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COMPARATIVE EVALUATION OF SELF-EMULSIFYING FORMULATIONS OF ARTEMETHER AND PIROXICAM.

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) are homogenous, single-phased blends of oil, surfactant and co-sourfactants used to solubilize drugs for improved bioavailability. The aim of this study is to prepare and evaluate artemether and piroxicam self-emulsifying drug delivery systems developed with glycerol monooleate (Peceol®), caprylocaproyl macrogol-8-glyceride (Labrasol®), diethylene glycol monoethyl ether (Transcutol®) and irvingia lipid for improved bioavailability. Solubility of artemether and piroxicam was studied in different lipids, surfactants and solvents by shake flask method, and pseudoternary phase diagrams were constructed by water titration method. Physicochemical properties, stability, self-emulsification, and drug delivery and dispersion were assessed. The drug-loaded self-emulsifying formulations were stable, very flowable with average self-emulsification time of 7.3 sec and 9.7 sec for artemether-loaded peceol and irvingia fat/wax SEDDS respectively, whereas piroxicam-based SEDDS prepared with peceol and irvingia fat/wax emulsified after 5.7 sec and 9.3 sec, respectively. Formulations containing 1:3 peceol/surfactant mixture showed up to 98% drug released and dispersed after 12 min. The formulated artemether and piroxicam SEDDS were stable, easily self-emulsifying and provide adequate drug release and dispersion.

KEYWORD: Self-emulsifying; surfactant; dispersion.

INTRODUCTION

Self-emulsifying drug delivery systems are usually oil-rich blends of oil, surfactant, co-solvent and solubilized drug (s) that appear as clear isotropic dispersions (Gursoy et al., 2004). Upon dispersion in water or aqueous environment with mild stirring or agitation, these preparations transform into oil-in-water (O/W) emulsions with fine droplets of measurable sizes containing possibly entrapped drugs.

The limited dissolution rate caused by low solubility attributes of some drugs usually result in low bioavailability of these drugs when administered orally, and compounds with aqueous solubility lower than 100 µg/ml commonly have dissolution-limited absorption (Horter and Dressman 2001). Lipid-based drug delivery systems present a channel for effective administration of lipophilic drugs since the drug will be solubilized in tiny lipid matrices or globules to facilitate solubilization in gastro-intestinal fluid and eventual absorption into systemic circulation. Lipid-based formulations of drugs such as SEDDS are very effective in enhancing drug solubility (Wu et al., 2006), and the motility of the GIT provides adequate and continuous agitation for self-emulsification (Elnaggar et al., 2009). Although solid lipids are effective drug carriers when controlled or targeted delivery is desired, self- emulsifying drug delivery systems seem favoured where immediate release and effect is the paramount objective.

Artemether and piroxicam are commonly used for the treatment of malaria and inflammation, respectively. These two drugs have different solubilities and physico-chemical behaviours, and a study of the application of SEDDS in the delivery of these drugs is desirable for improved immediate release and bioavailability of these drugs. Homogenous mixtures of oils, surfactants, co-surfactants and the drugs, and their effective application as dosage forms depend on the solubilities of the drugs in the oily mixtures since this will consequently determine the volume of the formulations required to obtain the needed doses. These drugs can be dissolved in self-emulsifying anhydrous vehicles that allow its filling into gelatin capsules. It is interesting to understand how solubility and nature of drug can affect the characteristics of self-emulsifying oil formulations. The aim of this research is to prepare, characterize and compare the properties of SEDDS loaded with different drugs of varied properties.

MATERIALS AND METHODS

Materials

Artemether (Hangzhou Dayang Chemical, China), Piroxicam (Pauco Pharmaceuticals, Awka, Nigeria) Peceol® - glycerol monooleate, Labrasol® - caprylocaproyl macrogol-8- glyceride, Transcutol® - diethylene glycol monoethyl ether (Gattefosse, St. Priest, France). All other reagents and solvents were analytical grade. Irvingia fat was prepared in Department of Pharmaceutical Technology and Industrial Pharmacy laboratory, University of Nigeria, Nsukka from the nuts of *Irvingia gabonensis var. excelsa*.

