IBUPROFEN SELF-EMULSIFYING DRUG DELIVERY SYSTEM.

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ABSTRACT

Self emulsifying drug delivery system (SEDDS), which is an isotropic mixture of oil, surfactant with or without cosurfactant, can be used to improve the oral absorption of poorly soluble drugs such as ibuprofen. Therefore, the aim of this study was to formulate ibuprofen SEDDS and evaluate its in vitro and anti-inflammatory properties. Pseudo ternary phase diagram construction was carried out to identify stable formulations. Subsequently SEDDS were formulated using mixture of labrafac lipophile or its blend with peceol (oil), labrasol (surfactant) and lauroglycol 90 (co-surfactant). The following evaluations were carried out on the formulations: visual isotropicity, emulsification time, drug content, in vitro drug release, infinite aqueous dilution, post dilution drug precipitation and in vivo anti inflammatory tests respectively. Results showed that all the batches passed the visual isotropicity test, recorded emulsification time of less than a minute and promoted fast drug release. Infinite aqueous dilution showed no phase separation and in vivo anti inflammatory study demonstrated significantly higher anti-inflammatory activity (p<0.05) than ibuprofen powder. In conclusion, all the evaluations showed that the SEDDS improved the aqueous solubility of Ibuprofen and its anti-inflammatory activity.

KEYWORDS: SEDDS, Labrasol®, Lauroglycol® 90, Labrafac® lipophile, Ibuprofen.

INTRODUCTION

One of the most persistent challenges faced by the formulation scientist has been the search for appropriate method of enhancing the bioavailability of poorly soluble drugs. A drug must
almost invariably be dissolved with the GIT prior to absorption through the mucosa. Evidently, poor water solubility may lead to incomplete and erratic absorption. Consequently, several therapeutic molecules such as poorly soluble drugs suffer from the problem of low bioavailability, high inter and intra-subject variability and lack of dose proportionality when per orally administered.\(^1\) Here, drug dissolution is the rate limiting step in the absorption process. The major limitation of lipophilic drugs vis-a-viz solubility and dissolution in GIT could be overcome if formulated into self-emulsifying drug delivery system (SEDDS).

SEDDS is a mixture of oil, surfactant and cosurfactant ideally isotropic which emulsifies spontaneously in aqueous phase to produce oil-in-water or water-in-oil emulsion under gentle agitation.\(^2\) These fine emulsions formed are relatively stable with a very small particle size diameter of above 100 nm.\(^3,4\) These small droplets occupy a large interfacial area thus facilitating drug diffusion into intestinal fluid.\(^5,6\) This system when taken orally gets mixed and diluted in the aqueous media of the GIT and the gut motility agitates the whole system for emulsion formation. With respect to oral delivery, fine oil droplets pass rapidly from stomach and help wide distribution of drug molecules throughout the GIT, and hence minimize the irritation encountered during prolonged contact between bulk drug substance and gut wall.\(^7,8\)

In the formulation of SEDDS, the following must be considered: the solubility of the drug in different oils, surfactants and cosurfactants/solvents and the outcome of the constructed pseudo ternary phase diagram.\(^9\) The addition of drug is also critical because drugs interfere with the self-emulsification process to a certain extent and thus may lead to a change in the optimal oil-surfactant ratio.

The advantages of SEDDS include improvement in drug solubility, absorption and bioavailability; stability and solubility of lipophilic drugs.\(^10\) In a previous work we produced ibuprofen SEDDS using a mixture of Tween 80, span 85 and vegetable oils.\(^11\) However our present investigation seeks to improve the solubility of ibuprofen using some synthetic oils and surfactants. The objectives of this work were therefore to prepare ibuprofen SEDDS using synthetic oil and oil blends and evaluate, it’s in vitro and anti-inflammatory properties.

**MATERIALS AND METHODS**
MATERIALS
Labrafac lipophile®, labrasol®, peceole®, lauroglycol® 90 (Gattefosse, France), distilled water, ethanol (Sigma Aldrich). Ibuprofen was a gift sample from Rajrab Pharmaceuticals Ilorin, Nigeria.

