3 h as shown in Table 2. The anti-inflammatory properties of the various piroxicam formulations with respect to the inhibition of paw edema are shown in Fig. 7. The results showed that batch D exerted more reduction in paw edema than the reference drug.

Table 2: Anti-inflammatory test of the various piroxicam formulations in experimental rats

Treatment	Mean increase in paw edema (mm)				
	1 h(±SD)	2 h(±SD)	3 h(±SD)	4 h(±SD)	5 h(±SD)
Control	4.31 ±0.04	6.05 ±0.02	7.25 ±0.06	7.04 ±0.01	6.39 ±0.04
Aqueous piroxicam suspension (APS)	4.18 ±0.03	5.13 ±0.05	5.83 ±0.05	5.50 ±0.05	4.79 ±0.06
Batch D placebo	4.29 ±0.03	6.04 ±0.05	7.19 ±0.07	6.99 ±0.04	6.40 ±0.06
Marketed formulation (MF)	3.68 ±0.03	4.86 ±0.04	5.45 ±0.03	5.20 ±0.02	4.52 ±0.06
Batch D	2.81 ±0.03	3.31 ±0.03	3.56 ±0.04	2.87 ±0.02	2.17 ±0.05

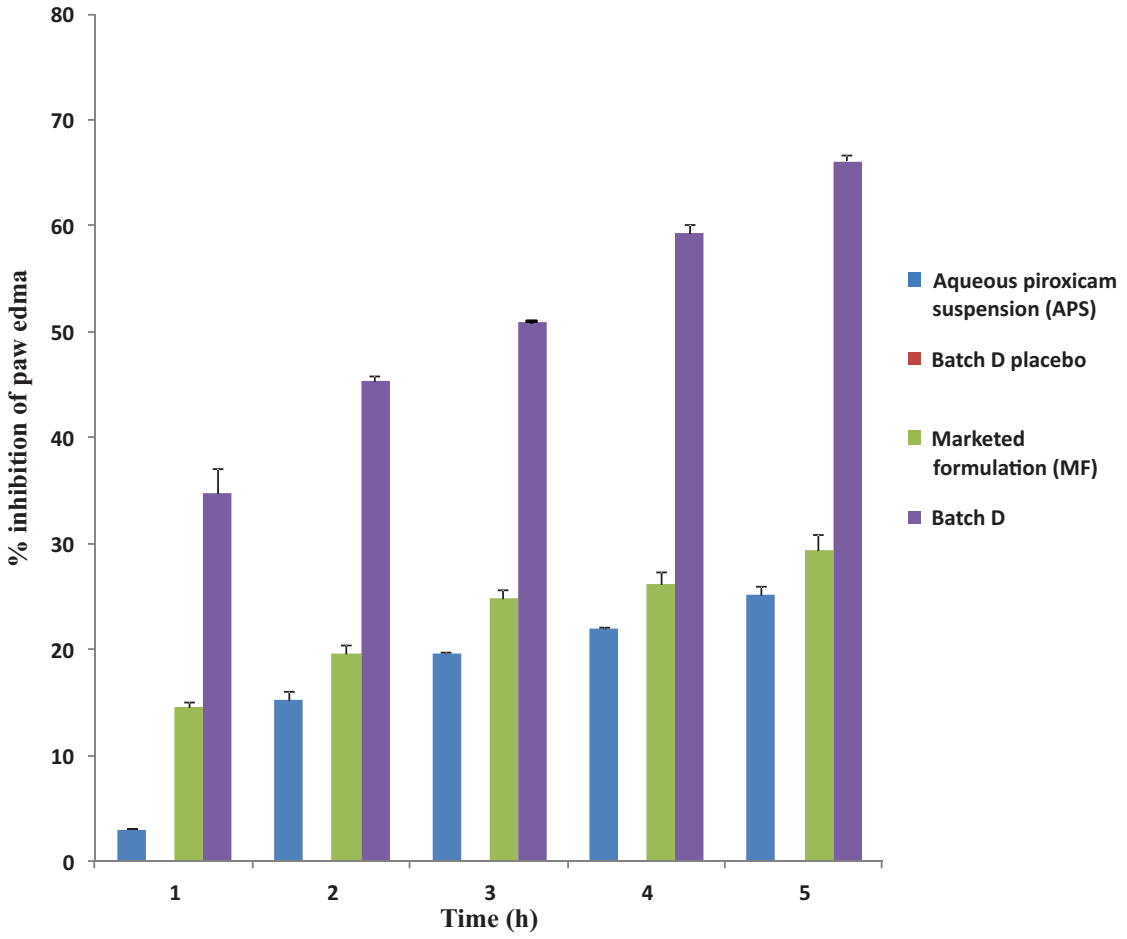


Figure 7: Percentage inhibitions of carrageenan-induced paw edema by different piroxicam formulations

4.0 DISCUSSION

4.1 Pseudo-ternary phase diagram

Pseudo-ternary phase diagrams provide the information of phase behavior between different formulation components, that is, they are a useful tool in determining miscibility/solubility, coacervation or gel-forming regions for multicomponent mixtures.[4] The optimized batch is made up of about 29.5 % oil, 55.0 % surfactant and 13.8 % co-surfactant. The surfactant concentration was within the prescribed range of 30 – 60 % and is a non-ionic surfactant, which is less toxic and less affected by pH and ionic strength.[5, 12] The surfactant used also has a high hydrophilic-lipophilic balance (HLB) value of 15 which will ensure immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. The oil represents one of the most important excipients in the SEDDS formulation because it can solubilize marked amounts of the lipophilic drug, facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system thereby increasing absorption from the GI tract.[5] N-L, been an unrefined natural sesame oil (vegetable source) is composed of long chain triglycerides, while Labrafac CC is a medium chain triglyceride obtained by re-esterification of fractionated coconut oil fatty acids with glycerin.[1] The oil phase in batch A and B was 100% N-L, 100 % labrafac CC in batch C and a mixture (1:1) of N-L and labrafac CC in batch D. SEDDS containing 100 % labrafac CC (batch C) as the oil phase was unable to maintain the drug in a solubilized form after three months of storage, hence exhibited the least capability to solubilized piroxicam. SEDDS composed of a mixture (1:1) of N-L and labrafac CC (batch D) exhibited the highest piroxicam solubilizing capacity. This may be attributed to the fact that combining the two oils provided a blend of fatty acids suitable for maintaining the drug in solution.

