

Development and Evaluation of Encapsulated Self-Emulsifying Drug Delivery System of Hydrochlorothiazide

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Formulation of solid self-emulsifying drug delivery system (Solid SEDDS) provides a dual benefit of improved drug stability and enhanced delivery system.

Objective: This study was aimed at developing and evaluating a solid self-emulsifying drug delivery system of hydrochlorothiazide.

Methods: Solubility of hydrochlorothiazide in some oils was determined and pseudo-ternary system of the most effective oil, water and surfactant system was constructed. Four Liquid SEDDSs were formulated to contain Tween 80/oleic acid or PEG 400/oleic acid (surfactant systems) and castor oil combined in ratio 2:8 or 3:7 based on the pseudo-ternary plot. Each preparation was made by adding the drug to the oil/surfactant system and heating up to 60 °C under continuous stirring followed by cooling to room temperature. Viscosity of each Liquid SEDDS was determined; Solid SEDDS was prepared by mixing the Liquid SEDDS with microcrystalline cellulose in 1:2 proportion and then encapsulated. Drug release profile of the Solid SEDDSs in comparison with a marketed product was studied.

Results: Castor oil was found to be the best solvent for hydrochlorothiazide and the viscosity of the Liquid SEDDSs was in the range of 79.41 and 187.32 mPa.s. The *in vitro* release studies showed 85.46 – 87.17 % drug release from the formulated SEDDSs with ratio 3:7 of surfactant mix being superior; and percentage drug release for each formulation was twice that of the marketed product.

Conclusion: The prepared Solid SEDDS of hydrochlorothiazide exhibited improved drug release characteristics, hence superior to the conventional commercial product.

Keywords: Self-emulsifying, Encapsulation, Hydrochlorothiazide, Drug delivery

INTRODUCTION

Enhancing the solubility of poorly water-soluble drugs has been approached by various techniques such as micronization, complexation and solid dispersion (Yadav *et al.*, 2014). Lipid-based formulation is another method of resolving formulation of such poorly water-soluble drugs (Jannin *et al.*, 2015) so as to increase the bioavailability (Cerpňak *et al.*, 2013). Lipid dosage forms include various formulations of therapeutic compounds dissolved in lipid matrices.

Formulation of hydrophobic drugs in this manner improves their solubility and enables them to be administered perorally as a unit dosage form (Khedekar and Mittal, 2013).

Self-emulsifying drug delivery systems (SEDDSs) as lipid-based formulations are characterized by the improvement in the solubility as well as increase in the permeability of the incorporated drug. The presence of the surfactant system reduces the interfacial tension

between the oil and the gastrointestinal fluid to cause emulsification (Olorunsola *et al.*, 2016) and also improves intestinal permeability to enhance absorption (Olorunsola *et al.*, 2017). The increase in the number of compounds that are poorly soluble and/or poorly permeable therefore, has increased the popularity of SEDDSs.

Other benefits of SEDDSs due to the presence of oils and surfactants include modification of drug delivery by moderating gastric residency, stimulation of bile salts and endogenous lipid secretion and stimulation of intestinal lymphatic transport through a reduction in first-pass metabolism (Mistry and Sheth, 2011; Nirosha *et al.*, 2011). Others are changes in the biochemical barrier function of the gastrointestinal tract (GIT) through the activity of efflux pumps, and changes in the physical barrier function of the GIT to improve permeability (Shinde *et al.*, 2020).

Self-emulsifying drug delivery systems are liquid dosage forms; and the development of solid self-emulsifying drug delivery systems (Solid SEDDSs) presents a number of advantages which include improved drug stability and compatibility. The system overcomes the issues associated with liquid formulations, among which are manufacturing challenges and instability.

Solid SEDDS formulation may involve direct conversion of the formulations from the liquid and semi-solid state to the solid forms. This can be

achieved through various solidification methods such as extrusion/spheronization, granulation, spray drying and adsorption onto inert solid substances. Further processing may involve compaction into tablets or filling into capsule shells. Spray drying results in the production of powder that can be processed into tablets or capsules (Cho *et al.*, 2016). Dry emulsions can also be formed by spray-drying or freeze-drying. Pellets can be manufactured using techniques like extrusion or spheronization, fluid bed coating or layering, to provide flexibility in the formulation process (Czajkowska-Kosnik, 2015).