METHODS
Solubility of ibuprofen in the oil, surfactant and co-surfactant
An excess quantity of ibuprofen was introduced into specimen bottles containing 1 ml of labrafac lipophile®, labrasol®, lauroglycol® 90 and peceol® respectively. Each suspension was placed on a mechanical shaker and shaken for 30 min. Each suspension was subsequently filtered and the filtrate made up to 5 ml with SIF (simulated intestinal fluid). It was assayed for ibuprofen content using spectrophotometer (Spectrumlab 752 UK) at the wavelength of 270 nm.

Pseudoternary phase diagram and preparation of 100 mg ibuprofen SEDDS
The water titration technique was used based on the previous pattern by Obitte et al. [12] The appropriate quantities of labrasol®, labrafac lipophile® and lauroglycol® 90 were mixed together to achieve a homogenous mixture of 5 g SEDDS. A 0.1 ml quantity of the SEDDS was pipetted into a 10 ml specimen bottle and drop-wise quantity of distilled water introduced until a transparent emulsion was formed. The transparent emulsions were adjudged stable and selected for further studies. Two groups of formulations were prepared; one containing labrafac lipophile (LL) and the other a blend of labrafac lipophile and peceole (LP). Consequently, only 5 batches turned out stable from LL and LP groups. These stable batches were then loaded with ibuprofen; the quantity of each dose of SEDDS (300 mg) and amount of drug (100 mg) were decided based on the solubility studies.

The appropriate quantity of ibuprofen was introduced in a beaker containing the oil and stirred for 10 min. The surfactant and cosurfactant were also introduced and stirred for 10 min on a water bath (50° C) to ensure complete drug dissolution. The SEDDS were encapsulated in # 2 hard gelatin capsules. Tables 1 and 2 represent the preparation formula.
Table 1: The formula for 400 mg SEDDS containing a single oil

<table>
<thead>
<tr>
<th>Batch</th>
<th>Oil:surfactant:cosurfactant</th>
<th>Labrafac lipophile (mg)</th>
<th>Labrasol (mg)</th>
<th>Lauroglycol 90 (mg)</th>
<th>Ibuprofen (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10: 80: 10</td>
<td>30</td>
<td>240</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>10: 70: 20</td>
<td>30</td>
<td>210</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>20: 70: 10</td>
<td>60</td>
<td>210</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>20: 60: 20</td>
<td>60</td>
<td>180</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>20: 50: 30</td>
<td>60</td>
<td>150</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: The formula for 400 mg SEDDS containing oil blend.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Oil:surfactant:cosurfactant</th>
<th>Labrafac lipophile (mg)</th>
<th>Pecel (mg)</th>
<th>Labrasol (mg)</th>
<th>Lauroglycol 90 (mg)</th>
<th>Ibuprofen (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10: 80: 10</td>
<td>15</td>
<td>15</td>
<td>240</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>B</td>
<td>10: 70: 20</td>
<td>15</td>
<td>15</td>
<td>210</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>C</td>
<td>10: 60: 30</td>
<td>15</td>
<td>15</td>
<td>180</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>D</td>
<td>20: 70: 10</td>
<td>30</td>
<td>30</td>
<td>210</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>E</td>
<td>30: 60: 10</td>
<td>45</td>
<td>45</td>
<td>180</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

EVALUATION OF SEDDS

Visual isotropicity
The SEDDS were observed for visual isotropicity and presence/absence of drug precipitation.

Particle size analysis and zeta potential determination
The particle size analysis of resultant microemulsion was determined by dynamic light scattering (DLS). 100 µl of the SEDDS was dispersed completely in 10 ml of water. Measurement was done using a Zetasizer 1000 HS (Malvern Instruments, Worcestershire, UK). Light scattering was monitored at 25 °C at a 90° angle. The zeta potential was carried out on the same diluted samples using the same equipment and operating conditions.

Emulsification time
SEDDS capsule was introduced into a beaker containing 150 ml of 0.1 N HCl under magnetic stirring (50 rpm) and temperature of 37±1 °C. Time required for complete emulsification was determined by visually observing change in turbidity as a function of time. Time point beyond which there was no increase in turbidity was recorded as the emulsification time.

Infinite aqueous dilution
Each SEDDS capsule was introduced into a 1000 ml measuring cylinder containing 100 ml distilled water, mildly stirred and allowed to stand for 4 h. It was later checked for phase
separation and drug precipitation. Thereafter it was further diluted to 1000 ml mark and again observed for phase separation and drug precipitation.

