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Alginate beads for transdermal drug delivery: II- *In vitro* permeation studies

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INTRODUCTION AND OBJECTIVES

The skin is a structurally complex, dynamic organ, designed to avoid problems of gastric emptying, effects of pH, enzyme desactivation and also first-pass hepatic effects, whose many properties may be used for a successful route of administration. (Walters et al. 2007)

In the 21st century, drug delivery companies are increasing in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast-dispersing dosage forms, techonology for insoluble drugs, and delivery of drugs through many administration routes. (Verma et al. 2001)

In this way, controlled release delivery systems, unlike conventional passive forms, can significantly improve the efficacy and safety of a drug molecule. (Verma et al. 2001) This technology has been employed in the delivery of molecules with challenging physico-chemical properties intended for delivery through the transdermal route.

Beads are solid drug carriers of natural, semi-synthetic, or synthetic polymeric origins that can be successfully included in controlled drug release systems. This study was conducted with alginate, a natural polymer, non-toxic, with broad spectrum of use, widely available and with high quality. Caffeine was selected as a model hydrophilic permeant.

The concept of measuring skin penetration by drugs or chemicals by using small pieces of skin removed from animals or humans is not a new one (Kemppainen et al. 1990). *In vivo* and *in vitro* methods are available for experimental studies, however due to ethical reasons and because of the less time consume equally reliable, the latter are preferred for preliminary studies. Percutaneous absorption experiments can use several membranes, synthetic and natural, and despite the anatomical differences, artificial membranes do not need pre-treatment and special conservation conditions, so they are used for studies of pre-formulation and validation of experimental techniques. (Dias et al. 2007)

The aim of this experiment was to study the transdermal delivery of caffeine encapsulated in two different alginate beads systems, using silastic membranes as a synthetic model for human epidermis. So, this study evaluates the influence of the nature of artificial silicone membranes on the release of caffeine and also the efficacy of two different delivery systems, dry and hydrated beads by comparison of the fluxes with an aqueous solution with free caffeine.ssss

MATERIALS AND METHODS

Formulations

Hydrated beads were produced by extrusion/external gelation process. Hydrated and dry beads were separated by filtration. The difference is that these beads remained in the fridge for three weeks to dry out.

Equal amounts of caffeine (1.5%) were included in three different systems:

1) Free drug in an aqueous solution;
2) Encapsulated drug in dry alginate beads suspended in distilled water (dry beads);
3) Encapsulated drug in hydrated alginate beads suspended in distilled water (hydrated beads).

Difusion cell preparation

Permeation of caffeine from the different formulations was investigated using Franz-type static glass diffusion cells (receptor volume 4 ml) immersed in a water bath at 37ºC. The receptor phase was a phosphate buffer, PBS (pH=7.4). A polydimethylsiloxane (silastic) membrane (75μm in thickness) was mounted between donor and receptor compartments and the effective area available to diffusion was 0.95 cm^2. Equal amounts of the different formulations, all containing 1.5% caffeine, were placed in the donor compartment of the diffusion cells. The donor compartment remained occluded throughout the experiment. At defined time points, 500 μl of receptor medium was collected for analysis and replaced with an equivalent volume of fresh receptor fluid.

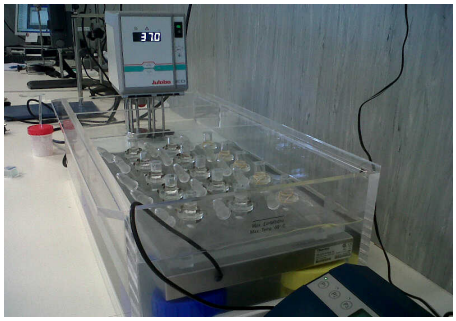

Figure 1 : Experimental set-up with Franz-diffusion cell

Data analysis

Sample analysis was performed on a UV detector set at 273 nm. Steady-state fluxes of caffeine in each system were determined through the slope of the graph cumulative amount diffused vs time obtained once steady-state diffusion was reached.

RESULTS AND DISCUSSION

The liberation profile of caffeine for the three delivery systems is shown in Fig. 2. According to the graph we see a linear profile for the liberation of caffeine with all vehicles and through the fluxes we can infer that the amount release is low, suggesting that the silicone membrane, a hydrophobic model, acts as a controlling barrier for caffeine and does not allow the free passage of the methylxantine.

Results indicate that the release rate of caffeine was increased when the molecule was encapsulated in the dry beads. Conversely, the lowest flux was achieved from the hydrated beads (Table 1 and Figure 2).

Table 1- Steady-state fluxes of caffeine in the different formulations (mean values ± SD)

Delivery systems	Flux ($\mu g/cm^2.h^{-1}$)
Aqueous solution n=4	8.99±0.97
Dry beads n=4	10.33±3.13
Hydrated beads n=5	6.42±0.39

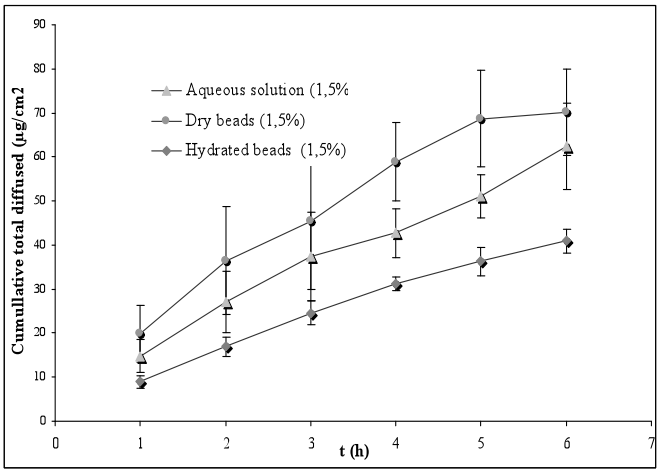

Figure 2: Permeation profiles of caffeine in the tested formulations (mean values ± SD)

The flux obtained in the hydrated beads system can be explained considering that free diffusion of the encapsulant is restricted by the gel porosity (Thu *et al*. 1996). Thus, the porosity of alginate beads restricts the drug diffusion of caffeine through the membrane of alginate, reducing the release rate.

In contrast, the release rate of caffeine in the dry beads system depends not only of the diffusion of the drug out of the gel matrix but also of the swelling of the beads (Sugawara et al. 1994). Results indicate that the latter seems to be the main factor affecting the release rate and, therefore, the flux.

CONCLUSION

These results indicate that this encapsulation technology can be successfully applied to modulate the bioavailability of drugs for transdermal administration. Further studies will be conducted with a lipophilic model molecule, followed by work with human skin and more therapeutically relevant drugs.

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