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Development and *in vitro* evaluation of cost effective amphotericin B polymeric emulsion

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ABSTRACT

The most significant drawback of low oral bioavailability associated with an effective antifungal and anti-leishmanial agent, Amphotericin B (AmB), has been overcome either through costly liposomal preparations or through simple preparations associated with higher toxicity. In consideration of these challenges, novel cost effective topical emulsion of AmB has been developed using readily available ingredients like canola oil, hydroxypropyl methylcellulose (HPMC) carbopol and Tween 80. The lipo-polymeric particles prepared by solvent evaporation of emulsion were characterized for size and shape through scanning electron microscopy (SEM). It was observed that freeze dried emulsions have relatively narrow particle size range of as small as 50 nm. The novel AmB emulsions were characterized for stability while thin layer chromatography (TLC) based assay confirmed the integrity of AmB in the formulated emulsion. AmB emulsion showed *in vitro* antifungal activity against *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger* and *Fusarium solani*. Additionally *in vitro* anti-leishmanial assay of emulsions showed 50% killing rate at 0.2 μg/ml of AmB and 100% mortality with emulsions containing 20 μg/ml of AmB. The novel emulsion has a great potential for large scale production of an AmB product for the treatment of topical fungal infections, cutaneous and post-kala-azar dermal leishmaniasis.

1. Introduction

Leishmaniasis is a major health problem in Africa and Asia, which is threatening day by day whereas invasive fungal infections are a major cause of morbidity as well as mortality in compromised patients [1,2]. Leishmaniasis, caused by a parasite named Leishmania, occurs in four forms in humans: life threatening visceral leishmaniasis (VL), commonly known as kala-azar; mucosal leishmaniasis (MCL), self-healing cutaneous leishmaniasis (CL), and post-kala-azar dermal leishmaniasis (PKDL) [3]. CL is a widespread tropical infection transmitted through bite of sand flies [4] which may be limited to a single lesion of the skin (localized cutaneous leishmaniasis) or may produce a large number of lesions (diffused cutaneous leishmaniasis) [5]. The parasite enters the human host with the bite and is pulled into macrophages through ingestion [6]. Topical fungal infections like candidiasis, aspergillosis, blastomycosis and histoplasmosis etc along with cutaneous leishmaniasis are important health problem in some developing countries [7].

Amphotericin B (AmB) has a broad antifungal and anti-leishmanial activity with low incidence of clinical resistance. AmB is a polyene (Fig. 1) which binds with ergosterol of cell membrane and stimulates the creation of pores followed by cell death. It is believed that the fungicidal activity is due to leakage of the essential nutrients and ions [8]. AmB is commonly used as antifungal/anti-leishmanial agent, administered intravenously, which is associated with toxicity particularly nephrotoxicity [9]. Topical application of AmB may be a safer approach in cutaneous leishmaniasis and other fungal infections.

The current preparations of AmB, available in market, have been developed utilizing conventional approach (Fungizone®; Bristol-Myers Squibb), lipid complex (Abelcet®; Enzon), colloidal dispersion (Amphocil®; AstraZeneca or Amphotec; Intermune Pharmaceuticals) and liposomal preparation (AmBisom®; Fujisawa Healthcare).

Nanotechnology has been applied in drug delivery approach to encapsulate the active ingredients utilizing different techniques such as solvent evaporation, nanoprecipitation, salting out, dialysis, Milling, supercritical fluid technology and emulsification/solvent diffusion [10–13]. Nagavarma et al.; reported methods for preparation of

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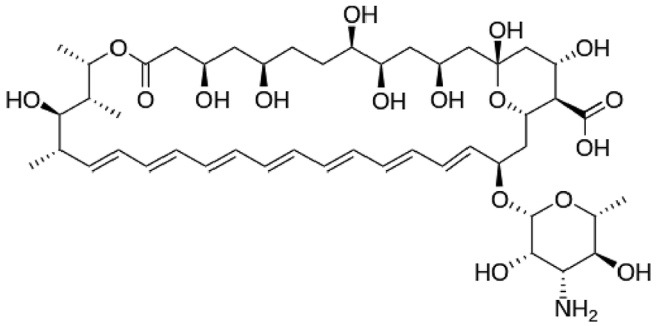

Fig. 1. Structure of amphotericin B.

nanoparticles from polymerization of monomers which are emulsion, mini emulsion, micro emulsion, interfacial and controlled/living radical polymerization [14]. Single and multiple emulsification techniques are frequently reported for the encapsulation of hydrophobic drugs and the nano/mircoparticles are being prepared using evaporation techniques [15,16].

