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Formulation, characterization and anti-malarial activity of homolipid-based artemether microparticles

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ABSTRACT

The anti-malarial activity of artemether is dependent on its bioavailability. The purpose of the research is to improve the solubility, bioavailability and therapeutic efficacy of lipophilic artemether using homolipid-based microparticles. Irvingia fat was extracted from *Irvingia gabonensis var. excelsa* (*Irvingia wombolu*), and its lipid matrices (LM) with Phospholipon® 90G (P90G) were characterized by differential scanning calorimetry (DSC) and wide angle X-ray diffraction (WAXD). Solid lipid microparticles were formulated, characterized, filled and compressed into capsules and tablets, respectively, and drug release studied. *In vivo* anti-plasmodial activity of artemether SLMs was evaluated in mice. The crystallinity of the phyto-lipid reduced in the presence of P90G, which was integrated into the irvingia fat crystal lattice. SLM dispersions with 3:1 irvingia fat/P90G composition showed higher diffusion and permeability through dialysis membrane while lower proportion of P90G (9:1 LM) favored increased dissolution rate of artemether from capsules ($p < 0.05$). Significant increase ($p < 0.05$) in % plasmodial growth inhibition and reduced parasitemia were observed in mice administered with the SLM dispersions compared with the controls. Therefore, SLMs prepared with composite mixtures of a homolipid and P90G could be used to improve the solubility, dissolution, permeability, bioavailability and anti-malarial efficacy of artemether.

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1. Introduction

The oral route has been a major route of drug delivery. However, the oral delivery of lipophilic drugs presents a major challenge because of their low aqueous solubility (Mandawgade et al., 2008). The limited dissolution rate arising from low solubility frequently results in the low bioavailability of orally administered drugs, and compounds with aqueous solubility lower than 100 μg/ml usually present dissolution limited absorption (Horter and Dressman, 2001). In such a case, higher doses would be required until the blood drug concentration reaches the therapeutic drug concentration range. This dose escalation may cause local toxicity in the gastro-intestinal tract upon oral administration, and such toxicity could lead to a reduction in patient compliance. The poor aqueous solubility of these drug moieties is associated with low bioavailability, high inter- and intra-subject variability and a lack of dose proportionality (Komuru et al., 2001).

Solid lipid microparticles (SLM) are micro-scale drug carriers possessing matrix made from fatty acids, glyceride, fatty alcohol and solid wax with high melting points (Long et al., 2006). The solid lipid matrix protects loaded labile substances against degradation and can possibly offer controlled drug release and drug targeting. It can also protect the GIT mucosa from the harsh irritations of some drugs. The suitability of lipid particles as prolonged release formulation for lipophilic drugs has been demonstrated (Eradel et al., 2009). Moreover, lipid matrices (LM) can be structured with phospholipids for improved functionality (Bekerman et al., 2004; Elgart et al., 2012).

Artemether is a methyl ether derivative of artemisinin, which is a sesquiterpene endoperoxide lactone isolated from the Chinese anti-malarial plant, *Artemisia annua*. Artemether is anti-malarial. The mode of anti-malarial action of artemether involves iron catalyzed generation of a carbon-centered free radical, followed by the alkylation of malaria specific proteins (Kamchonwongpaisan and Meshnick, 1996). Its mechanism of action involves the heme-mediated decomposition of the endoperoxide bridge to produce

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carbon-centered free radicals, which generates alkylated heme and proteins (Meshnick, 2002). In the presence of intra-parasitic iron, these drugs are converted into free radicals and other electrophilic intermediates which then alkylate specific malaria target proteins (Meshnick et al., 1996). It has been shown that both heme and also free intracellular reduced iron species can lead to the bioactivation of artemisinin, a prerequisite for the drug to become covalently bound to macromolecules throughout the whole parasite. Artemether, therefore covalently modifies multiple targets (Muller and Hyde, 2010). The peroxide structure of artemether is therefore necessary for its activity.

Irvingia gabonensis var. excelsa or *Irvingia wombolu* is a tropical tree, now generally recognized to belong to Irvingiaceae family. *Irvingia* species are commonly known as African mango, bush mango or wild mango and the nut commonly called dika nut. The seed or nut contains fat which can be used for food, pharmaceutical and cosmetic applications (Ejiofor et al., 1987). Fat derived from the nut is generally regarded as safe.

2. Materials and methods

2.1. Materials

Artemether (Fig. 1) was obtained from Hangzhou Dayang Chemical (China). Phospholipon® 90G (P90G) was obtained from Phospholipid GmbH (Cologne, Germany). Labrasol® (caprylocaproyl macrogol-8-glyceride) was a gift from Gattefosse (St. Priest, France). Other materials used were Avicel® – microcrystalline cellulose, Ac-Di-Sol® – croscarmellose sodium (FMC biopolymer, USA) and maize starch (BDH, England). Simulated gastric fluid (SGF), without pepsin, was prepared and titrated to pH 1.2. Irvingia fat was prepared in Department of Pharmaceutical Technology and Industrial Pharmacy Laboratory, University of Nigeria, Nsukka.

