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Optimization of formulation processes using Design Expert® Software for preparation of polymeric blends-artesunate-amodiaquine HCl microparticles

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ABSTRACT

A 2^3 Factorial design of cissus-gelatin B polymer blends was developed to formulate amodiaquine HCl-artesunate (AQ-AS) microparticles by varying the polymer blend concentration (2 %w/v, 5 %w/v), crosslinking time (0.5 h, 1 h) and glutaraldehye volume (0.5 ml, 1 ml). The formulations were evaluated using drug entrapment efficiency (EE), particle size, polydispersity index, thermal behavior with differential scanning calorimetry, crystallinity with powder X-ray diffraction, morphology with scanning electron microscope and *in vitro* release using combination of simulated gastric fluid (SGF, pH = 7.4, 95%) and methanol (5%). The expected responses, EE and *in vitro* release were fitted into Design Expert®.

The polymer blends exhibited pseudoplastic behavior and there was no marked change in rheology behavior of 2% w/v dispersion at 55 °C. The AQ-AS formulated microparticles were dark brownish discrete mass, physically stabilized, irregular shape, polydisperse, and partially crystalline system. An optimal formulation comprising polymer blend (5 %w/v), glutaraldehyde (1 ml) and cross-linking time (0.5 h) was identified to provide desired values for EE, amodaquine HCl (47.41%), artesunate (36.42%) and *in vitro* release. This study proposes the best opportunity for selection of factors required for optimum microparticles formulation using the polymer blends and the drugs.

1. Introduction

Drug delivery systems offer numerous advantages such as improved efficacy, reduced toxicity, reduced frequency of doses, and convenience when compared with conventional formulations. Of the different drug delivery systems reported, drug-loaded nanoparticles and microparticles attained importance because of the possibility to achieve passive targeting when their sizes are in particular ranges. The special interest for polymeric micro- and nanoparticles for oral drug delivery especially poorly water soluble drugs is owing to their small size and large surface area which favour their absorption compared to larger carriers as drug particles in the nanometer size range will dissolve more rapidly than a conventional formulation [1]. Biodegradable microparticles most often used as controlled drug delivery system (injectable, oral, transdermal, etc) have widely been studied in the area of controlled release and works have been done in combining the microparticles with other polymers for novel drug delivery systems.

Artesunate-amodiaquine incompatibility resulting in severe degradation of the drugs, short stability of the combination coupled with reported side effects caused by the high strengths of the drugs combination in Ghana in 2005 worsened the challenges in the AQ-AS formulations [2]. Therefore it is pertinent to formulate the drugs in microparticles for oral administration at reduced drugs amount but maintaining the same combination ratio using polymer blends of *cissus populnea* gum and gelatin.

Cissus gum (C) is a natural, nonionic polysaccharide derived from the incised sliced root of *Cissus polpunea* Guill. and Perr. (Vitaceae). It is a natural, biosynthetic, edible substance consisting of sugars-galactose, xylose, glucose, mannose, and D-glucuronic acid, used locally as thickener in foods, attracting attention in many

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works owing to a lot of its pharmaceutical uses; binder [3–5], medicinal uses [6,7]. Till date, no work has been reported on its use as a polymeric carrier matrix in novel drug delivery system in combination with another natural polymer.

A polymer blend or polymer mixture is a member of a class of materials analogous to metal alloys, in which at least two polymers are blended together to create a new material with different physical properties having most common specific interactions such as hydrogen bonding, dipole −dipole, and ionic interactions [8]. An important attribute of such hybrid polymers or polymer blends is that the new species either combine the qualities of the components in terms of functional and physicochemical properties or new functional properties different from the primary materials are obtained. This may result in superior functional and physicochemical properties when compared with the primary materials. Modification of naturally occurring polymers by formulations of polymer composites are popular methods by which new polymers and pharmaceutical excipients are produced for purpose of drug delivery as novel polymer biomaterials with effective multifunctional properties are continually being sought for drug delivery purposes [9–11]. In order to address the multifaceted oral delivery challenges, more sophisticated carrier systems are required, either as polymer-polymer or polymer-lipid hybrid systems, developed with the primary aim to combine the valuable features of both polymeric and lipid-based systems [12].

