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Solid effervescent formulations as new approach for topical minoxidil delivery

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ABSTRACT

Currently marketed minoxidil formulations present inconveniences that range from a grease hard aspect they leave on the hair to more serious adverse reactions as scalp dryness and irritation. In this paper we propose a novel approach for minoxidil sulphate (MXS) delivery based on a solid effervescent formulation. The aim was to investigate whether the particle mechanical movement triggered by effervescence would lead to higher follicle accumulation. Preformulation studies using thermal, spectroscopic and morphological analysis demonstrated the compatibility between effervescent salts and the drug. The effervescent formulation demonstrated a 2.7-fold increase on MXS accumulation into hair follicles casts compared to the MXS solution (22.0 ± 9.7 μg/cm^2 versus 8.3 ± 4.0 μg/cm^2) and a significant drug increase (around 4-fold) in remaining skin (97.1 ± 29.2 μg/cm^2) compared to the drug solution (23.5 ± 6.1 μg/cm^2). The effervescent formulations demonstrated a prominent increase of drug permeation highly dependent on the effervescent mixture concentration in the formulation, confirming the hypothesis of effervescent reaction favoring drug penetration. Clinically, therapy effectiveness could be improved, increasing the administration interval, hence, patient compliance. More studies to investigate the follicular targeting potential and safety of new formulations are needed.

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1. Introduction

Minoxidil is the only topical agent approved by FDA for the treatment of male and female hair loss. Several studies have proven its effectiveness in reversing the progressive miniaturization of hair follicles associated with androgenetic alopecia (Messenger and Rundegren, 2004). Nonetheless patient compliance is still a reason for therapy failure due the inconveniences of the twice a day application of formulations with undesirable sensorial aspects. Market formulations are constituted of propylene glycol–water–ethanol since minoxidil is poorly water-soluble. Besides leaving a greasy hard aspect to the hair, these components may also cause severe adverse reactions (*e.g.* scalp dryness, irritation, burning and allergic contact dermatitis) (Friedman et al., 2002; Yildirim et al., 2015). Hence, there is room for the development of novel formulations for the topical treatment of hair loss.

For decades it has been known that the minoxidil sulphate (MXS) metabolite is directly responsible for the hair-growth effects of minoxidil (Buhl et al., 1990). MXS is water soluble (~50 mg/mL) and therefore has been used for the development of novel topical formulations including nano and microparticles intended for follicle targeting (Gelfuso et al., 2011, 2013, 2015; Matos et al., 2015). One still non-exploited strategy is the use of powder MXS formulations to be hydrated during use for topical delivery. After hydration the drug could form a complex, a suspension or even be formulated to generate effervescence.

In effervescent technology, gas bubbles occur from the liquid after chemical reaction between alkali salts and organic acids (mainly citric or tartaric). Formulation is administered as a tablet or powder and the reaction occurs after adding water (Ipci et al., 2016). Even though some studies suggest enhanced buccal delivery from effervescent tablets in comparison to non-effervescent ones (Darwish et al., 2006; Jaipal et al., 2016), to our knowledge there are no studies to date evaluating the effect of effervescence reaction for topical follicular delivery, especially regarding follicle deposition of powder particles higher than 10 μm.

Indeed, one of the strategies to enhance the driving force for molecule penetration is to increase the thermodynamic activity of the drug in the vehicle. After topical application of a common solution, the thermodynamic activity is expected to increase as vehicle components evaporate. The maximum permeation flux would then be achieved at the drug supersaturation point. Hence, we hypothesized if the drug were administered in a solid state, once the powder is hydrated, saturation points formed adjacent to the particle would enhance skin permeation. In addition to that there is the need to investigate whether the particle mechanical movement triggered by effervescence would lead to follicle accumulation.

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Therefore, the aim of this study was to assess the influence of effervescent powder formulation on MXS topical permeation and follicular targeting potential. Besides the proof of concept, a stable effervescent powder formulation could be convenient to transport and to maintain the therapy in occasional situations as during travel.

2. Material and methods

2.1. Material

MXS (99%) was kindly provided by Galena Química e Farmacêutica Ltda. (Campinas, Brazil). Anhydrous citric acid (CitAc), tartaric acid (TartAc), sodium bicarbonate (NaBic) and saccharose were obtained from Sigma-Aldrich (Steinheim, Germany).

Scotch book tape (3 M, St Paul, MN, USA) was used for tape stripping and cyanoacrylate superglue (Henkel Loctite, Dublin, Ireland) was used for follicles biopsies. HEPES salt and NaCl were from Acros (Berkeley, NJ, USA). The solvents used for extraction and chromatographic analysis were all of HPLC grade.

Porcine ears were obtained from a local abattoir (Bonasa Alimentos, Brazil) <2 h post-sacrifice of the animal. The whole skin was removed from the outer region of the ear, separated from its underlying layer, and used "full-thickness" to guarantee the intactness of the hair follicles (Patzelt and Lademann, 2015). The skin was stored frozen at −20 °C for a maximum of 1 month before use.