Methods

Solubility of artemether and piroxicam in select oils, surfactant and co-surfactant

Solubility studies of artemether and piroxicam in Peceol ®, Labrasol ®, Transcutol ®, different oil-surfactant mixtures and irvingia fat were done by shake flask method. The solubility was observed visually by first saturating the select vehicle with a known weight of the drug and subsequently adding an increasing dropwise quantities of the medium with continuous mixing. The samples were allowed to equilibrate for 24 h before further addition of medium until complete dissolution of drug. The solubility study was then performed using the shake flask method. An excess of each of artemether and piroxicam was added to 5 ml of oil, surfactants and oil/ surfactant mix in a screw capped tube and mixed. The tubes were then kept at 37±1 °C in an isothermal water-bath shaker for 24 h after which each sample was centrifuged. The resulting supernatant was filtered, diluted appropriately with 0.1 M methanolic HCl (piroxicam test solution) and 1 M methanolic HCl and heated at 60 ±2 °C for 3 h (artemether test solution). Thereafter, the test solutions were analyzed using the UV-VIS spectrophotometer at wavelengths of 330 nm (piroxicam) and 254 nm (artemether). The solubility of the drugs was evaluated in irvingia fat at 50 °C.

Construction of pseudoternary phase diagrams

The pseudoternary phase diagrams were constructed using the water titration method. Different SEDDS were prepared using mixtures of varying oil/surfactant (or surfactant, S_{mix}) in mass ratios of 9:1 to 1:9. A 3:1 mass ratio of surfactant to co-surfactant was applied based on result from our previous study (Agubata et al. 2014). Each pre-concentrate mixture was titrated dropwise with distilled water at room temperature and agitated after addition of each drop (14 µL). Peceol oil, Labrasol/ Transcutol were studied to understand outcomes using liquid oil. However, irvingia fat was also mixed with the surfactants and studied for solid lipid investigation in which case the water titration was done with the system maintained at 50 °C. The pseudoternary phase diagram was constructed to dileanate the area of microemulsion and boundary of phases, and the diagram was plotted using SigmaPlot software.

Determination of Surfactant efficiency (S_{min})

The surfactant efficiency was determined at equal oil to water weight fractions as the amount of surfactant (surfactant mix) required to completely homogenize the oil/water mixture (Sjoblom et al., 1996). The surfactant efficiency of the surfactants or S_{mix} was determined at ambient temperature (25±1 °C) for peceol-based formulations and investigated at 50 °C for irvingia fat-based systems. The S_{min} is determined as the minimum concentration of the surfactant needed to create a monophasic microemulsion (S_{min}, %w/w). This can also be roughly deduced from graph extrapolation. The transparent samples containing surfactant at levels equivalent to S_{min} were allowed to equilibrate for 72 h and examined for transparency.

Formulation of unloaded self-emulsifying drug delivery systems

Optimized quantities of Peceol® (oil), Labrasol® (surfactant) and Transcutol® (co-surfactant) were mixed together in different selected ratios to obtain homogenous self-emulsifying systems (Table). The experimental design involved mixtures of varied quantities of Peceol and surfactant mix at 4:6, 1:2 and 1:3 ratios while the labrasol and transcutol were in a fixed 3:1 (K_{min}) mixture. Irvingia fat-based SEDDS pre-concentrate were also formulated at 50 °C by mixing Liquified irvingia fat/wax with the surfactant mix before allowing to cool to ambient temperature.

TEST FOR PHASE SEPARATION AND SELF-EMULSIFICATION TIME OF UNLOADED SEDDS

Phase separation

A 2 g quantity of each formulation was stored for 48 h at 25 °C and observed for phase separation. Also 1 g sample of each SEDDS batch was diluted with 10 ml and 100 ml distilled water at 25 °C, stored for 24 h and examined for phase separation.