**Loading efficiency**

The content of each SEDDS capsule was emulsified in 100 ml of simulated intestinal fluid (SIF) in a 100 ml volumetric flask. A 0.1ml quantity was introduced into a test tube and diluted with agitation to 5ml with fresh SIF. Drug content was determined using the UV spectrophotometer (phonix-220 DPC V model) at a wavelength of 270 nm.

**In vitro drug dissolution:** The basket method was adopted for this experiment. A capsule of ibuprofen SEDDS was introduced into the dissolution test apparatus (Veego, India) containing simulated intestinal fluid (500ml). The dissolution medium temperature was maintained at 37°C ± 1°C while the rotation speed was set at 100 rpm. Aliquots (5ml) were withdrawn at predetermined time interval and replaced with fresh dissolution medium. The drug content was analyzed using the UV spectrophotometer (phonix-220 DPC V model) at 270 nm to obtain corresponding absorbance values.

**Anti-inflammatory Study**

Rat paw edema method was used; twelve albino rats divided into 4 groups of 3 animals per group and weighing 105-200 g were fasted for 12 hrs. They were deprived of water during the experiment to ensure uniform hydration and to minimize variability in edematous response. [13] Inflammation of the hind paw was induced by injecting 0.1ml of 100% fresh albumen (phlogistic agent) into the sub plantar surface of the right hind paw. This treatment was found to cause swelling of the paw which reached a peak in 2-6 h. Group 1 was administered distilled water and served as negative control. Group 2 was administered ibuprofen and served as positive control. Labrafac lipophile-based SEDDS (T1) was administered to group 3 while labrafac lipophile/peceol SEDDS (T2) was administered to group 4.

Amount of SEDDS equivalent to 6 mg Kg\(^{-1}\) of ibuprofen was dispersed in 1 ml of distilled water and administered to the appropriate group of animals. Similarly the same amount of ibuprofen powder was dispersed in distilled water prior to administration to group 2 animals. Thirty minutes later this was followed by the administration of 0.1 ml of fresh egg albumin (phlogistic agent) into the sub planter portion of the right hind paw.
Edema was assessed by measuring the volume of water displaced by the hind paw using a plethysmometer at 30 min, 1 h through 6 h ($V_t$) post induction of edema.

Percent inflammation was calculated as % edema inhibition as shown in the equation below:

$$\% \text{ inflammation} = \frac{V_o - V_t}{V_o} \times 100 \quad \text{......................... \quad Eq 1}$$

$$\% \text{ inflammation} = \frac{\text{Average inflammation of treated group at time } t}{\text{Average inflammation of negative control at time } t} \times 100 \quad \text{........ \quad Eq 2}$$

Where $V_t$ is the volume of oedema in reference group at time $t$ and $V_o$ is the volume of edema in control rats at the same time.\(^{[14]}\)

The percentage inflammation can be calculated using the formula above.

**RESULTS**

**Pseudoternary phase diagram**

Figures 1-4 show the pseudoternary phase diagrams of blends of oil surfactant and cosurfactant. The black circles in Figures 1 and 2 represent areas where oil, surfactant and cosurfactant blends would exhibit stable emulsion characteristics whereas the white circles indicate areas occupied by unstable preparations. In Figures 3 and 4 the delineated small regions represent self-emulsifying domains.
Figure 2: Pseudo-ternary phase diagram of SEDDS prepared with Labrafac Lipophile/Pecol as oil phase, Labrasol as surfactant and Lauroglycol 90 as cosurfactant. Black circles show isotropic pre-concentrates while white circles show biphasic regions.

Figure 3: Pseudoternary phase diagram for SEDDS prepared with Labrafac Lipophile as oil phase, Labrasol/Lauroglycol 90 as surfactant phase and water.