2.2. Preformulation

2.2.1. Samples preparation

In order to evaluate the compatibility of MXS with effervescent salts, equal weight binary mixtures of MXS and each excipient (CitAc, TartAc and NaBic) were mixed using a vortex. Samples (compounds alone and binary mixtures) were aged using two treatments. Moist samples simulating a granulation process were obtained by adding purified water into the material, homogenizing and finally drying at 30 °C for 6 h. Heated samples were obtained by heating the material to 150 °C in a rate of 10 °C min^{-1}. The selected temperature for this last treatment was below the onset decomposition temperature of any of the materials used (Silva et al., 2014).

2.2.2. Thermal characterization

Differential scanning calorimetry (DSC) analyses were performed using a DSC-60A (Shimadzu, Japan). Samples of 2–4 mg placed in aluminum crucibles pans were analyzed under dynamic nitrogen atmosphere at a flux of 50 mL/min using heating rates of 10 °C min^{-1} from 30 °C to 300 °C.

2.2.3. Fourier transform infrared spectroscopy (FTIR)

STIR spectra were recorded at wavelengths ranging from 4000 to 600 cm^{-1} with a resolution of 4 cm^{-1}, using a Varian 640-IR FTIR spectrometer connected to an imaging ATR accessory (Varian Inc., Brazil).

2.2.4. Morphological analysis

Morphological characteristics of samples were analyzed using an SZ-SZT stereomicroscope connected to a video camera (Laborana, Brazil). Image processing was performed using an ISCapture software.

2.3. Experimental design

Effervescent systems were prepared according to a 2^2 factorial design (Table 1). The factors studied were the concentration of effervescent mixture (EM%) and the concentration of TarAc (TarAc%) in the formulation. The responses evaluated were MXS skin penetration in stratum corneum, follicular casts and remaining skin after 3 h. Model predictor equations for each response were calculated using step-wise multiple regression analysis with a significance level of 0.05. The coefficient of determination and the lack of fit were estimated in order to validate the models. All statistical calculations were performed using Design-Expert version 8 software (Minneapolis, MN, USA).

Table 1
Components used in MXS effervescent formulations according to 2^2 factorial design.

	F1	F2	F3	F4
MXS (%)	30.0	30.0	30.0	30.0
Citric acid (%)	17.9	35.8	9.3	18.6
Tartaric acid (%)	–	–	7.2	14.4
Sodium bicarbonate (%)	12.1	24.2	13.5	27.0
Saccharose (%)	40.0	10.0	40.0	10.0

2.4. Characterization of powder MXS effervescent formulations

2.4.1. Particle size distribution

Particle size distribution of effervescent formulations was assessed in triplicate using an automatic sieve shaker (Bertel, Brazil) and different sieves of mesh size from 62 μm to 850 μm. The mean equivalent diameter and standard deviation were estimated by probit transformation (Cunha-Filho et al., 2008).

2.4.2. Compressibility

Flow determinations were obtained on the basis of bulk and tap density values. Specifically, 10-mL beakers were filled with powder and tapped until stabilization of the volume. Compressibility was calculated using the following equation:

$$Compressibility = 100 \times (d_t - d_a)/d_t, \quad (1)$$

where: d_a is the bulk density of the freely settled material and d_t is the tapped density of the material.

2.4.3. Disintegration time and pH

MXS effervescent formulations equivalent to 200 mg of drug were added to 10 mL of water at 25 °C. The time required for the effervescence reaction occurrence was measured (Cunha-Filho et al., 2014). pH measures were then performed using a pH meter (Digimed, Brazil).

2.5. Permeation studies

Modified Franz diffusion cells (diffusion area = 1.3 cm^2) were assembled with the skin of the porcine's ear separating the donor to the receptor compartment. The receptor compartment was filled with 15 mL of a pH 7.4 HEPES buffer. Donor compartment was filled with either a MXS aqueous solution (20 mg/mL) or MXS in solid state (20 mg of MXS following by the addition of 1 mL of water) or effervescent MXS formulation (correspondent amount of 20 mg of MXS following by the addition of 1 mL of water). All experiments were conducted for 3 h with at least five replicates. At the end of each series of experiment, receptor solution was withdrawn from the diffusion cells and analyzed for MXS content. The skin was removed from the diffusion cell and placed onto a flat surface with the stratum corneum facing up. The skin was cleaned with a water-soaked gause pad and tape-stripped 15 times, using Scotch book tapes. A drop of cyanoacrylate superglue was applied to the stripped skin area and covered with a further tape-strip using light pressure. After total polymerisation of the glue (~5 min), tape-strip was removed and the skin surface biopsy containing follicular casts obtained, from which MXS was extracted with methanol and quantified. Finally, reminiscent skin was cut into small pieces and placed in plastic tube along with methanol for 12 h for drug extraction. The resulting suspensions were filtered on 0.22 μm filters and quantified by HPLC. The efficiency of recovery of MXS from follicular material and viable epidermis was previously determined (Gelfuso et al., 2013), with

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