Hydrochlorothiazide, 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide, belongs to the thiazides class of diuretics. It has a low aqueous solubility of 250 µg/mL in 0.1 N hydrochloric acid at 25 °C (Khedekar and Mittal, 2013). Several strategies such as the use of lipidic excipients have been suggested for its delivery (Nipun and Ashraf Islam, 2014; Yadav *et al.*, 2014). Being that hydrochlorothiazide belongs to the BCS (Biopharmaceutics Classification System) Class IV and it is lipophilic, formulation as SEDDS will invariably improve its solubility and permeability due to the presence of the surfactant system (Alebiowu and Femi-Oyewo, 1998). The aim of this work is to formulate the drug as a Solid SEDDS, assess the stability and then determine the release rate in comparison with a marketed product.

METHODOLOGY

Materials

Hydrochlorothiazide powder (Hopkins & Williams, England), castor oil (Halewood Chemicals Ltd., England), peanut oil, olive oil, cod liver oil, coconut oil and oleic acid (Merck, England), polyethylene glycol 400 (Central Drug House Limited, India), Tween 80 (BDH Chemicals, England) and a marketed hydrochlorothiazide tablet formulation registered in Nigeria by the National Agency for Food and Drug Administration and Control (NAFDAC) are some of the materials used for the work. Other materials used are of analytical grade.

Solubility studies

A 2 mL quantity each of castor oil, olive oil, coconut oil, arachis oil and cod liver oil was obtained. Hydrochlorothiazide powder (0.5 g quantity) was added to 2 mL portion of oil in a vial. The vial was corked and the content stirred in a water bath at a temperature of 30 °C for a period of 48 h. The absorbance was read and thereafter related to Beer-Lambert's plot constructed for hydrochlorothiazide

solution in acetone so as to obtain how much of the drug was dissolved in each oil; and the solubility was calculated.

Construction of pseudo-ternary phase diagram

Water titration method was used for constructing the phase diagram of castor oil, water and surfactant/co-surfactant mix (SMIX) as described by Yahaya *et al.* (2020). Two sets of SMIX were obtained (Tween 80/oleic acid and PEG 400/oleic acid separately used as surfactant/co-surfactant system in combination with castor oil as the oil phase).

Surfactant and co-surfactant added in the ratios 1:1, 2:1, 3:1, and 4:1 for the sets while distilled water was added drop by drop to the mixture in the weight ratios of 9: 1, 8: 2, 7: 3, 6: 4, 5: 5, 4: 6, 3: 7, 2: 8, and 1: 9 of oil and surfactant/cosurfactant (SMIX). A magnetic stirrer was used to achieve a proper mixture in each case. Observation of clarity was observed in the mixtures thereafter. Phase diagram was plotted using CHEMIX School 3.50 software (Arne Standnes, Bergen, Norway).

Two pseudo-ternary plots were made; one for castor oil, water and Tween 80/oleic acid, and the second was constructed for castor oil, water and PEG 400/oleic acid. The results were evaluated based on the diagram, and the dark portion was identified as the region for strong emulsification.

Selection of ingredients for the preparation of solid SEDDS formulations

Four SEDDS compositions were selected based on the emulsification region observed in the pseudo-ternary plots. The compositions were as shown in Table 1.

Table 1: Compositions of the various SEDDSs

	Surfactant/Co-surfactant	Ratio of surfactant mix to oil
1	Tween 80/oleic acid	2: 8
2	Tween 80/oleic acid	3: 7
3	PEG 400/oleic acid	2: 8
4	PEG 400/oleic acid	3: 7

Preparation of emulsions

A 30 mL quantity of each SEDDS was prepared; commenced by first calculating the required amount of the emulsifier blend and the amount of the oil based on the formula in Table 1. The emulsifier blend was prepared by mixing the emulsifier and the co-emulsifier together and stirring for 5 min using homogenizer while 0.25 g of the drug was dissolved in the required volume of castor oil.

The delivery system was prepared by adding the oil containing the drug and the surfactant/co-surfactant in a vial and then heating up to 60 °C while stirring continuously. The resulting mixture was mixed thoroughly in a vortex until a clear solution was formed (Yahaya *et al.*, 2020). After a complete dissolution, the mixture was stored at room temperature until required for use.

Viscosity determination and physical examination

Using distilled water, each SEDDS (1 mL) was diluted 10 times in a beaker while constantly stirring with a magnetic stirrer. The viscosity of the emerging emulsion was measured using a viscometer (Model

NDJ-5S, Brookfield, United Kingdom). The physical appearance was also observed (Adedokun *et al.*, 2017).