Self-emulsification time

Self-emulsification of the formulations was evaluated using a magnetic stirrer – beaker apparatus. A 1 g portion of each self-emulsifying formulation was added to 250 ml of distilled water, stirred at 50 rpm and maintained at 37±1 °C while being timed. The self-emulsification time was taken as the time for an oily pre-concentrate to form a homogenous mixture upon dilution.

Formulation of artemether and piroxicam self-emulsifying formulations

Artemether and piroxicam were each dissolved in specified quantities of Peceol® oil (Table 1 and 2). The dispersions were continuously stirred for 2 h and thereafter stored for 24 h to facilitate complete dissolution. Labrasol and transcutol were added and mixed adequately until a transparent and homogenous sample was achieved.

Table 1: Quantities of Oil, surfactant, co-surfactant and fat used for SEDDS.

Oil/Surfactant Mix ratio	Km	Peceol (g)	Labrasol (g)	Transcutol (g)	Irvingia fat (g)
4:6	3:1	0.40	0.45	0.15	---
1.2	3:1	0.33	0.50	0.17	---
1:3	3:1	0.25	0.56	0.19	---
4:6	3:1	--	0.45	0.15	0.40
1:2	3:1	--	0.50	0.17	0.33
1:3	3:1	--	0.56	0.19	0.25

Table 2: Artemether and piroxicam self-emulsifying formulations.

Code	Drug	Drug amount (mg)	Peceol (g)	Labrasol (g)	Transcutol (g)	Irvingia fat (g)
A-PLT1	Artemether	67	0.40	0.45	0.15	---
A-PLT2	Artemether	67	0.33	0.50	0.17	---
A-PLT3	Artemether	67	0.25	0.56	0.19	---
A-LTI1	Artemether	67	--	0.45	0.15	0.40
A-LTI2	Artemether	67	--	0.50	0.17	0.33
A-LTI3	Artemether	67	--	0.56	0.19	0.25
P-PLT1	Piroxicam	2.5	0.40	0.45	0.15	---
P-PLT2	Piroxicam	2.5	0.33	0.50	0.17	---
P-PLT3	Piroxicam	2.5	0.25	0.56	0.19	---
P-LTI1	Piroxicam	2.5	--	0.45	0.15	0.40
P-LTI2	Piroxicam	2.5	--	0.50	0.17	0.33
P-LTI3	Piroxicam	2.5	--	0.56	0.19	0.25

The pH and viscosity of test samples

The pH of the SEDDS samples was evaluated using a validated pH meter (HANNA Instruments, Padova, Italy). The instrument electrode was immersed into 50 ml quantities of each formulation and the reading recorded. Each measurement was taken in triplicate and the average and standard deviation calculated.

The viscosity of the self-emulsifying formulations was measured using an Ostwald u-tube viscometer suspended in a thermo-regulated water-bath maintained at ambient temperature (25 °C). The time of flow was recorded, and average of triplicate measurements was calculated. The result was related to flow times of water.

STABILITY STUDIES OF ARTEMETHER AND PIROXICAM-LOADED SEDDS

Phase separation and drug precipitation

Phase separation was investigated as earlier described by storage and dilution. Drug precipitation in 2 g of test samples was visually examined after storage at 25 ℃ for 48 h and after a 1:10 and 1:100 dilution with distilled water and subsequent storage at 25 ℃ for 48 h.

Refrigeration-thaw cycle

Some 2 g artemether and piroxicam test SEDDS samples in transparent screw capped bottles were stored in a refrigerator at 4 ℃ for 24 h after which these were withdrawn and stored at 25 ℃ and 40 °C. A single refrigeration thaw cycle test was performed. The samples were then observed for phase separation and drug precipitation as described earlier.

Centrifugation

A 5 ml sample of each formulation was transferred into a clean glass test tube and inserted to laboratory centrifuge (Uniscope SM800B, England). Centrifugation was done at 4,000 rpm for 5 min and samples observed thereafter for phase separation and drug precipitation.