Figure 4: Pseudoternary phase diagram for SEDDS prepared with Labrafac Lipophile/Pecol oil phase, Labrasol/Lauroglycol 90 as surfactant phase and water.
Particle size, polydispersity index and zeta potential values

Table 3: Particle size, PDI, Zeta Potential for batches with oil blends (LP)

<table>
<thead>
<tr>
<th>Batches</th>
<th>Size (nm)</th>
<th>PDI</th>
<th>Zeta potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP 10:80:10</td>
<td>6197 ± 382.5</td>
<td>1 ± 0</td>
<td>-12.9 ± 1.27</td>
</tr>
<tr>
<td>LP 10:70:20</td>
<td>5312 ± 1625</td>
<td>1 ± 0</td>
<td>-19.7 ± 0.28</td>
</tr>
<tr>
<td>LP 20:70:10</td>
<td>6793 ± 618</td>
<td>0.9 ± 0.12</td>
<td>-27.5 ± 0.56</td>
</tr>
<tr>
<td>LP 10:60:30</td>
<td>6952 ± 2764</td>
<td>0.31 ± 0.2</td>
<td>7.58 ± 1.3</td>
</tr>
<tr>
<td>LP 30:60:10</td>
<td>3036.4 ± 224.9</td>
<td>1 ± 0</td>
<td>-42.3 ± 0.69</td>
</tr>
</tbody>
</table>

Table 4: Particle size, PDI, Zeta potential for batches with single oil (L)

<table>
<thead>
<tr>
<th>Batches</th>
<th>Size (nm)</th>
<th>PDI</th>
<th>Zeta Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L 10:80:10</td>
<td>1070 ± 258.4</td>
<td>0.94 ± 0.1</td>
<td>-5.65 ± 0.99</td>
</tr>
<tr>
<td>L 10:70:20</td>
<td>2640 ± 83.3</td>
<td>0.91 ± 0.09</td>
<td>-18.9 ± 0.73</td>
</tr>
<tr>
<td>L 20:70:10</td>
<td>1968 ± 419.2</td>
<td>0.98 ± 0.03</td>
<td>-14.1 ± 1.94</td>
</tr>
<tr>
<td>L 20:60:20</td>
<td>4648 ± 789</td>
<td>0.39 ± 0.1</td>
<td>-30.2 ± 0.46</td>
</tr>
<tr>
<td>L 20:50:30</td>
<td>4676 ± 1149</td>
<td>0.35 ± 0.1</td>
<td>25.3 ± 0.48</td>
</tr>
</tbody>
</table>

*PDI = Polydispersity Index

Emulsification time

The batches containing labrafac had the highest emulsification time of 51.5±1 seconds; the next to it was 50.5 ± 1 seconds. On the other hand for labrafac/peceol-containing batches, the highest emulsification time was 54.5 ± 0.5 sec, followed by 51.5 ± 2 seconds.

Loading efficiency (%)

Batch 1 containing labrafac lipophil had the highest loading efficiency (LE) (Figure 1) while batches 2 and 5 recorded the least values. Out of the SEDDS containing oil blend batch A recorded the highest value while batch E the least.

Table 5: Showing Loading Efficiency values

<table>
<thead>
<tr>
<th>SEDDS containing labrafac</th>
<th>SEDDS containing labrafac/peceole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>Oil:Surf:Cosurf</td>
</tr>
<tr>
<td>1</td>
<td>10:80:10</td>
</tr>
<tr>
<td>2</td>
<td>10:70:20</td>
</tr>
<tr>
<td>3</td>
<td>20:70:10</td>
</tr>
<tr>
<td>4</td>
<td>20:60:20</td>
</tr>
<tr>
<td>5</td>
<td>20:50:30</td>
</tr>
</tbody>
</table>

Infinite aqueous dilution

All the batches containing labrafac lipophile and its blend with peceol demonstrated no phase separation on dilution with water.
In vitro Dissolution

The in vitro release results are represented graphically below. The release profiles of both batches as shown in Fig 5 indicated the same $T_{50}$ and $T_{85}$ values of approximately 3 minutes and 5 minutes respectively.

Anti inflammatory studies

The percentage inflammation recorded from 30 minutes through 6 hours was recorded. The results are summarized in the table below:

Table 6: Showing % Inflammation

<table>
<thead>
<tr>
<th>Batch</th>
<th>$\frac{1}{2}$ h</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>5 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive control</td>
<td>180.7±2</td>
<td>177.0±1.4</td>
<td>156.6±3</td>
<td>136.9±1.7</td>
<td>108±2.5</td>
<td>70.8±2</td>
<td>62.0±1</td>
</tr>
<tr>
<td>SEDD T₁</td>
<td>168.7±3</td>
<td>156.6±0.9</td>
<td>156.6±1</td>
<td>136.9±2.2</td>
<td>120±2</td>
<td>70.8±3.5</td>
<td>32.7±3</td>
</tr>
<tr>
<td>SEDD T₂</td>
<td>171.0±1</td>
<td>159.0±0.6</td>
<td>134.9±2</td>
<td>126.0±3</td>
<td>110±1</td>
<td>69.9±2</td>
<td>57.5±2</td>
</tr>
</tbody>
</table>