Granulation and encapsulation

The Solid SEDDSs were obtained by mixing each Liquid SEDDS with microcrystalline cellulose in the ratio 1:2. Microcrystalline cellulose was added to form granules and the granules were dried for 3 h using desiccators before they were filled into empty capsule shells. Formulation quantities of the Solid SEDDS were prepared by incorporating granules equivalent to 25 mg hydrochlorothiazide into hard gelatine shells.

Stability studies

Capsules containing SEDDS formulations were wrapped in aluminium strips, and then stored for three days in a stability chamber after which they were examined for physical stability.

Dissolution studies

Dissolution studies was carried out on three samples from each batch as well as on a marketed hydrochlorothiazide product. One capsule was introduced into each beaker of dissolution apparatus containing 0.1 N hydrochloric acid (HCl). Samples (5 mL) were taken in 10 min intervals for a duration of 60 min. Using Whatman filter paper (No. 2), each of the samples were filtered, and solutions obtained were analysed at the wavelength of 273 nm using an Ultraviolet-spectrophotometer (UNICO UV-2100 PC, Shanghai instrument Co., China). The absorbance of each solution was related to the Beer-Lambert's plot of hydrochlorothiazide solution in acetone in order to obtain the percent drug released. Cumulative percent drug released was plotted against time for each of the formulations on a graph (Olorunsola *et al.*, 2021).

Statistical analysis

Mean and standard deviation were obtained as the data were subjected to the Analysis of Variance (ANOVA) followed by multiple comparison (Tukey-Kramer) using Graph pad software (Instan-3). The significance of difference was taken as p-value < 0.05.

RESULTS AND DISCUSSION

Drug solubility

The solubilities of hydrochlorothiazide in various oils are shown in Table 2.

Table 2: Solubilities of hydrochlorothiazide in the various oils used

S/N	Oil	Solubility (g/L)
1	Olive oil	56.66 ± 1.53
2	Arachis oil	37.33 ± 2.08
3.	Castor oil	147.67 ± 1.53
4	Cod liver oil	28.20 ± 1.00
5	Coconut oil	104.33 ± 3.06

The solubility study was aimed at selecting the appropriate oil for the SEDDS formulation. Hydrochlorothiazide had the highest solubility in

castor oil and the least solubility in cod liver oil. Hence, castor oil is the most suitable for the preparation and was selected for use in the dissolution of the drug and also for the construction of the pseudo-ternary phase diagrams.

Pseudo-ternary phase diagrams

The pseudo-ternary phase plot of castor oil - Tween 80/oleic acid - water system is shown in Figure 1 while that of castor oil - PEG 400/oleic acid - water system is shown in Figure 2. The diagrams represent the emulsion system in two dimensions using three axes.

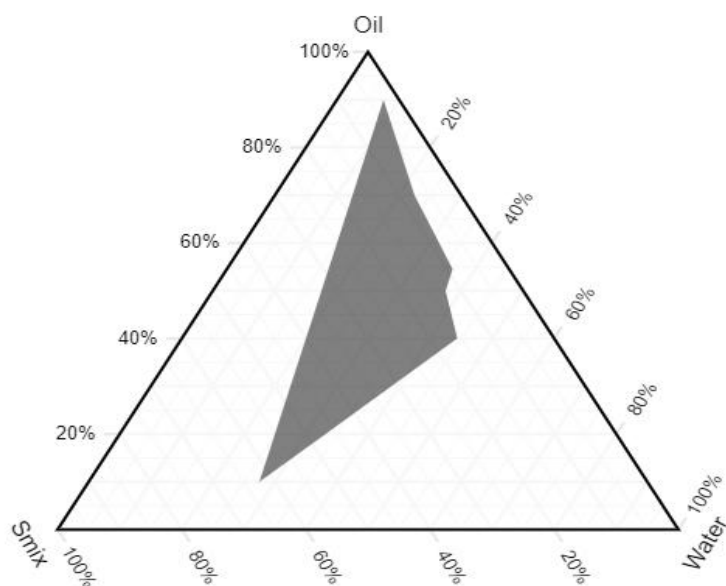


Figure 1: Pseudo-ternary phase diagram of castor oil – Tween 80/oleic acid - water system