Test for self-emulsification time of drug-loaded SEDDS

Self-emulsification of the loaded formulations was studied using a magnetic stirrer–beaker apparatus as described. A 1 g of each of artemether and piroxicam-loaded SEDDS was added into a beaker containing 250 ml of distilled water, stirred at 50 rpm and maintained at 37 ± 1 °C.

Drug release and dispersion of encapsulated SEDDS

Drug release and dispersion studies was performed using a magnetic stirrer-beaker assembly. Test capsules containing the different drugs and vehicles were introduced into 250 ml SGF in a beaker maintained at 37 ± 1 °C and stirred at 50 rpm. Test solutions (5 ml) were withdrawn at 2 min interval and replaced with 5 ml of fresh SGF. For artemether samples, the solutions were heated with 1N HCl (5 ml) at 80 °C for a period of 30 min, cooled to 25 °C and diluted with distilled water to 20 ml. The treated test solutions were filtered and assayed at 254 nm using the UV-VIS spectrophotometer. For piroxicam samples, the solutions were diluted appropriately with 0.1 M methanolic HCl and analyzed at wavelengths of 330 nm.

RESULTS AND DISCUSSIONS

Solubility

The solubility of artemether in Peceol was 64.5 mg/ml, which would easily allow capsule filling with volume constraint based on size of common oral hard capsules. Higher solubilities were observed for Transcutol (285 mg/ml), Labrasol (135 mg/ml), Pec-S 4:6 (220 mg/ml)) and Pec-S 1:3 (223 mg/ml) as expressed in fig.1. The chemical nature of these vehicles allowed for improved solubility of artemether. The solubility of artemether in molten irvingia fat/wax (667 mg/ml) was significantly higher than the ones obtained with other vehicles studied. However, the solubility study for irvinigia fat was done at elevated temperature since it presents as solid at room temperature (25 °C) and this may be responsible for this increased solubility. Artemether is methyl ether derivatives of dihydroartemisinin and it is usually administered dissolved in oils for oral or imtramuscular administration. The solubility of piroxicam in peceol, labrasol, transcutol, Pec-S 4:6, Pec-S 1:3 and irvingia fat/wax are 3.45, 7.3, 8.3, 10.5, 11 and 2.4 mg/ml, respectively (fig. 2). Piroxicam is very much less soluble in the vehicles studied and this imply that only a low dose can be filled into capsules.