DISCUSSION

Pseudoternary phase diagram

The pseudoternary phase diagram construction was to determine stable isotropic mixtures of oil and surfactant. Subsequently the optimal formulations were identified and used for further formulations. Actually after phase diagram construction the plot delineates a self emulsifying region that is informative of stable batches. It is from the several options that an optimal batch is chosen. However in this work we preferred to utilize all the batches that were stable.

Visual isotropicity

The visual isotropicity observed in the batches is confirmatory of appropriate choice of excipients and their corresponding ratios. Phase separation or creaming bespeaks of emulsion
instability and loss of isotropicity. Furthermore, transparent oil, surfactant and cosurfactant that combine to result into a coloured mixture is outrightly nonisotropic. This is why preliminary studies are inevitable in SEDDS formulations.

**Particle Size Analysis, Polydispersity Index (PDI), Zetapotential**

The droplet sizes of the SEDDS were above 1000 nm. The SEDDS formulations containing single oil had significantly (p<0.05) smaller droplet sizes compared to the formulations with oil blends. PDI results depicted size variation within each batch. PDI runs on a scale of 0-1.0 with lower values signifying tendency toward monodispersity.\(^{[15]}\) Negative zeta potential of oil-in-water emulsions is a common phenomenon, attributed to the fatty acid component of triglycerides. All the zeta potentials were negative, except for batches (20:50:30) and LP (10:60:30). This charge discrepancy may be attributed to the high concentration of the oily cosurfactant.

**Emulsification time**

The rate of emulsification is an important index for the assessment of the efficacy of emulsification and disintegration.\(^{[16,17]}\) The importance of this is that the formulation should disperse completely and quickly when subjected to aqueous dilution under mild agitation. A time of 2 mins has been used as evaluation index in emulsification process.\(^{[18]}\) The result obtained showed that all the batches have emulsification time less than one minute as fast emulsification cause rapid drug release which results in an increased oral absorption, bioavailability and efficacy.

**Aqueous dilution**

Infinite aqueous dilution test seeks to investigate the stability status of SEDDS when diluted with water. In the GIT the SEDDS intimate contact with aqueous phase initiates emulsification and dilution is a critical test that talks about the inseparability nature of a stable emulsion. Stability of emulsion remains a factor in the investigation of an emulsion. In the result obtained, dilution of the SEDDS even up to 1000\(^{th}\) ml mark, showed no phase separation on the different batches. That shows that microemulsion or SEDDS prepared were very stable.

**Loading efficiency**

The unit dose of Ibuprofen in the various SEDDS formulated was 100 mg. The results showed loading efficiency between 82% - 97%, with highest loading efficiency of 97% for
batch L (10:80:10) and 95% for batch LP (10:80:10). Generally there was good drug loading in the droplets of the SEDDS.

**Anti-inflammatory studies**

The positive control ibuprofen is a known poorly soluble drug that may suffer from inconsistent bioavailability owing to inconsistent dissolution and absorption. It is well established that dissolution is the rate limiting step to absorption. Therefore a formulation design like SEDDS that presents the drug as dissolved liquid droplets overcomes the physicochemical limitation of the ibuprofen powder. This was why the SEDDS formulations enhanced anti-inflammatory effect. On the other hand T2 was observed to maintain significantly higher (p<0.05) anti-inflammation for up to 3 h because of its oil blend comprising of medium and long chain triglycerides. This is likely to combine the absorption characteristics profile of both medium and long chain fatty acids. The presence of long chain triglycerides may have promoted lymphatic drug transport while the medium chain fatty acid may be responsible for improved absorption. Drug transport via the lymphatic system avoids first pass effect and may consequently result to increased plasma concentration and faster on set of action.

**CONCLUSION**

Blending of two oils in the formulation of ibuprofen SEDDS contributed to improved anti-inflammatory activity of ibuprofen while increasing droplet size.

**ACKNOWLEDGEMENT**

Labrafac lipophile®, labrasol®, lauroglycol® 90 and peceol® were kind gift samples from Gateffose, France

**REFERENCES**