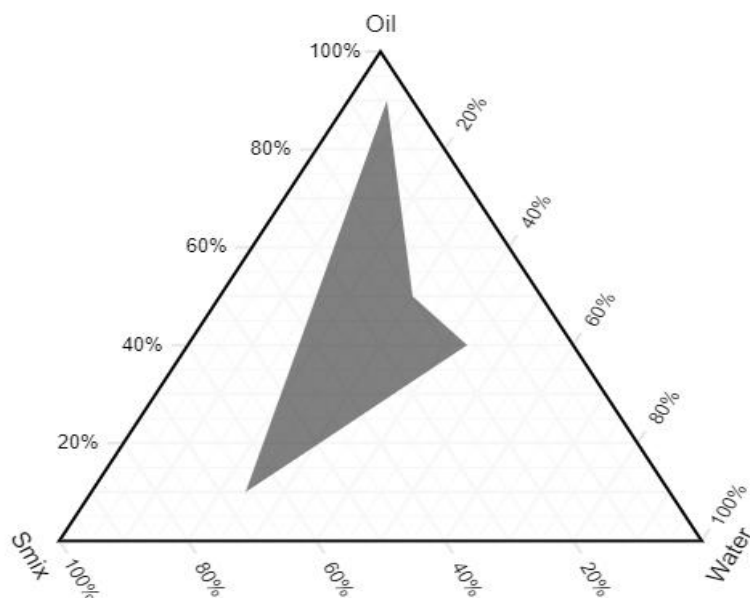


Figure 2: Pseudo-ternary phase diagram of castor oil – PEG 400/oleic acid - water system

The miscibility of the drug component is necessary in deciding the composition of the constituents for the preparation of a SEDDS. A self-emulsifying formulation should be made up of a lipid, co-surfactant and surfactant for the formulation of a clear monophasic drug product (Yahaya *et al.*, 2020). Tween 80 and oleic acid constituted the surfactant mixture (SMIX) for a set of studies while PEG 400 and oleic acid constituted the surfactant mixture for the second set.

From the two plots, any point within the shaded region will give a perfect micro-emulsion (Yahaya *et al.*, 2020). Hence, ratios 2:8 and 3:7 were selected as the ratios of the surfactant-mix to oil for the formulation of the Liquid SEDDSs.

Formulations

The results of the solubility studies on hydrochlorothiazide and the pseudo-ternary plots of the oil, surfactant mix and water provided the basis for

the selection of the ingredients. Castor oil was used as the oil, while Tween 80/oleic acid and PEG 400/oleic acid were separately used as the surfactant mix. The essence of the oil is the dissolution of the drug.

Due to the fact that the surfactant gets selectively absorbed at interfaces, there will be a reduced interfacial energy which in turn poses a mechanical barrier to fusion. This is where the co-surfactant (oleic acid) comes in to play as it helps to achieve emulsion formation which is a prerequisite and also ensures a tightly packed surfactant film, one that is also flexible. Besides, high concentration of surfactants causes gastric irritation. With the co-surfactant, less amount of the surfactant is required; hence the need for the surfactant/co-surfactant system (Khedekar and Mittal, 2013).

Viscosity of the formulations

The viscosity values of the various prepared Liquid SEDDSs are shown in Table 3.

Table 3: Viscosities of the various Liquid SEDDSs

S/N	Surfactant/Co-surfactant	Ratio of surfactant mix to oil	Viscosity (mPa.s)
1	Tween 80/oleic acid	2 : 8	187.32
2	Tween 80/oleic acid	3 : 7	151.10
3	PEG 400/oleic acid	2 : 8	112.73
4	PEG 400/oleic acid	3 : 7	79.41

Viscosity of the SEDDSs was found to be between 79.41 and 187.32 mPa.s. Formulations containing lower amount of surfactant system or higher amount of oil generally had higher viscosity. Also, SEDDSs

containing Tween 80 as surfactant generally had higher viscosity. A higher viscosity implies poorer flow. This reduces the risk of leakage from capsules. On the other hand, low viscosity ensures better

dilution and ease of drug release from formulations. Therefore, formulations containing higher amount of the surfactant which is ratio 3:7 is more likely to produce better drug release.

Product stability

The physical appearances of the SEDDSs before granulation and after encapsulation are shown in Table 4.

Table 4: Physical appearances of the various SEDDSs before granulation and after encapsulation

S/N	Surfactant/Co-surfactant	Ratio of surfactant mix to the oil	Colour of the SEDDS before granulation	Morphology of the capsules
1	Tween 80/oleic acid	2 : 8	White-creamy	Distinct two-layered
2	Tween 80/oleic acid	3 : 7	White-creamy	Distinct two-layered
3	PEG 400/oleic acid	2 : 8	White-creamy	Distinct two-layered
4	PEG 400/oleic acid	3 : 7	White-creamy	Distinct two-layered

The four Liquid SEDDS formulations appeared white-creamy showing emulsification status. Furthermore, no phase difference or drug precipitation was observed with them. They are all stable emulsion systems. This is an indication of the stability of the drug in the Liquid SEDDS formulation.