4.2 Emulsification time, drug precipitation, phase separation, globule size and polydispersity index

Batch C exhibited drug precipitation after three months of storage, hence it was dropped. The three other batches (A, B and D) however demonstrated physical stability against both drug precipitation and phase separation. Creaming, cracking and precipitations are massive threats to the stability of emulsions, resistance against such stability threats is a desirable attribute of an emulsion.[15] Rapid spreading of the formulation in the aqueous media (good self-emulsifying performance) was achieved with all the stable batches, with all exhibiting self-emulsification time of less than 10 s. This indicates that the formulations will rapidly form fine oil-in-water emulsions when dispersed in aqueous media under mild agitation. The digestive motility of the stomach and intestine is expected to provide the agitation necessary for self-emulsification in vivo.[11]

Droplet size is thought to have an effect on drug absorption, the smaller the droplet size, the larger the interfacial area for drug absorption.[12, 16, 17] Small droplet size shows the formation of a better close-packed film of the surfactant at the oil-water interface, thereby stabilizing the oil droplets.[18,19] All the stable batches gave emulsions with mean globules sizes less than 50 nm. Batch D had the least globule size of 32.0 nm and the best PDI (0.175). PDI describes the degree of uniformity in droplet size within a formulation. The higher the polydispersity index (PDI), the lower the uniformity of the droplet size in the formulation.[19] Oils consisting of long chain triglycerides (e.g., sesame) have higher viscosity, this impact on the emulsification process which in turn has a substantial effect on the emulsion globule size.[20] Recall that 50 % of the oil phase in batch D is labrafac CC (a medium chain triglyceride), this, therefore, explains why it yielded an emulsion with a lower mean globule size compare to the emulsion prepared with 100 % N-L, Atef and Belmonte [6] reported similar findings.

Piroxicam been an acidic drug was favored in the alkaline pH of SIF (7.5) leading to enhanced solubilization and subsequent improvement in release rate compared to in SGF (pH 1.2). At 20 min, 96.5 % of the drug was released from batch D (in SGF) while the unformulated piroxicam powder only showed 3.0 % drug release representing about 32-fold increase over the unformulated sample, suggesting that the formulation will achieve a fast onset of action. The peak concentration (98.3 %) (in SIF) was achieved at 15 min; 100 % drug release could not be achieved, this perhaps suggests that some amounts of piroxicam must have been adsorbed onto or trapped in the dialysis membrane.

The significant ($P < 0.005$) improvement in release rate from batch D may be due to the presence of surfactant and cosurfactant which has been shown to promote effective dispersion of hydrophobic drug in aqueous media by the solubilization process, in addition to drug spreading in oil droplets.[4,21]

4.3 Stability studies

The FT-IR spectra of the freshly prepared (day 1) and six (6) weeks old batch D showed no formation of new peaks, no disappearance of old peaks nor shifting of their positions, indicating the absence of chemical interaction between the formulation components, hence suggesting that the formulation is stable and the various ingredients are compatible.[22]

4.4 Anti-inflammatory studies

Injecting of carrageenan into the hind paw induced progressive edema reaching its maximum at 3 hours. The percentage inhibition of paw edema by batch D, aqueous piroxicam suspension and the marketed piroxicam formulation are 51 %, 16 % and 22 % respectively. This represents a 2.1 and 2.6 fold increase inhibition by batch D over the marketed formulation and aqueous piroxicam suspension respectively. This demonstrates the superiority of SEDDS over the marketed formulation. The enhanced anti-inflammatory activity of the piroxicam-SEDDS is not unconnected to the formulation's fast and efficient emulsification yielding o/w emulsion with a droplet size of colloidal dimension which provides large interfacial area for drug absorption. The formulation can maintain and present the drug to the GIT in solution, thereby avoiding the dissolution step and replacing it with a rapid liquid-liquid partitioning step between the solubilized reservoir and drug in free solution.[4, 23] Co-administration of drugs with lipids have been shown to promote the assembly of triglyceride-rich lipoproteins in the enterocyte, whose subsequent transport from the intestine occurs via the intestinal lymph hence avoiding first-pass metabolism.[21, 24] Also, lipids (contained in SEDDS) are known to activate the "ileal brake" which reduces small intestine motility thereby increasing the time available for digestion and absorption.[7] In addition, lipids, and the other components of SEDDS (surfactants and co-solvents), have been described to positively impact intestinal permeability by opening tight junctions, inhibition of efflux transporters and promoting transcellular permeability and membrane solubilization.[21]

5.0 CONCLUSION

The natural lipophile alone or when blended with labrafac CC was found suitable in formulating stable piroxicam-loaded SEDDS using coliphor HS-15 or cremophor EL respectively as surfactant and PEG-400 as cosolvent. The formulation released over 90 % of its drug content within 15 min and demonstrated significantly ($p < 0.05$) higher anti-inflammatory effect than the unformulated piroxicam powder. Therefore, the natural lipophile and its blend with labrafac CC have proved their suitability as lipid constituents of SEDDS that improved the solubility of piroxicam and enhanced its anti-inflammatory effect.

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