One of recent trends in Pharmaceutical preparations is utilization of natural materials as much as possible in both conventional and nanotechnology based formulations for the better outcomes of therapeutic regimens [15,17–20]. In this study, canola oil made from the seeds of an edible form of the rapeseed plant, with high health benefits compared to other oils, is utilized. It is rich in omega-3 fatty acids, helps to reduce inflammation, acts as a moisturizer and does not show any side effect to the skin. Various researchers worked to present the solutions for addressing the issues according to their own understanding and ideas [21]. In this regard, a soybean oil based formulation have been evaluated for Leishmaniasis [22], however, any formulation containing canola oil which is also a cheaper source could not be found in literature. Polyoxy ethylene sorbitan mono oleate (Tween 80) is a hydrophilic surfactant with the highest solubilization capacity as compared with Polyoxy ethylene sorbitan mono laurate (Tween 20) and low toxicity [23]. In present work, exploitation of nanotechnology in formulation development, characterization, delivery and evaluation of AmB in both fungal and leishmanial infections is proposed. Main

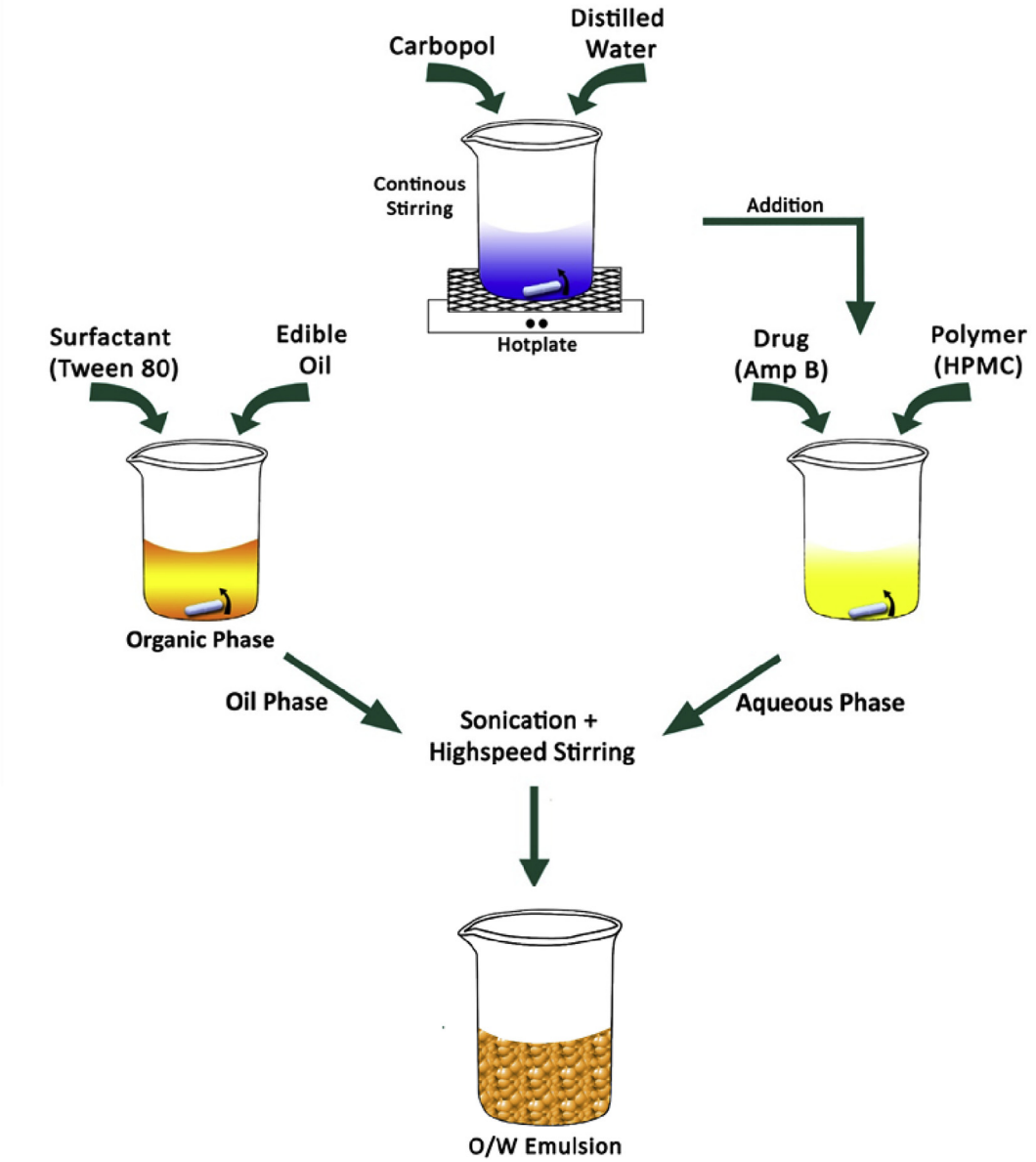

Fig. 2. Scheme of preparation of O/W Emulsion.