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Full Length Research Paper

Preparation and *in vitro* evaluation of suppositories of halofantrine hydrochloride

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Halofantrine (HF) hydrochloride is commercially available only as oral dosage forms. Limitations of oral dosing of the drug coupled with non-availability of the safe parenteral preparations prompted the need to develop and evaluate suppository HF formulations, which may serve as a practical alternative. The effects of type of suppository base and incorporation of non ionic surfactants on *in vitro* release characteristics of HF from suppositories were investigated. The release rates were determined using a modification of the continuous flow bead-bed dissolution apparatus for suppositories. The results showed that the drug release from water-soluble base (polyethylene glycol) was significantly greater than that from lipophilic bases (Shea butter and Witepsol H15) ($P < 0.05$). Incorporation of non ionic surfactants (Tweens 20 and 80, Spans 20 and 60) at different concentrations did not improve the *in vitro* availability of the drug from composite polyethylene glycol base (1500:4000, 80:20, w/w) suppositories. The extent of drug release was very low (maximum of 2.3%) It is suggested that further studies are required for development of modalities to enhance the release of halofantrine from polyethylene glycol suppositories so as to optimize this dosage formulation of the drug.

Key words: Halofantrine suppository, suppository bases, non ionic surfactants, *in vitro* release.

INTRODUCTION

Halofantrine (HF) is a weakly basic and highly lipophilic (estimated log P, 8.5) 9-phenanthrenemethanol (Figure 1) antimalarial drug available for oral administration as the hydrochloride salt. The drug has a place in the treatment of multi-resistant malaria including chloroquine-resistant strains of *Plasmodium falciparum* (Weinke et al., 1992; Karbwang and Na-Bangchang, 1994). The pharmacokinetics of HF is characterized by a low and highly variable oral absorption, and the mean oral bioavailability, which is further decreased in malaria patients, and is reported to be 4.7% (Karbwang et al., 1991; Ajayi and Fleckenstein, 1994; Humberstone et al., 1996). Although HF prolongs the QTc interval resulting in serious cardiotoxicity in predisposed individuals, it is still an important drug in the context of the continuing spread of resistant strains of the malaria parasite.

Currently, only the oral formulations are available as tablets, suspensions and capsules of HF HCl. In some circumstances such as during nausea and vomiting or convulsion, or in uncooperative patients, oral route becomes impractical or even impossible. Another drawback associated with the oral administration of HF is its gastrointestinal side effects such as abdominal pain, diarrhea, nausea and constipation (Karbwang and Na-Bangchang, 1994). Parenteral administration could serve as an alternative to the oral route for HF dosing but, an intravenous formulation of HF that has been tested clinically in humans was found to have adverse effects including severe local irritation as well as serious cardiac side effects (Krishna et al., 1993). A new intravenous nanocapsule formulation of HF has been investigated but its safety and efficacy in humans are yet to be established (Mosqueira et al., 2004). These limitations with the oral and new parenteral formulations of HF prompt the need for development and evaluation of suppository formulations of the drug, with the goal of introducing a practical alternative. There is no information

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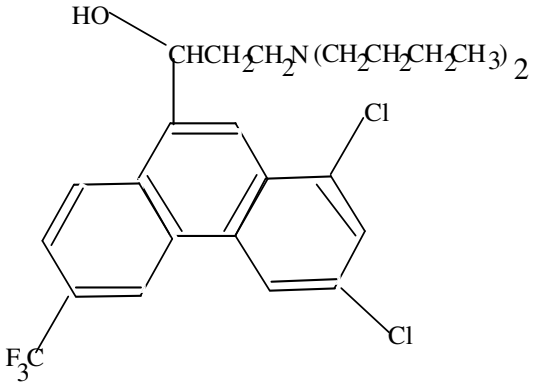

Figure 1. Chemical structure of halofantrine.

in the literature regarding the formulation of HF hydrochloride suppositories. The clinical value of rectal formulations has been demonstrated for various drugs such as analgesics, anticonvulsants, antiemetics, antibacterial agents, non-steroidal anti-inflammatory drugs as well as antimalarials including artemisinin and its derivatives (artesunate, artemether and dihydroartemisinin) (van Hoogdalem et al., 1991; Wilairatna et al., 2000; Karunajeewa et al., 2003).

