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THE USE OF LIQUID SELF-EMULSIFYING DRUG DELIVERY SYSTEMS BASED ON PEANUT OIL/TWEEN 80 IN THE DELIVERY OF GRISEOFULVIN

[*]K. C. Ofokansi, K. I. Chukwu[1], and S. I. Ugwuanyi[1]
Department of Pharmaceutics
[1]Department of Pharmaceutical Technology and Industrial Pharmacy,
Faculty of Pharmaceutical Sciences,
University of Nigeria, Nsukka,
Enugu State, Nigeria

Abstract
Peanut oil and Tween 80 were employed in the formulation of liquid self-emulsifying drug delivery systems (LSEDDS) containing griseofulvin. The LSEDDS were evaluated using the following parameters: phase separation, globule size, viscosity, solubility of griseofulvin and partition coefficient. The release profile of griseofulvin from the optimized LSEDDS was evaluated in acetate buffer solutions of different pH (pH 6.5, 7.4 and 2.0). Results obtained indicated that there was significantly higher (P=0.05) percentage cumulative amounts of griseofulvin released from the LSEDDS in comparison with that released from peanut oil alone. The release of griseofulvin from the LSEDDS into aqueous media of pH 6.5 and pH 7.4 showed enhanced dissolution of the drug from the formulation.

Keywords: *Liquid self-emulsifying drug delivery system*; p*eanut oil*; *Tween 80*; g*riseofulvin*; r*elease profile*

INTRODUCTION

Peroral drug administration is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility. For this class of compounds, defined as "low solubility/high permeability class", dissolution in the lumen environment is the rate-controlling step in the absorption process (Amidon *et al*., 1995). Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles (Aungst, 1993), such as oils (Burcham *et al*., 1997), surfactant dispersions (Serajuddin *et al*.,1988; Aungst *et al*., 1994), self-emulsifying formulation (Wakerly *et al*., 1986; Charman *et al*., 1992; Shah *et al*., 1994; Craig *et al*., 1993), emulsions (Toguchi *et al*., 1990; Palin *et al*., 1986; Myers and Stella, 1992; Stella *et al*., 1978; Kararli *et al*., 1992) and liposomes (Schwendener and Scholt, 1996)]. These formulation approaches have their specific advantages and limitations.

Liquid self-emulsifying drug delivery systems (LSEDDS) have been previously described in the literature as homogeneous mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents (Constantinides, 1995; Craig, 1993). The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by aqueous phases.

* Corresponding author. E-mail: kcofokanci@yahoo.com; Tel: +234-(0)-803-779-4873
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This property makes LSEDDS good candidates for the oral delivery of hydrophobic drugs especially those which have adequate solubility in oil or oil/surfactant blends. Griseofulvin represents a classical example of drugs exhibiting poor aqueous solubility and complex technical formulation problems. Vegetable oils such as fractionated arachis and peanut oils are employed as vehicles for preparing oil solutions for injection (Relly, 2000). The objective of this study was to design and formulate LSEDDS incorporating griseofulvin for the purpose of enhancing the dissolution of the drug. The suitability of peanut oil/Tween 80 blends for this purpose was assessed by evaluating some of the physicochemical properties of the emulsion formed as well as the efficiency of incorporation of the drug in the LSEDDS.

MATERIALS AND METHODS

Materials

Griseofulvin (Astrazeneca), Tween 80 (Merck), sodium acetate, acetic acid (BDH), and peanut oil (pharmaceutical grade) were used as procured from their suppliers without further purification. Distilled water was obtained from an all-glass still. All other reagents were analytical grade and used as such.

Methods

Formulation of various liquid self-emulsifying drug delivery systems

Liquid self-emulsifying drug delivery systems (LSEDDS) were formulated with different proportions of peanut oil and Tween 80 as shown in Table 1. The mixtures in test-tubes were mildly agitated for 2 min in a reciprocating mixer to ensure thorough homogenization while maintaining them at a temperature of 251°C in a thermostated water bath.

Phase separation studies of the various LSEDDS

Using a micropipette, 0.05 ml volume of each LSEDDS was added to a glass test-tube containing 5 ml of distilled water at room temperature (25°C). The mixture was again placed in the reciprocating agitator and homogenized for 2 min and allowed to stand maintained at the same temperature for a period of 2 h. The phase separation was noted by visual inspection.

Measurement of globule sizes of the LSEDDS

The mean globule sizes of the various LSEDDS loaded or free from griseofulvin in various media (distilled water, 0.1 N HCl and acetate buffer, pH 7.4) were measured at room temperature using microscope with a calibrated eyepiece (Koywa, Tokyo). The mean size of 50 globules measured on a single mount was used for each preparation.

