Abstract

Nano-enabled Fast-Dissolving Orodispersible Films of Amphotericin B for Buccal Candidiasis

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Introduction

Fungal infections in the oral cavity are opportunistic, usually caused by *Candida albicans,* and occur more frequently in patients with predisposing factors such as immunosuppression (e.g. HIV, cancer patients), diabetes mellitus, antibiotic and corticosteroid therapy, poor buccal hygiene and ill-fitted dentures [1]. A major challenge to effective topical treatments remains the residence time of the antifungal in the buccal cavity in high enough drug concentrations to be able to elicit adequate local action, as the majority of formulations rely on oral suspensions that are swished around in the mouth for a few seconds, gargled, and swallowed or spit out. Amphotericin B (AmB) possesses high activity against *Candida* spp. with low risk of resistance. However, AmB's high molecular weight compared to other antifungal drugs, such as miconazole and clotrimazole, and poor water solubility hampers its efficacy at the physiological conditions of the buccal cavity (saliva pH, limited volume for dissolution) and thereby limits its clinical use in buccal candidiasis. Here we present an optimised fast disintegrating orodispersible film (ODF) of AmB that is physically stable, loaded with high amounts of drug and designed to ensure AmB solubility in small volumes of saliva, while being taste masked and able to localise the formulation for a prolonged residence time on affected mucosa.

Materials and methods

AmB was purchased from Azelis (Barcelona, Spain). All chemicals were purchased from Sigma-Aldrich (Madrid, Spain). To ensure AmB solubility at the physiological pH of the buccal cavity, we entrapped AmB in sodium deoxycholate micelles that are then embedded within an ODF. Design of experiment (DoE) studies enabled us to identify the optimal drug:excipient ratio needed to ensure a high drug loading (1% AmB) that is critical to ensure concentrations well above the IC_{50} against *Candida albicans*. Films were optimised in order to minimise disintegration time and improve overall appearance and mechanical strength. A full evaluation was performed including particle size and zeta potential (after disintegration in artificial saliva), DSC, XRD, FTIR, DVS and SEM [2]. *In vitro*

antifungal activity was tested by the agar diffusion assay of the European Pharmacopoeia, as previously described [1]. ODFs were cut into circles of 6 mm diameter and compared to commercially available AmB Neo-Sensitabs tablets (10 μg) or AmB dissolved in DMSO.

Results and discussion

Optimisation of the AmB-loaded ODFs was achieved by QbD studies combining dextran and/or maltodextrin as dextrose-derived-polymer film formers with cellulose-derived film formers (HPMC/HPC in a 1:4 weight ratio), sorbitol for taste masking, microcrystalline cellulose (Avicel 200) or microcrystalline cellulose-carboxymethylcellulose sodium (Avicel CL-611) for enhancing the mechanical strength of the film and PEG 400 and glycerol (1:1 w/w) as plasticizers. The first-order mathematical model generated for each response variable was found to be significant statistically ($p<0.05$ in each case). Coefficients with p values > 0.1 were considered insignificant through Pareto charts and ANOVA analysis. High R^2 values for the polynomial equations obtained for all the response variables indicate a good fit to experimental data. ODFs with lower disintegration time were obtained when lower amounts of Avicel and cellulose-derived film formers were used and with higher percentages of plasticisers (Fig. 1A). In terms of the mechanical strength, the use of maltodextrin and Avicel 200 resulted in films with higher burst strength. The higher the amount of Avicel, HPMC AS/HPC and methanol, the better the mechanical strength of the films (Fig 1B). Regarding the appearance of the ODFs, it was improved when maltodextrin was used (Fig. 2A). However, very high amounts of maltodextrin led to very sticky films. The optimised AmB ODF formulation (containing 1% AmB, 25% dextran, 25% maltodextrin, 5% sorbitol, 10% Avicel 200, 10% PEG 400, 10% Glycerol, 3% HMPC AS, 12% HPC) possessed a fast disintegration time (60 ± 3 s), high burst strength (2,190 mN mm and overall good appearance (Fig. 2A). Regarding the water sorption kinetic profile (Fig. 2B), AmB-loaded ODF showed a large water uptake of 40% increase in mass at 90% relative humidity which can be associated with the hydrophilicity of the film. The optimised AmB-loaded ODF showed a good *in vitro* antifungal activity against *C. albicans* (with an inhibition zone > 15 mm) equivalent to that of AmB dissolved in DMSO and the commercially available disks, which indicates good drug release from the film and diffusion across the agar of the solubilised AmB (Fig. 3).

Conclusions

Preparing AmB loaded ODFs will enable a solid formulation that patients can use with increased residence time within the oral cavity compared to available suspensions that only remain a few seconds. This novel AmB ODF is a promising formulation with potential wide application in clinical practice, especially for immunocompromised patients suffering from buccal candidiasis.

Fig. 1

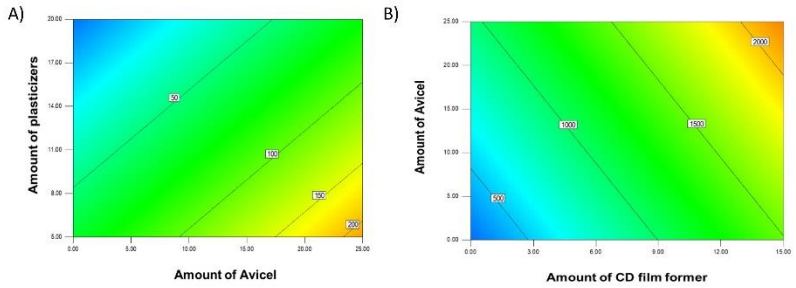


Fig. 2

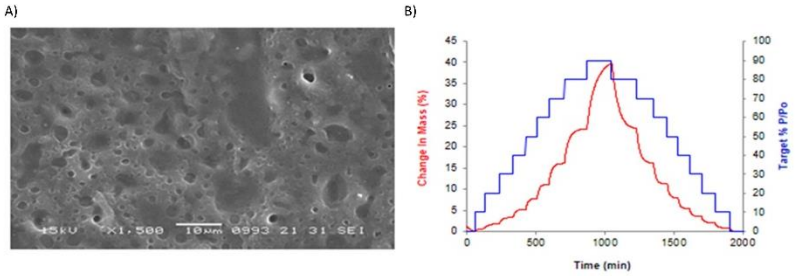
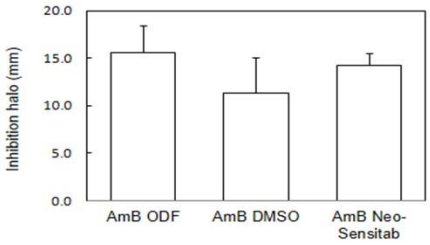


Fig. 3



References

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