2.2. Extraction of fat from I. gabonensis var. excelsa (I. wombolu)

Irvingia fat was extracted from nuts of *I. gabonensis var. excelsa* with petroleum ether (40–60 °C) as solvent, using column extraction and concentrated with a rotary evaporator. The nuts were dried and milled to coarse form before extraction. Further, purification was performed by heating a 2%w/w suspension of activated charcoal and bentonite (1:9 ratio) in the lipid at 50 °C for 1 h. Thereafter, the slurry was vacuum-filtered using Buchner funnel. The yield of extracted irvingia fat (dika fat) was calculated using Eq. (1);

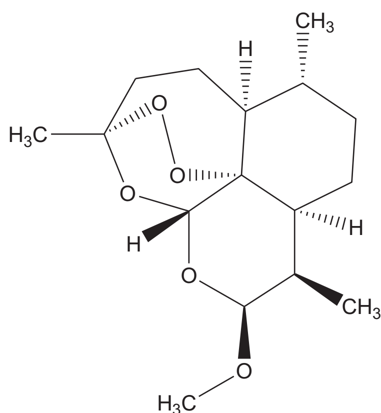

Fig. 1. Chemical structure of Artemether.

$$\text{Yield}\% = \frac{\text{Weightof extracted Irvingia fat}}{\text{Weight of dried Irvingia nut}} \times 100 \quad (1)$$

2.3. Characterization of extracted irvingia fat

2.3.1. Differential scanning calorimetry (DSC) of irvingia fat

Differential scanning calorimetry (DSC) was performed on irvingia fat sample using a DSC instrument (NETZSCH DSC 204 F1, Germany) at a temperature range of 30–300 °C and heating rate of 10 K/min on an aluminum pan with a pierced lid. The DSC of the sample was used to assess its thermal property and crystallinity. A thermogram was obtained, while the peak/melting point and enthalpy were recorded.

2.3.2. Wide angle X-ray diffraction (WAXD) of irvingia fat

Wide angle X-ray diffraction was performed on the irvingia fat sample using the X-ray generator (PW3040/60 X'Pert PRO, Fabr. DY2171, PANalytical, Netherlands) connected to an X-ray tube (copper anode, PW3373/00 DK147726Cu LFF) that delivered X-ray of wavelength $\lambda = 0.1542$ nm at a high voltage of 40 kV and anode current of 25 mA. The WAXD measurements were taken with a goniometer (PW3050/60 MPD-system, PANalytical Netherlands). The interlayer spacing, *d*, was determined from the diffraction peaks according to Bragg's equation (Eq. (2)).

$$n\lambda = 2d\sin\theta \quad (2)$$

2.4. Thermal properties, crystallinity, stability and diffraction of lipid matrices

2.4.1. Differential scanning calorimetry of artemether-loaded lipid matrices

The thermal, crystallinity and stability of artemether lipid matrices were evaluated by DSC. The DSC was performed on the drug-loaded lipid matrices (LM) using a differential scanning calorimeter (DSC Star Excellence System Autosampler Mettler-Toledo®, Switzerland). The thermal properties were determined between 5 and 150 °C at a scan rate of 5 K/min, while the DSC was controlled by the software, Star^e SW 10.000.

The crystallinity index (C.I) was used to evaluate the degree of crystallinity of the lipid matrices. This was determined from the enthalpy of the transition according to Eq. (3):

$$\text{C .I}_{\text{LM}}\% = \frac{\text{Enthalpy}_{\text{LM}}(\text{J/g})}{\text{Enthalpy}_{\text{irvingia fat(J/g)}}} \times 100 \quad (3)$$

$\text{Enthalpy}_{\text{LM}}$ is the enthalpy of the lipid matrices in J/g while $\text{Enthalpy}_{\text{irvingiafat}}$ is the enthalpy of irvingia fat in J/g. In this study, enthalpies of the artemether-loaded lipid matrices and irvingia fat were used as $\text{Enthalpy}_{\text{LM}}$ and $\text{Enthalpy}_{\text{irvingiafat}}$, respectively.

2.4.2. WAXD of lipid matrices (LM)

WAXD was performed on samples of drug-free and artemether lipid matrices using the X-ray generator (PW3040/60 X'Pert PRO, Fabr. DY2171, PANalytical, Netherlands) connected to an X-ray tube (copper anode, PW3373/00 DK147726Cu LFF) that delivered X-ray of wavelength $\lambda = 0.1542$ nm at a high voltage of 40 kV and anode current of 25 mA. The WAXD measurements were taken with a goniometer (PW3050/60 MPD-system, PANalytical Netherlands). Interlayer spacing of the crystal lattice of the matrices were determined from Eq. (2).

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