Therefore, there is always the need to develop an approach for determining the relationship between various process parameters and responses with the various desired criteria and searching the significance of these process parameters on the coupled responses [13]; after Box and Wilson [14] described the original basic theoretical and fundamental aspects of response surface methodology (RSM). Optimization using factorial designs is a powerful, efficient and systematic tool that shortens the time required for the development of pharmaceutical dosage forms, improves research and development work by reducing the number of experimental trials needed to evaluate multiple parameters and their interactions thereby making the process less laborious. Factorial designs which entails studying all the factors in all possible combinations, are considered to be the most efficient in estimating the influence of individual variables and their interactions using minimum experiments [15] and has played a key role in understanding the relationship between the independent variables and the responses to them in pharmaceutical formulations development [16]. The independent variables or parameters or factors are controllable, whereas responses are dependent. The contour plot gives a 2-D visual while the responses surface gives a 3-D visual of the representation values of responses and helps the process of optimization by providing an empirical model equation for the response as a function of the different variables [17–19].

Our research group, have been developing different novel microparticulate delivery systems especially lipid based formulations for antimalarial studies [20–23] but the microparticles production described here includes polymer blend systems (cissus and gelatin B at ratio 1:1) in which biodegradable microparticles containing drugs [amodiaquine HCl and artesunate (AQ-AS)] are embedded within the polymer blend matrix and the drug released through the porous polymeric matrices with desirable properties. Rapid opsonization by cells of the phagocytic system is a major limitation for achieving effective drug targeting to the site of action by gelatin B formulations. Thus, to maximize the therapeutic benefits of drug loaded microparticles, they should be able to evade the reticuloendothelial system (RES) through the use of various surface coatings of hydrophilic polymers, as opsonization of hydrophobic formulations may occur more quickly in comparison to hydrophilic formulations due to the enhanced adsorption of opsonins on their surfaces [24]. This was collaborated by Parveen and Sahoo [25] who investigated chitosan and polyethylene glycol (PEG) modification in order to reduce uptake of encapsulated hydrophobic drug (paclitaxel), hence the introduction of another natural hydrophilic polymer, cissus polymeric gum which is also biodegradable.

Development of really new anti-malarial drugs to market level is a very rare event as a lot of lead structures have already been screened and discarded, coupled with the administrative barriers that are increasingly high and costly [26]. Of the two major aspects to drug development for antiparasitic; pathogen-specific biochemical intervention strategy, and optimal formulation and application strategy, we focused on the later in our research using polymer blend of cissus and gelatin B after characterization of the polymer blends and the AQ-AS loaded formulations.

The objective of this work is to prepare, and evaluate cissus gum-gelatin (polymer blend) generated by compatibilized reactive polymer blending of colloidal dispersions of cissus gum and gelatin B at controlled temperature conditions. The AQ-AS microparticles formulated from the polymer blends were characterized and evaluated *in vitro* for oral drug delivery.

2. Materials and methods

The following materials were used as procured locally without further purification: gelatin B (Acofarma, Barcelona, Spain), Span 80 (Sigma Aldrich, Germany), sodium hydroxide (Merck, Germany), light paraffin oil, dilute hydrochloric acid, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate absolute ethanol, sodium chloride, conc. hydrochloric acid, acetone, glutaraldehyde (BDH, England). *Cissus populnea* was sourced from Uvuru Town in Uzo-Uwani LGA of Enugu State, Nigeria, while artesunate and amodiaquine HCl were gift samples from Emzor Pharma (Lagos, Nigeria). All other reagents were of analytical grade and were used as such.

2.1. Experimental design

The Design of experiment (DoE) was constructed in this study using Design Expert® Software (Version 9.0.3.1, Stat-Ease Inc, Minneapolis, MN) by adapting the 2^3 factorial design approaches to optimize the polymeric blended loaded microparticles. The independent parameters for optimization were; polymer blend concentration in the aqueous phase ($A = X_1$), volume of crosslinking agent, glutaraldehyde ($B = X_2$) and the crosslinking time ($C = X_3$). Preliminary studies also provided a setting of the levels for each formulation variable. In addition, the design is appropriate to study the quadratic response surfaces and to construct the second-order polynomial models. The selected responses were the encapsulation efficiency (Y_1) and cumulative % of *in vitro* drug released after 7 h (Y_2) of the study. Each independent variable was given a high and low level value as shown in Table 1 and a total of eight experimental runs of polymer blends AQ-AS microparticles formulations, as depicted in Table 1, were prepared.

Table 1
Factorial design parameters and experimental conditions.

Factors	Levels used, actual (coded)	
	Low (−1)	High (+1)
volume of glutaraldehyde (ml)	0.5	1
crosslinking time (h)	0.5	1
polymer blends concentration (%)	2	5