Viscosities of the LSEDDS

The viscosities of the various LSEDDS in different media were measured using a torsion viscometer (Gallenkamp, England) at room temperature. About 5 ml of the dispersion was employed for each determination and the mean of five determinations was taken as the viscosity of each preparation.

Determination of the partition coefficient of griseofulvin between the oil and buffer solutions

This was determined at 371°C. Each buffer solution (2 ml) containing griseofulvin was added to 2 ml of peanut oil. The mixture was agitated at 371°C for 24 h using a thermostated water bath shaker. After standing for 1 h, 1 ml each of both the oil and buffer phases was collected and diluted with 9 ml of ethanol. The griseofulvin concentrations in both phases were determined spectrophotometrically at a predetermined wavelength of 291 nm using a digital UV-Vis double-beam spectrophotometer (SP8-100, Pye Unicam) by extrapolation from a standard Beer's plot.

Solubility of griseofulvin in the LSEDDS

Griseofulvin (100 mg) was incorporated into the various LSEDDS to achieve approximate concentrations of 4.7 mg/ml of the drug in each system. Each mixture was agitated for about 5 min using a stirrer and further vigorously agitated at 371°C using a water bath shaker to equilibrate griseofulvin in the peanut oil and Tween 80 dispersion. Twelve hours was adjudged sufficient time to achieve equilibrium distribution of the drug in the two phases. The equilibrium mixture was centrifuged at 3000 rpm for 10 min and filtered. The filtrate (0.1 ml) was diluted with ethanol and griseofulvin concentrations determined Spectrophotometri -Cally at 291 nm.

Release profile of griseofulvin from the LSEDDS

The USP 1999 Method II (paddle stirred system) was employed as follows: A volume of the LSEDDS containing 20 mg of griseofulvin was transferred into a dialysis bag and the open end tied up to prevent leakage. The dialysis bag was immersed in 300 ml of each buffer solution maintained at 370.5°C, held to the bottom of the vessel attaching to a stainless steel gauze and stirred continuously at a rate of 50 rpm. The paddle clearance from the dialysis bag was about 2 cm. At predetermined time intervals, 1 ml portions of the dissolution medium were withdrawn, appropriately diluted and their absorbance determined using a spectrophotometer. The volume of the dissolution medium was kept constant by replacing it with 1 ml of fresh buffer solution after each withdrawal. The concentrations of the drug in the samples were determined with reference to the standard Beer's plot. The experiment was similarly repeated using an equivalent amount of griseofulvin powder dispersed in peanut oil alone. Four replicate release studies were carried out.

RESULTS AND DISCUSSION

Fig. 1 shows the variation of globule size of the LSEDDS with concentration of the surfactant used in the formulation. Increasing concentration of the surfactant (Tween 80) decreased the globule size of the LSEDDS until an optimum value was attained at 35 % surfactant concentration. It is discernible from Fig. 2 that the globule size at the optimal value of surfactant concentration increased in the presence of griseofulvin. This may be due to the interference, of the drug, with self-emulsification process by altering the optimal oil/surfactant ratio and by interacting with the liquid crystalline or gel phase of the emulsion droplets (Gershanik and Benita, 2000).

Emulsion droplet size is known to be a very important factor in the formulation of liquid self-emulsifying systems because of its influence on the rate and extent of drug release and absorption (Shah *et al*., 1994; Tarr and Yalkowsky, 1989). Some authors (Shah *et al*., 1994) have defined efficient self-emulsification as a system, which produces mean emulsion droplet diameter values of less than 5 m. The optimal formulation, with or without the drug yielded emulsion with droplet size below 1 m indicating that the oil/surfactant pair employed in this formulation has very efficient self-emulsification ability.

The optimal surfactant concentration of 35 % that yielded the optimal formulation is also ideal for a preparation that will traverse the gastrointestinal (GI) tract. It has been reported that the usual surfactant concentration in liquid self-emulsifying formulation required to form and maintain an emulsion state in the GI tract ranged from 30 to 60 % w/w (Gershanik and Benita, 2000). A large quantity of surfactant may irritate the GI tract. It is noteworthy from Fig. 1 that distilled water provided the most suitable aqueous phase for enhanced self-emulsification performance in comparison with 0.1 N HCl and acetate buffer, pH 7.4. In earlier work (Wakerly *et al*., 1986) it was suggested that the ease of emulsification could be associated with the ease with which water penetrates into the various liquid crystalline or gel phases formed on the surface of the droplet.

This ease of penetration of water into the gel phases of the droplet seems to be faster in distilled water than in 0.1 N HCl or acetate buffer pH 7.4.