All the capsules, at the end of the three days, maintained the distinct two-layered structure with no content leakage. There were no observable changes in the appearance of the shells indicating the compatibility of the formulations with the capsule shells.

In vitro dissolution

Drug release profiles of all the formulations and that of a marketed product are shown in Figure 3. The plot shows a constant release of the drug from the Solid SEDDS formulations to the extent of 85.46 – 87.17 %. All the Solid SEDDS formulations showed significantly higher drug release compared to the marketed hydrochlorothiazide tablet which showed drug release of 42% at Time 60 min.

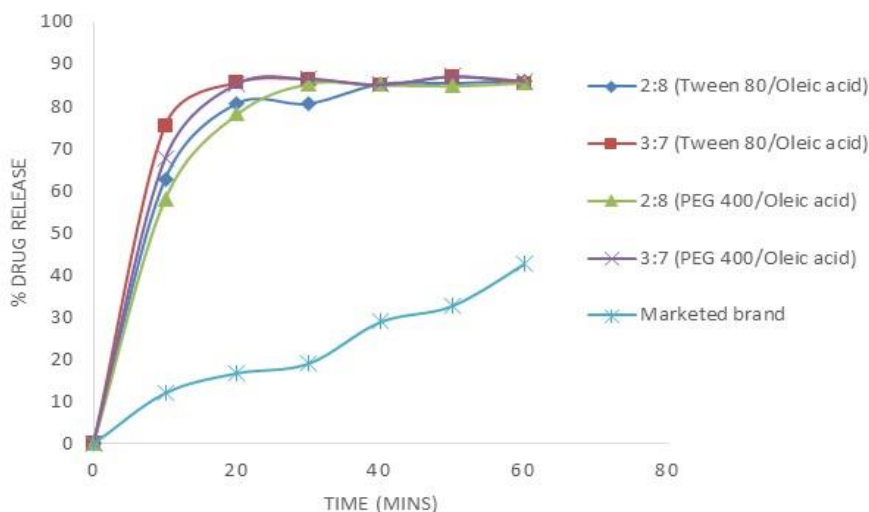


Figure 3: Release profiles of the formulated SEDDSs and that of a marketed hydrochlorothiazide tablet.

Previous work of Matsaridou *et al.* (2012) showed that the properties of SEDDSs are influenced by the nature of the surfactant and the surfactant/oil ratio. In this present work, a direct relationship was observed to exist between the proportion of surfactant in the SEDDS and the rate of drug release from the formulation. The two formulations containing surfactant system to oil ratio as 3:7 (both Tween 80/oleic acid and PEG 40/oleic) had better drug

release compared to the corresponding formulation with ratio of surfactant system to oil as 2:8. This observation is in agreement with the report of Femi-Oyewo (1982) which stated that surfactant facilitates the dissolution of hydrophobic drugs.

The rate of drug release from the formulations was also found to be inversely related to the viscosity of the initial Liquid SEDDSs. The two formulations with surfactant system to oil ratio as 2:8 with the

characteristic higher viscosity had lower drug release compared to the corresponding formulations which showed lower viscosity.

Quick formation of emulsion of Solid SEDDS formulation could be considered as a reason the drug was released into the aqueous solution at a fast rate. The increased rate of release of HCT from SSEDSS

compared to marketed formulation can be explained by the ease of dispersion of the constituents of the SEDDS maintaining the drug in the dissolved state (Balata and Essa, 2016). The more the drug can be maintained in the dissolved state, the better the absorption and the higher the bioavailability (Kohli *et al.*, 2010; Olorunsola *et al.*, 2021).

CONCLUSION

The oil selection process showed castor oil as a superior dissolution oil for hydrochlorothiazide. Both Tween 80/oleic acid and PEG 400/oleic acid combinations can be used as surfactant/co-surfactant systems. Hydrochlorothiazide can be successfully formulated as a self-emulsifying drug delivery system using either of the two surfactant/co-surfactant systems and castor oil in the ratio 2:8 or 3:7. The Solid SEDDS formulations are characterized by good

release to the extent of 85.46-87.17% compared to the marketed tablet which is characterized by 42% drug release. Surfactant mix to oil ratio as 3:7 is better than 2:8 in term of prompt release of the drug for both Tween 80/oleic acid and PEG 400/oleic acid mix. Solid SEDDS formulation using Tween 80/oleic acid or PEG 400/oleic acid is an approach that can be used to address the poor dissolution and low bioavailability of hydrochlorothiazide.

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