In general, rectal bioavailabilities tend to be lower than the corresponding oral values, except in some cases of partial avoidance of hepatic first-pass metabolism after rectal absorption. Since oral bioavailability of HF is low (Ajayi and Fleckenstein, 1994), it is reasonable to expect that rectal absorption of the drug will also be low. Improvements in drug absorption following rectal administration have been achieved by incorporation of absorption-promoting agents into suppositories (Van Hoogdalem et al., 1991; de Boer et al., 1990). Some absorption-promoting agents, especially surfactants, have been shown to, not only enhance rectal drug absorption but also improve drug release from suppositories (Abdel-Gawad et al., 1988; Nakanishi et al., 1994). Similar studies in our laboratories have demonstrated that incurporation of non-ionic surfactants (Tween 20, Tween 80 and Brij 35) results in significant increase in the rate and extent of release of chloroquine from suppository formulations (Onyeji et al., 1999). Since HF or its hydrochloride salt has very poor aqueous solubility (Humberstone et al., 1996), its slow release from suppository formulations may be anticipated. Hence, an absorption enhancer that can improve the drug release has the potential of being more beneficial. Therefore, the objective of this study was to evaluate some suppository bases in order to determine bases capable of ensuring a rapid release of HF. Possibility of improvement of the drug release by incorporation of different absorption enhancers (surfactants) was also investigated.

MATERIALS AND METHODS

Materials

HF hydrochloride was extracted from Halfan® tablets (Smithkline Beecham, Lagos, Nigeria) following powdering the tablets and extraction with dichloromethane. The organic layer was evaporated to dryness and the product re-crystallized from aqueous methanol. Characterization of the extracted compound involved melting point determination, thin layer chromatography and U.V. analysis. The comparison of the values obtained with those from reference halofantrine hydrochloride powder, kindly provided by Smithkline Beecham (Welwyn, United Kingdom), enabled the confirmation that the extracted compound was indeed HF. Polyethylene glycol (PEG) 4000 and 1500 were purchased from British Drug House (B.D.H, United Kingdom). Other suppository bases included Witepsol H15 (Dynamit-Nobel, Germany), and shea butter (obtained from a local market in Ile-Ife, Nigeria), and purified following established methods of Mital and Dove (1971). Tween 20® and Span 20® (BDH), Tween 80® (Sigma Chemical Co,. St Louis, USA) and Span 60® (Honey Hill, England) were the non ionic surfactants used.

Experimental design

A single factor was varied at each time and a minimum of three replications were made. In the first stage, the single factor varied was the suppository base, while all other factors (drug concentration, dissolution medium, temperature, dissolution apparatus and agitation) were kept constant. Three different suppository bases were used. Secondly, the single factor varied was the type of surfactant incorporated, while other factors as earlier indicated, in addition to the suppository base and surfactant concentration were kept constant. Four surfactants were used. Thirdly, the concentration of surfactants was the single factor that varied, all other parameters remained the same.

Preparation of halofantrine suppositories

HF hydrochloride suppositories containing 100 mg of the drug were prepared by the fusion method using a metal mould with six cavities. The composition of the bases was a blend of polyethylene glycols (PEG 1500, 80% w/w and PEG 4000, 20% w/w); Witepsol H15; and shea butter. Drug displacement values of the bases used were first determined and the amount of drug required was calculated. The drug powder was passed through a mesh sieve of 100 µm prior to its incorporation into the base. Also, 100 mg of the drug with and without a surfactant (Tweens 20 and 80, Spans 20 and 60) at concentrations indicated in Table 2 were added into the composite PEG base, using the displacement values calculated.

Determination of release rates of drug and analysis of samples

The method used for drug release determination was a modification (Onyeji et al., 1999) of the continuous flow bead-bed dissolution apparatus for suppositories earlier described by Roseman et al. (1981). The design of the method was such that it provided a reasonable control over the interfacial area during the dissolution, and this is a key factor in obtaining experimentally reproducible release data. The release chamber consisted of a Gallen Kamp sinta glass No. 3 with the suppository enclosed in a bed of glass beads. The chamber was suspended in 400 ml, 0.1 M HCl in a 1000 ml beaker, and the whole set-up was placed on a magnetic stirrer thermostat hot plate (set at speed No. 6) and maintained at

37 ± 1°C (Akala et al., 1991; Onyeji et al., 1999). Samples (4 ml each) were taken at specified time intervals for up to 180 min and assayed for HF. The volume of the dissolution medium was kept constant by replacing the withdrawn volume of the sample with equal volume of fresh dissolution medium maintained at the same temperature. A minimum of triplicate release rate determinations were made for each suppository preparation.