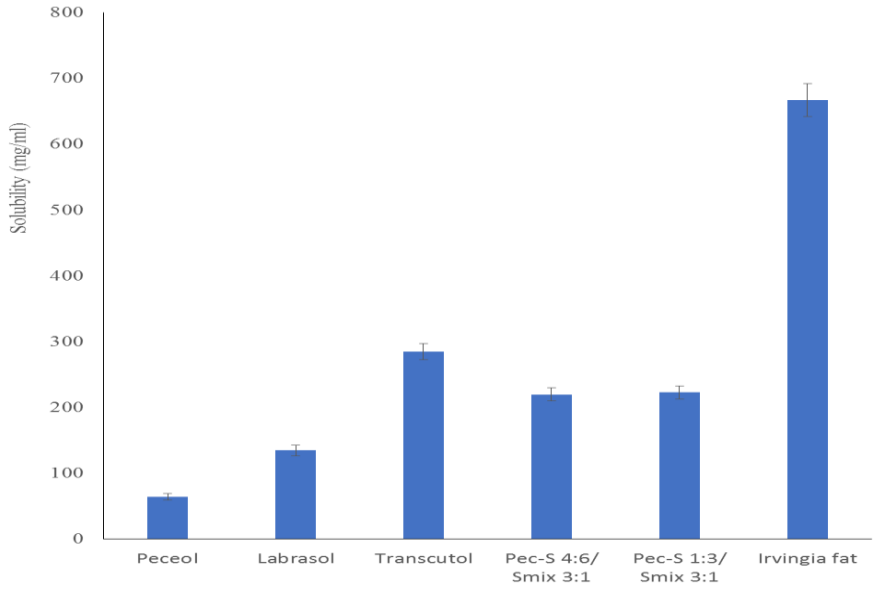


Fig. 1: Solubility of artemether in selected vehicles

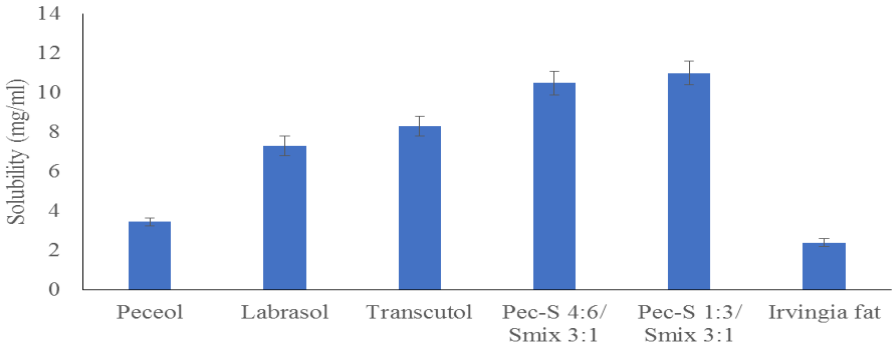


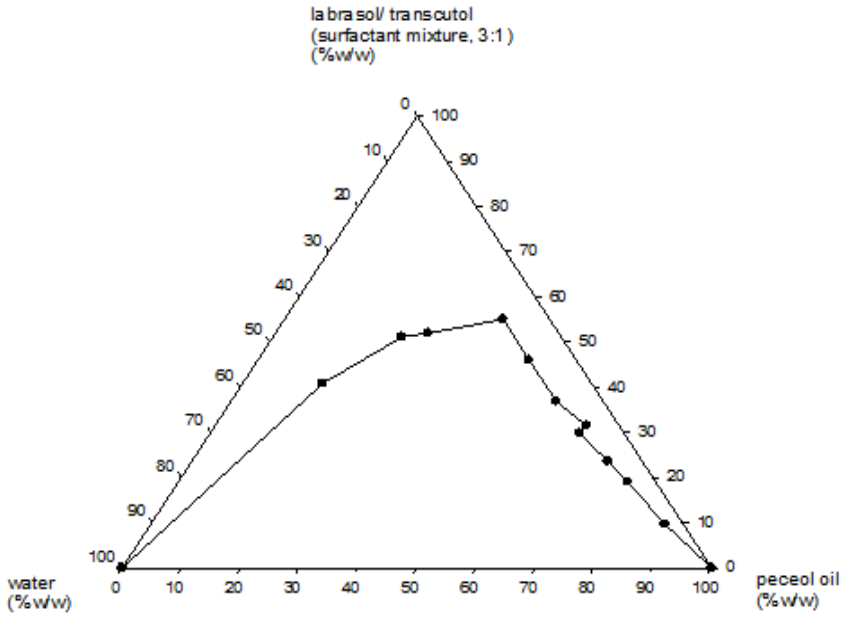
Fig. 2: Solubility of piroxicam in selected vehicles

