**P-083** **Alginate beads for transdermal drug delivery: I – Design and characterization studies**

**Fernandes, C.[1,#], Rosado, C.[2], Carvalho, P.[2] and Pinto Reis, C.[1]**
[1]Lab Nanosc & Biomed Nanotechnol, Univ Lusófona de Humanidades e Tecnologias, Lisboa Portugal [2]Experimental Dermatology Unit, Univ Lusófona de Humanidades e Tecnologias, Lisboa Portugal
[#] catiamendesfernandes@gmail.com

## INTRODUCTION AND OBJECTIVES

The skin is the largest organ of the human body, and the one enable to promote a most intimately contact between the body and the environment.

Transdermal and topical routes have become popular alternatives to more traditional methods of drug delivery since it offers many advantages like decrease of first-pass metabolism, reduction of side effects and possible sustained drug release, among others.

Caffeine was selected as a hidrophilic model drug because it has been widely used as an effective compound in the cellulite treatment. Caffeine acts by the stimulation of lipolysis by inhibiting phosphodiesterase (Cunha et al. 2006). According to Cunha et al. (2006), hydrolysis of the triglycerides is the only way to reduce the volume of the cellulitic nodules, since it removes the lipidic reserves which are eliminated via the lymphatic system.

The objective of this study was to design a system which encapsulates caffeine, but also permits drug delivery. Cellulite is a mynor cutaneous dysfunction which affects the cells of the subcutaneous layer (adipocytes). Thus, caffeine must be able to cross the stratum corneum that acts as a barrier.

Encapsulation has attracted considerable interest as a technology and stimulates the exploration of new drug delivery systems (Reis et al. 2005). We decided to encapsulate caffeine in alginate gel beads, which is a spherical gel prepared by dropping sodium alginate solution into calcium chloride solution (Sugawara et al. 1994).

Alginate was selected as encapsulant because it is natural, non-toxic, biodegradable and biocompatible polymer; furthermore, it is inexpensive (Reis et al. 2005). Alginate gels in the presence of multivalent cations (Reis et al. 2006) such as calcium ions. Calcium insoluble salt is the most widely used because it is considered as clinically safe, easily accessible and economical (Reis et al. 2005).

We selected the extrusion/external gelation method. However, the productivity of this method is inversely proportional to the bead volume (Poncelet 2001) and the size of the alginate particles depends on the size of the initial extruded droplet (Reis et al. 2005). There are several advantages of this technique such as high encapsulation efficiency (Vandenberg et al. 2001; Quong et al. 1998) and high retention of the drug (Vandenberg et al. 2001). The surface compactness of beads formed by external gelation offers a higher resistance to diffusion, playing a role similar to a membrane (Poncelet 2001). So, this characteristic will can be use for controlled drug delivery.

## MATERIALS AND METHODS

Beads were produced by extrusion/external gelation process. According to, Quong et al. (1998), a solution containing 2% of sodium alginate (SIGMA, S. Louis) was pressed through a syringe tip needle (22G) into 0,05M calcium chloride (FAGRON) solution (figure 1).

**Figure 1: Extrusion/external gelation method.**

Beads were separated by filtration and then called hydrated beads. Dried beads were produced using same method. The difference is that these beads remained in the fridge for three weeks to dry out. Bead size was measured. Encapsulation efficiency (EE) was determinate by indirect method, measuring the caffeine lost or non-encapsulated in the supernatant. The measurement was done by spectrophotometry at UV 273 nm.

## RESULTS AND DISCUSSION

Experimental evidences shows that alginate beads have been successfully prepared by extrusion/external gelation as seen in figure 2.

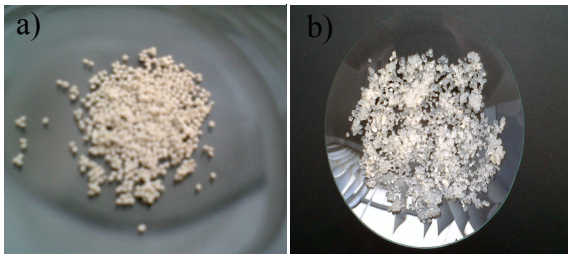


**Figure 2: a) Dried and b) hydrated beads.**

Caffeine beads size ranges from 2-3 mm for hydrated and 1mm for dried beads, as seen in table 1. The difference may be due to water loss.