HF samples were analysed using an ultraviolet spectrophotometric method. A calibration curve was generated from a concentration range of the drug (0.25 to 8 µg/ml) prepared in 0.1 M HCl and UV absorbance measured at 254 nm. Following observation that HF suppository prepared with the composite PEG bases exhibited the best release characteristics, the formulation was subjected to pharmaceutical quality assessment following the British Pharmacopoeia (1988) tests. The mean content of the suppositories, determined using UV spectrophotometric method was 99 ± 2.4% (mean ± SD). The uniformity of appearance, weight and content, as well as disintegration tests was evaluated. All the tests complied with the pharmacopoeia standards.

Data analysis

The extent of drug release was assessed from the total amount of drug present in the dissolution medium at the end of the 180 min drug release experiment. The type of drug release kinetics applicable for the suppository bases was determined by evaluation of three models, viz: zero-order kinetic model (Q vs t), diffusion-controlled model (Q vs square-root of t) and first-order model (log(Qo – Q) vs t), where Q is the amount of drug released at time 't' and Qo is the initial amount of the drug. The model that consistently produced the highest correlation among the suppository preparations was used for the assessment of drug release rates, and a slope obtained from linear regression analysis of the plot was determined as the drug release rate constant. The results expressed as mean ± SD were generated from replicate determinations for each suppository preparation. Analysis of variance for a randomized complete block design together with F-test was conducted and comparison among treatment means was carried out using Duncan's multiple range tests.

RESULTS AND DISCUSSION

Adequate characterization of drug release rate from suppositories requires the determination of its appropriate release kinetics model. Kinetics of drug release from suppositories may vary from zero-order through first-order to diffusion-controlled. Plots of logarithm of the HF amounts remaining versus time for the suppository formulations with the three bases showed a linear relationship, with a correlation of not less 0.996 for only the hydrophilic base (polyethylene glycol). On the other hand, a straight line relationship was obtained when the drug amounts released was plotted against the square root of time for all the bases, with a correlation coefficient ranging from 0.98 to 0.99. This implies that the kinetics of release of HF from the hydrophilic bases can appropriately be described by either a first-order or diffusion-controlled model, while mainly diffusion-controlled mechanism governs the drug release from the lipophilic bases (Shea butter and Witepsol H15). Similar diffusion-controlled release mechanism has been reported for other antimalarial drugs such as amodiaquine hydrochloride and chloroquine phosphate (Akala et al., 1991; Onyeji et al., 1999).

The mean extents and rates of release of HF from different suppository bases are shown in Table 1 with the drug release profiles depicted in Figure 2. While the release rate was significantly higher with PEG suppositories than from either of the lipophilic bases ($P < 0.05$), the extents of release of HF in the bases were very poor. Such poor release characteristics are not likely caused by degradation of the drug or its interaction with the bases. Though incompatibilities of PEG, shea butter and Witepsol with some drugs have been reported (Boylan et al., 1986), the chemical class of drug to which HF belongs (Phenanthrine methanol with a tertiary amino group) has not exhibited any physical or chemical incompatibility with these bases (Lund, 1994; Crowley and Martini, 2002). Thus, the release pattern observed may be related to the solubility of HF in the bases, its diffusibility from them and its subsequent solubility in the dissolution medium. HF hydrochloride is a lipophilic drug and its solubility in hydrophilic bases is expected to be low. Consequently, the drug has a higher tendency to diffuse out of hydrophilic bases. Another important factor that can influence the drug release is the water-absorbing property of the base which can facilitate penetration of the dissolution medium into the base with subsequent wetting and desorption of the embedded drug. The literature abounds with reports on improvement of dissolution of poorly water-soluble drugs from polyethylene glycol - based solid formulations and, this is due to the water-absorbing properties of polyethylene glycols with their subsequent solubility-enhancing effects (Khoo et al., 2000; Emara et al., 2002). The finding in this study is consistent with other reports which show that polyethylene glycol was found to be an optimal base for the formulation of suppositories containing poorly water-soluble drugs (Usayapant and Iyer, 1999; Reglon et al., 2001). It can therefore be asserted that the hydrophilic character of the suppository base promotes the release of HF. This assertion is further buttressed by the observation that Witepsol H15, with a hydroxyl value of <15 which is less than that of Shea butter (hydroxyl value of 30) (Odusote and Ifudu, 1987), has the lowest water-absorbing property and this reflected in the slowest drug release. In all the experiments in this study, the block or replication effect was not significant, indicating the reproducibility of the suppository preparations and drug release.