Pseudoternary phase diagram and surfactant efficiency

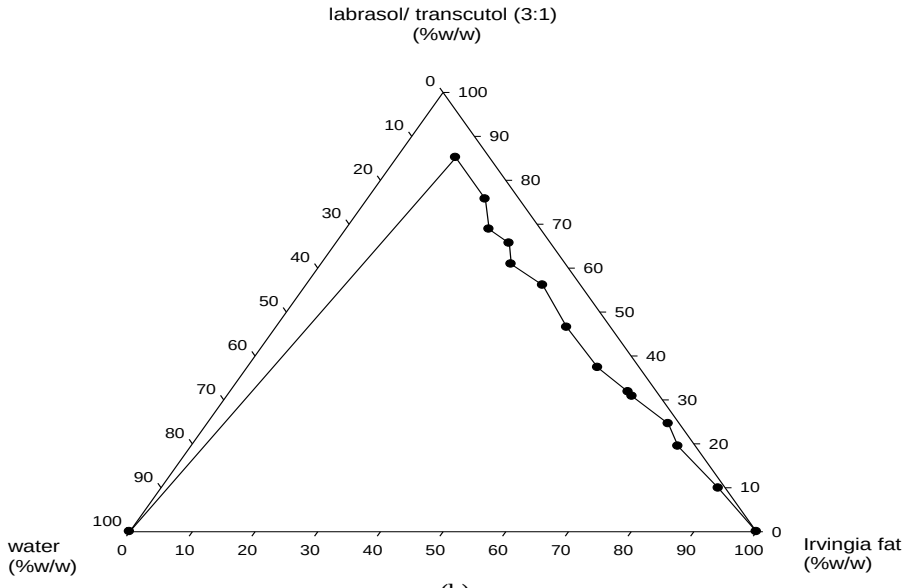
The pseudoternary phase diagrams showed that the zone of microemulsion (upper zone) was larger in peceol/labrasol/transcutol system than in the irvingia fat/labrasol/transcutol system (fig. 3). This imply that more mixtures can be derived from the former system that can form microemulsions upon dispersion in water. The reduced ease of forming microemulsion in irvingia fat-based systems may be attributed to its tendency to solidify or become viscous which seem opposite to the dynamic spread observed in self-emulsification. Pre-concentrates with very high surfactant or Smix remained as microemulsion even upon infinite water titration or dilution.

Increasing the concentration of surfactant or S_{mix} have been shown to decrease droplet size and vice versa (CzajkowskaKosnik et al., 2015), and this could cause the expansion of the microemulsion zone.

A surfactant efficiency of 52 % w/w was observed for the peceol/labrasol/transcutol system whereas irvingia fat-based systems had S_{min} value of 85 % w/w. Lower S_{min} values show improved surfactant efficiency of the system. Therefore, the surfactant/co-surfactant mixtures showed higher capacity (low minimum concentrations) to solubilize and emulsify peceol-water than irvingia-water mixtures



(a)



(b)

Fig. 3: Pseudoternary phase diagram of peceol/labrasol-transcutol/water system (a) and irvingia fat/labrasol-transcutol/water system (b).

Phase separation and drug precipitation

The Self-emulsifying formulations did not show any phase separation both for drug-free formulations and drug-loaded ones. The samples remained single-phased and homogenous throughout the observed storage period (48 h), after low dilution, single refrigeration thaw cycle and centrifugation. Furthermore, no drug precipitation was observed. However, higher level of dilution (1:100) caused cloudy formulations and post-dilution phase separation was observed in SEDDS prepared with irvingia lipid and 4:6 mixtures of Peceol/ Smix. The thermodynamics studies were used to evaluate the kinetic stability of the system. Temperature changes affects and adjusts the equilibrium state of thermodynamically stable formulation (Anton and Vandamme 2010; Rehman et al., 2022).

The pH and viscosity of formulations

The pH of artemether and piroxicam SEDDS was approximately 5. This shows the formulations were slightly acidic. Oils are usually slightly acidic This property allows the formulations to be orally ingested safely. The acidity of the oils might have facilitated the solubility of artemether in in them considering the drug is basic although artemether also has intrinsic lipid solubility. The formulations were free flowing although those prepared with irvingia fat/wax thickened.

The viscosity of the preparations are presented in Table 3.

Self-emulsification time

SEDDS prepared with Peceol-Labrasol-Transcutol system emulsified within 8 seconds. Artemether-loaded formulations prepared with Peceol had self-emulsification times longer than those of piroxicam-based SEDDS (Table 3) and this may be caused by higher artemether content in the former which could be attributed to higher solubility of artemether in the vehicles. However, no significant difference ($p<0.05$) was observed in self-emulsification times of irvingia lipid-based SEDDS and this could be showing that the solidifying nature of the irvingia lipid is the most critical determinant of rate of self-emulsification. As the difference in amounts of the oil and surfactant increases (eg 1:3), there is observable difference in self-emulsification time.

Table 3: Viscosity and self-emulsification time of the lipid formulations.