**Table 1: Size and encapsulation efficiency.**

| | Size (mm) | EE (%) |
|---|---|---|
| **Dried** | 1 | 34 |
| **Hydrated** | 2-3 | 43 |

In table 1, is also presented the results for encapsulation efficiency, 34% e 43% for dried and hydrated beads, respectively.

Results show that more than half of caffeine is present in calcium chloride solution. There are two explanations for what happened here. First, one of the advantages of external gelation is the presence of a more surface compactness (Reis et al. 2006). We used a low molecular weight compound (caffeine with 194,19g/mol). Secondly, the technique used in the production of beads is also a factor (Thu et al. 1996).

In fact, the amount of drug released from alginate gel beads depends not only on the swelling of the beads but also the diffusion of the drug in the gel matrix (Sugawara et al. 1994). Free diffusion is restricted by the gel porosity (Thu et al. 1996). The porosity of alginate beads combined with the low molecular weight of caffeine, leads to the drug diffusion through the membrane of alginate, reducing the encapsulation efficiency.

Moreover, the calcium source is external. Thus, ions diffusion through alginate matrix may promote the output of caffeine.

However, the technique used to prepare alginate beads is simple, safe and reproducible but the industrial scale-up may be a difficult task since it requires multiple needles to produce a suitable amount of beads in industry (Vandenberg et al. 2001).

The next step will be the in vitro evaluation of the releasing behavior of the drug from alginate beads.

## CONCLUSIONS

The present data confirm that external gelation is a promising method to encapsulate hydrophilic drugs. However, further studies with low molecular weight drugs should be optimized, since depending on the physicochemical characteristics of the drug, it is now possible to choose the best method of preparation and the best polymer to have the best encapsulation efficiency.

## REFERENCES


- Cunha Â., J. B. Costa, C. Rosado (2006) *Cellulite : Functional Characterization and overview oh the Main Compounds used in the Cosmetological Approach*. Rev. Lusófona de Ciências e Tecnologias da Saúde (3) 1 : 77-85.
- Poncelet, D. (2001) Production of alginate beads by emulsification/internal gelation. *Ann. New York Acad. Sci.,* 944**,** 74-82.
- Quong D., R. J. Neufeld, G. Skjak-Braek, D. Poncelet (1998) *External Versus internal source of calcium during the gelation of alginate beads for DNA encapsulation*. Biotechnology and Bioengineering, 57 (4) 438-446.
- Reis, C., R. J. Neufeld, S. Vilela, A. J. Ribeiro, F. Veiga (2005) R*eview and current status of emulsion/dispersion technology using an internal gelation process for the design of alginate particles*. Journal of Microencapsulation, 23: 245-257.
- Reis, C. P., R. J. Neufeld, A. J. Ribeiro & F. Veiga (2006) *Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles*. Nanomedicine: Nanotechnol., Biol. and Medicine 2, 8-21.
- Sugawara S., T. Imai, M. Otagiri (1994) *The controlled release of prednisolone using alginate gel*. Pharmaceutical Research, 11 (2), 272-277.
- Thu B., P. Bruheim, T. Espevik, O. Smidrsod, G. Skjak-Braek (1996) *Alginate polycation microcapsules I. Interaction between alginate and polycation*. Biomaterials, 17 (10) 1031-1040.
- Thu B., P. Bruheim, T. Espevik, O. Smidrsod, P. Soon-Shiong, G. Skjak-Braek (1996) *Alginate polycation microcapsules II. Some functional properties*. Biomaterials, 17 (11) 1069-1079.
- Vandenberg, G., J. de la Noüe (2001) *Evaluation of protein release from chitosan-alginate microcapsules-produced using external or internal gelation*. J. Microencapsulation, 18 (4) 433-441.