The results in Table 1 show that the rate of drug release correlates with the extent of release from the different bases. A maximum of only 2.25% of the drug was released from the polyethylene glycol suppositories within the 3-hr drug release experiment. It is apparent that this is attributable to the poor aqueous solubility of

Table 1. Mean extents and rates of release of halofantrine hydrochloride from different suppository bases with each suppository preparation containing 100 mg of the drug.

Suppository Base	Release rate constant(mg $min^{-½}$)	Extent of release (%)
Polyethylene glycol	0.38 (0.05)[a]	2.25 (0.32)[a]
Shea butter	0.22 (0.06)	1.66 (0.12)
Witepsol H15	0.17 (0.07)	1.32 (0.3)

*Standard deviation values in parenthesis.
[a]Significantly higher than that of Shea butter and Witepsol H15.

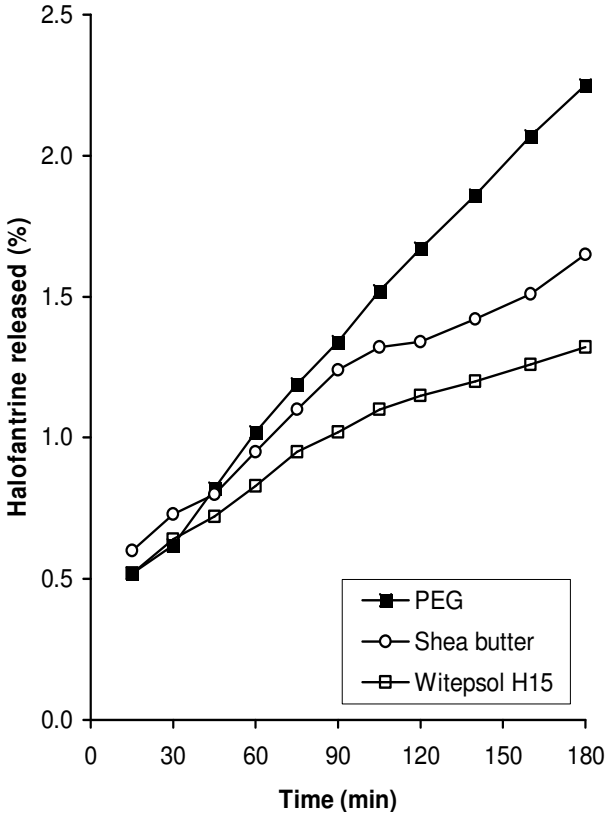

Figure 2. Release profiles of halofantrine from suppositories of different bases, each containing 100 mg of the drug.

the drug which has been reported to have a maximal solubility of 1.3 µg ml^{-1} in an aqueous system (Humberstone et al., 1996). In studies of mechanisms underlying *in vitro* availability of different drugs from suppositories, the water solubility of drugs was found to be the fundamental factor influencing the release rate and extent (Realdon et al., 2001). Different approaches have been used to improve solubility and dissolution rate of poorly water-soluble drugs from suppositories. These include solid dispersion and crystallization of the drug with carriers such as urea, sodium salicylates and beta-cyclodextrin (Celebi et al., 1991; Usayapant and Iyer, 1999; Sany et al., 2000) or through surfactant incorporation (Abd el-Gawad et al., 1988; Nakaishi et al., 1994).