Code	Viscosity (cP)	Self-emulsification time (Sec)
A-PLT1	32	7
A-PLT2	30	7
A-PLT3	30	8
A-LTI1	38	10
A-LTI2	37	10
A-LTI3	37	9
P-PLT1	30	6
P-PLT2	28	6
P-PLT3	27	5
P-LTI1	37	10
P-LTI2	36	9
P-LTI3	35	9

Drug release and dispersion profile of artemether and piroxicam self-emulsifying capsules

In both artemether and piroxicam self-emulsifying capsules (SE-capsules), the capsules prepared with 1:3 peceol/Smix released the highest amounts of their drug content with 98% released in 12 min for artemether whereas in the case of piroxicam 99 % was released after 12 min (fig. 4 and 5). The low dose of piroxicam in the capsules relative to artemether also influenced its release pattern. In both artemether and piroxicam, drug release was higher in Peceol/ S_{mix} systems than the irvingia/ S_{mix} system. The lower self-emulsification time of the Peceol/S_{mix} system could have contributed to this observed pattern. Higher change in entropy and formation of liquid crystalline phase improve the ease of emulsification which consequently increases drug dispersion (Agubata 2020). However, the irvingia fat-based SEDDS may exist as tiny solid particles surrounded by surfactant mixture at room temperature (25 °C) in which case the particles will soften at the study temperature of 37 °C then release and disperse their entrapped drug slowly.