Partition coefficient values of 1.43, 1.26 and 1.21 were obtained in buffer solutions of pH 5.5, 6.5 and 7.4 respectively. This shows a slight decrease in partition coefficient values with increase in pH. Additionally, the intermediate values of partition coefficient obtained are an indication of easy partitioning of griseofulvin between lipid and aqueous phases (Gulati *et al*., 1998). This is remarkable considering the fact that drug release from LSEDDS depends on diffusion rate of the drug from the oil phase to the aqueous phase. This occurs as the droplets are transported along the GI tract in the presence of aqueous intestinal fluid. Griseofulvin is known to be poorly water soluble but in this formulation, there is high diffusion rate of the drug to the aqueous phase, which ensured its rapid dissolution. It may be reasonable to infer that in a medium of pH 5.5, griseofulvin incorporated in LSEDDS would dissolve very rapidly.

The variation of mean viscosity of the LSEDDS with concentration of Tween 80 in different media is depicted in Fig. 3. It is apparent from Fig. 3 that the viscosities of the LSEDDS increased gradually with increasing concentration of the surfactant up to the optimal surfactant concentration of 35 % (w/w) after which, the mean viscosity began to decrease. Viscosity is known to have a direct relationship with mean globule size, which in turn has an inverse relationship with the surfactant concentration below the optimal concentration (Figs. 1 and 2). In addition, the highest mean viscosity was recorded in LSEDDS formulated in distilled water as medium, further confirming distilled water as the most suitable aqueous phase for self-emulsification involving peanut oil and Tween 80 in comparison with the other aqueous phases. Generally, viscosity of LSEDDS is known to give indication as to the emulsion globule size, which further influences the rate and extent of drug release and absorption.

The effect of concentration of the surfactant on the solubility of griseofulvin in the LSEDDS is shown in Fig. 4. The solubility of griseofulvin was highest in LSEDDS composed of 35 % w/w Tween 80. Beyond this optimal surfactant concentration, the solubility decreased sharply, confirming this concentration to be the optimum needed for efficient self-emulsification performance. The surface active agents are ampliphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively high quantities of hydrophobic drugs. This ability to solubilize hydrophobic drugs has been found to be of prime importance for preventing precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is vital for effective absorption (Serajuddin *et al*., 1988 , Shah *et al*., 1994).

Fig. 5 shows the release profile in different media of griseofulvin from the LSEDDS and the peanut oil at an agitation speed of 50 rpm. There was rapid initial release of griseofulvin within the first one hour followed by a much slower release over the remaining release period. Release of the drug from the LSEDDS was significantly higher ($P<0.05$) than from peanut oil alone. This is foreseen since the presence of surfactant in LSEDDS has been shown to promote effective dispersion of hydrophobic drug in the lumen by the solubilization process, in addition to drug spreading in oil droplets (Toguchi *et al*., 1990; Yoon and Burgess, 1996). It is equally discernible from Fig. 5 that there was an extended release of griseofulvin from the LSEDDS and from the oil as less than 35 % of the drug was released within a six-hour period. This may be an advantage for a drug such as griseofulvin, which is used in the treatment of chronic fungal infections; the rapid initial release within the first one hour, as earlier noted, causing a rapid attainment of the

minimum inhibitory concentration *in vitro*. This may have interesting implications in *in vivo* situations. Release of griseofulvin was also observed to be higher in media of high pH (6.5 and 7.4) in comparison with that at low pH of 2.0. This is also expected since griseofulvin, a weakly acidic drug, should show increased solubility in an alkaline environment.

Release of griseofulvin from the LSEDDS may occur essentially from the globules following their rupture or disintegration in the agitated medium. It is possible that some amount of drug may be released by passive diffusion from the oil globules, but the rupture of the globules in the infinitely diluted medium seems to play a

Table 1: Quantities of materials used in formulating the LSEDDS

Batch	Ratio (w/w)	Peanut oil (ml)	Tween 80 (ml)
A	9.5 : 0.5	10.90	0.46
B	9.0 : 1.0	10.30	0.93
C	8.,5 : 1.5	9.70	1.39
D	7.5 : 2.5	8.60	2.30
E	7.0 : 3.0	8.00	2.80
F	6.5 : 3.5	7.50	3.20
G	6.4 : 3.6	7.30	3.30

Conclusion

Peanut oil/Tween 80 admixtures have been formulated to show a combination of micelle and emulsion formation for the delivery of a known poorly water soluble drug, griseofulvin. The emulsion droplet size was generally small, indicating that the formulation has efficient self-emulsification ability. The formulated LSEDDS enhanced the dissolution and extended the release of griseofulvin, overcoming the problem of irregular dissolution and absorption associated with conventional griseofulvin tablets. A separate investigation to correlate these results with *in vivo* bioavailability is currently being carried out.

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