In this study, the possibility of increasing the release of HF from suppositories was evaluated by incorporation of non-ionic surfactants with varied HLB values ranging from 4.7 to 16.7 into polyethylene glycol suppositories (Table 2). The different surfactants were compared at concentration of 4% (w/w) because that reflects the intermediate range of concentrations that have been found to be safe following rectal administration to humans (Davis et al., 1985; Van Hoogdalem et al., 1991). The release rates produced by Span 20 and Span 60 at 4% (w/w) concentration were not significantly different from that of the control (without adjuvants) ($p > 0.05$). On the other hand, the same concentrations of Tween 20 and Tween 80 resulted in significant decreases in drug release ($p < 0.05$). The effects of the surfactants were shown to be concentration-dependent (Table 2). For example, increasing the concentration of Span 60 from 4 to 8% (w/w) was associated with a significant reduction in the drug release. Also, there was a progressive decrease in the release rate with increase in concentration of Tween 20. The drug release from suppositories containing Tween 20 at concentration of 2% (w/w) was not significantly different from that of the control ($P > 0.05$) but the release reduced significantly at 4% and further diminished at 8% (w/w) incorporation. It was anticipated that the surfactants may decrease the interfacial tension between the drug and the dissolution medium with resultant improvement of drug solubility and subsequent release. An anionic surface-active agent, sodium taurocholate, has been shown to produce a significant enhancement of solubility and dissolution rate of halofantrine hydrochloride (Humberstone et al., 1996). Such a class of surfactants was not used in this study since they have low safety margins when applied internally. The non-improvement of the drug release by surfactants as observed is not unusual as other studies have revealed that incorporation of surfactants may increase or decrease drug release from suppositories (Ibrahim et al., 1980; Lee and Wang, 1999). The decrease in drug release at higher surfactant concentration as obtained is most likely attributable to micellar entrapment of the drug, resulting in retardation of the drug release. Although the surfactants at optimum concentration did not improve drug release, their incorpo-

Table 2. Mean extents and rates of release of halofantrine from composite polyethylene glycol (1500:4000; 80:20, w/w) suppositories containing different non ionic surfactants.

Treatment	Release rate constant (mg $min^{-½}$)	Extent of release (%)
Control (PEG with no surfactant)	0.38 (0.05)*	2.25 (0.32)
Tween 20 (4%, w/w)	0.22 (0.02)[a]	1.75 (0.05)[a]
Tween 80 (4%, w/w)	0.27 (0.01)[a]	1.72 (0.10)[a]
Span 20 (4%, w/w)	0.31 (0.02)	1.96 (0.15)
Span 60 (4%, w/w)	0.39 (0.03)	2.40 (0.15)
Span 60 (2%, w/w)	0.32 (0.06)	1.96 (0.20)
Span 60 (8%, w/w)	0.29 (0.07)[a]	1.67 (0.20)[a]
Tween 20 (2%, w/w)	0.40 (0.01)	2.20 (0.22)
Tween 20 (8%, w/w)	0.18 (0.03)[a]	1.49 (0.05)[a]

Each suppository preparation contained 100 mg of halofantrine hydrochloride.
*Standard deviation values in parenthesis.
[a]Significantly lower than that of control.

ration into the suppositories may still be useful since they have absorption-promoting effects.

The pH of the dissolution medium used in this study (pH 1) does not reflect that of the rectal fluid (pH about 7). An acidic pH was deliberately used after preliminary *in vitro* release experiments with the drug using water as the dissolution medium, revealed that the drug amounts released within the first one hour from lipophilic suppository bases yielded concentrations that were less than the limit of the UV spectrophotometric assay. This study being a formulation development investigation, it was rationalized that the use of a medium of pH 1 rather than that of pH 7 would not likely result in a change in the pattern of the influence of the type of suppository base and nature/amount of surfactant incorporated, on drug release. Rather, comparatively higher release rates and extents are expected in acidic dissolution medium since the drug is a weakly basic compound and, hence, more soluble at acidic pH. This point is premised on the fact that the penetration of the matrix of the suppository bases by an aqueous fluid and liquefaction or melting of the bases are not known to be influenced by an acidic pH of 1. Also, the surfactants used being non ionic, are not affected by pH changes. However, the release rates obtained in this study may not have a direct *in vivo* significance due to the disparity in pH of the rectal and dissolution medium.

In conclusion, a hydrophilic bases polyethylene glycol, was established to be superior to the lipophilic bases (shea butter and Witepsol H15) in terms of their ability to release HF from the suppository formulations. Incorporation of non ionic surfactants at different concentrations did not result in improvement of the drug release, which was a maximum of 2.3%. The low extent of *in vitro* availability of HF is most likely a major factor of the very poor water-solubility of the drug. There is a need for further studies to enhance HF release for optimization of polyethylene glycol suppository formulation of the drug. This may be achieved through development of modalities, such as complexation with beta-cyclodextrin, for possible improvement of HF solubility. Further studies are underway in this regard.

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