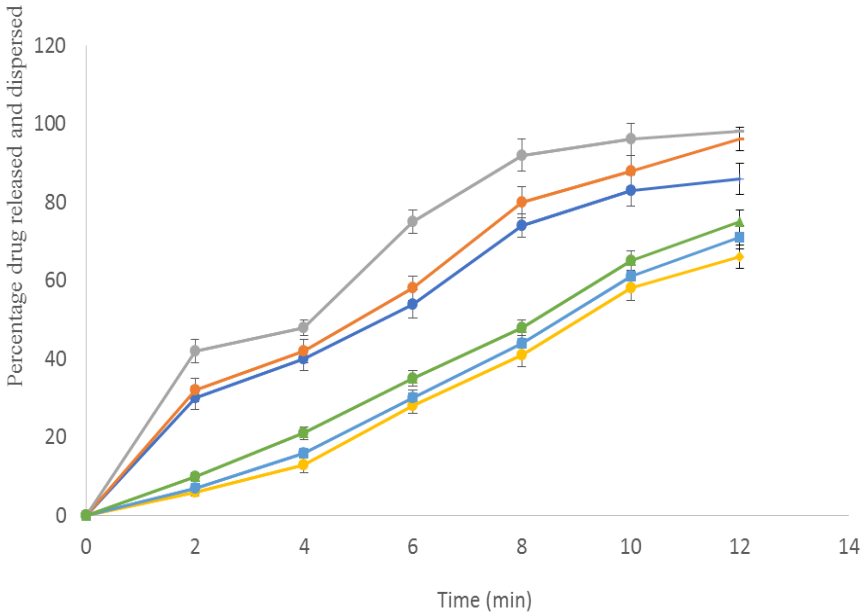


Fig. 4: Release and dispersion profile of artemether SE-capsules

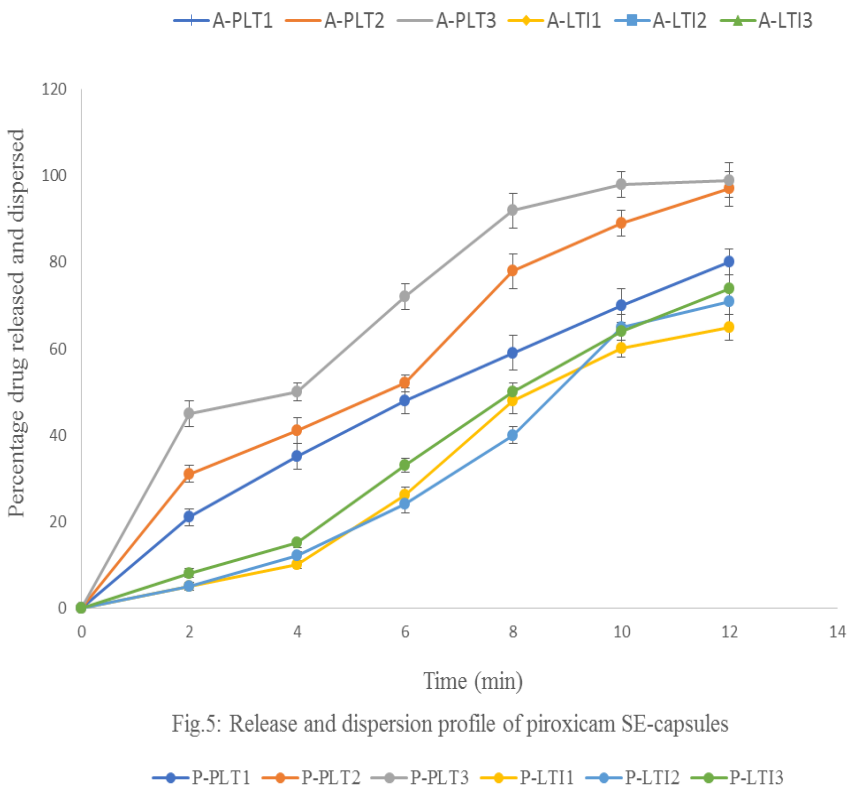


Fig.5: Release and dispersion profile of piroxicam SE-capsules

CONCLUSION

Artemether and piroxicam SEDDS were prepared, characterized and comparatively evaluated for improved delivery of artemether and piroxicam, respectively. Solubility, physicochemical properties, stability, self-emulsification, drug release and dispersion were favourable for formulation of effective and safe drug delivery systems.

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REFERENCE

1. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2004; 58: 173–182.
2. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. Adv Drug Deliv Rev., 2001; 46: 75–87.
3. Wu W, Wang Y, Que L. Enhanced bioavailability of silymarin by self- microemulsifying drug delivery system. Eur. J. Pharm. Biopharm., 2006; 63: 288–294. doi:10.1016/j.ejpb.2005.12.005
4. Elnaggar YS, El-Massik M.A, Abdallah OY. Self-nanoemulsifying drug delivery systems of tamoxifen citrate: design and optimization. Int. J. Pharm., 2009; 380: 133–141. doi:10.1016/j.ijpharm.2009.07.015
5. Sjoblom J, Lindbergh R, Friberg SE. Microemulsions–phase equilibria characterization, structures, applications and chemical reactions. Adv Colloid Interf Sci., 1996; 65: 125-287.
6. Czajkowska-Kosnik A. Szekalska M, Amelian A, Szymanska E, Winnicka K. Development and evaluation of liquid and solid self-emulsifying drug delivery systems for atorvastatin. Molecules, 2015; 21010–21022. doi:10.3390/molecules201219745
7. Agubata C. Self-Emulsifying Formulations: A Pharmaceutical Review. Journal of Drug delivery and Therapeutics, 2020; 10(3): 231-240.
8. Anton N, Vandamme TF. Nano-emulsions and Micro-emulsions: Clarifications of the Critical Differences. Pharm. Res., 2010; 28: 978–985.
9. Rehman FU, Farid A, Shah SU, Dar MJ, Rehman AU, Ahmed N, Rashid SA, Shaukat I, Shah M, Albadrani GM, Kamel M, Altyar AE, Abdel-Daim MM, Shah KU. Self-Emulsifying Drug Delivery Systems (SEDDS): Measuring Energy Dynamics to Determine Thermodynamic and Kinetic Stability. Pharmaceuticals, 2022; 15: 1064. https://doi.org/10.3390/ph15091064
10. Agubata CO, Nzekwe IT, Obitte NC, Ugwu CE, Attama AA, Onunkwo GC. Effect of oil, surfactant and co-surfactant concentrations on the phase behavior, physicochemical properties and drug release from self-emulsifying drug delivery systems. Journal of Drug discovery, Development and Delivery, 2014; 1: 1-7.