P-069	**Development and *in vitro* characterization of drug-loaded gelatin nanosystem**	

Pinto Reis, C.[1,#], Nunes, F.F.[2], Rosado, C.[1], Rodrigues, L.M.[1]
[1]Universidade Lusófona de Humanidades e Tecnologias, Campo Grande, Lisboa – Portugal
[2]Universidade Federal do Paraná, Curitiba, PR - Brasil
[#] catarinapintoreis@gmail.com

INTRODUCTION AND OBJECTIVES

Transdermal drug delivery is one of the most promising methods for drug application since it offers several advantages over conventional dosage forms including extended duration of activity, avoidance of first-pass metabolism, minimization of pain, reduction of side effects and possible prolonged drug release.

Indomethacin was selected as a lypophilic model drug since it has been widely used as a non-steroidal anti-inflammatory drug for external pharmaceutical preparations. It works by inhibiting the production of prostaglandins, molecules known to cause symptoms such as pain, stiffness and swelling. The oral therapy with indomethacin is very effective but its clinical use is often limited mainly due to adverse effects. The administration of indomethacin via the transdermal route has been adopted to overcome the disadvantages of the oral route and maintain relatively consistent plasma levels for long-term therapy.

The present study was carried out to design a effective transdermal system of indomethacin. As well-known, the stratum corneum, the outermost layer of the skin, acts as a barrier. Thus, it is necessary to disrupt this function to improve the transdermal delivery of this drug. Herein, nanoencapsulation technologies were applied in order to enhance bioavailability of indomethacin after transdermal administration. Nanoparticles are solid sub-micronic drug carriers of natural, semisynthetic or synthetic polymeric nature in the nanometer size range (Reis et al. 2006). They have many advantages over traditional formulations. As well, other promising strategy in nanotechnology field is the use of multifunctional biodegradable polymers exhibiting permeation enhancing properties. The encapsulatant selected was gelatin since it is a non-toxic polymer/protein with broad spectrum of use and easy access.

MATERIALS AND METHODS

Nanoparticles were produced by two-step desolvation process (Lu et al. 2004). Parameters such as mean particle size and zeta potential were characterized. The *in vitro* permeation profiles of free indomethacin in cellulose-based system and encapsulated indomethacin in the same cellulose-based system were also studied using *Franz* cells. The cumulative amount of indomethacin passing across silicone membrane was calculated. Drug release was determined by UV spectrophotometry.

RESULTS AND DISCUSSION

Nanoparticles appear as a very good alternative system to deliver and to protect drugs (Reis et al. 2006). Gelatin nanoparticles were easily included in cellulose-based system as seen in figure 1.

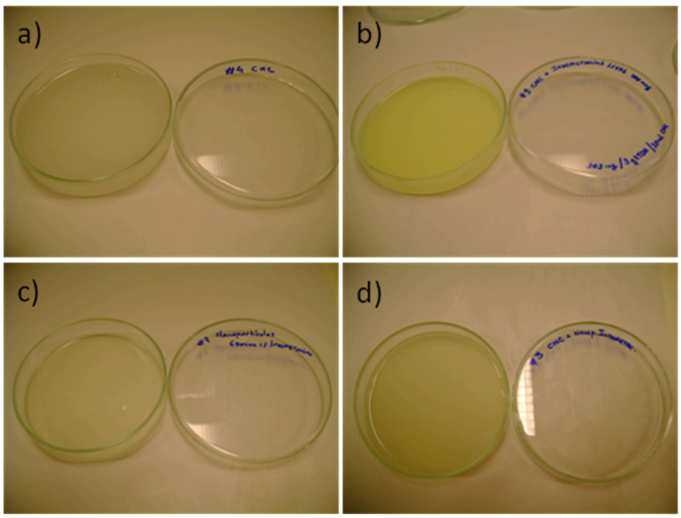

Figure 1: a) CMC-based system; b) CMC with free indomethacin; c) indomethacin-loaded nanoparticles and d) indomethacin-loaded nanoparticles in CMC-based system.

Gelatin nanoparticles showed a small mean particle size. Particle size ranged from 290 to 350 nm. The polidispersivity index was lower than 0,199.

The penetration of the skin barrier is size dependent (Hoet el al. 2004). At the skin surface, molecules contact with other molecules which negligibly affect permeation. The penetrant has three potential pathways to the target tissue: through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages. Sizes up to 200–300 nm can penetrate intact skin (Barry 2001). They may penetrate follicles and stratum corneum. In general, colloidal particles >10 μm remain on the skin surface; those 3–10 μm concentrate in the follicle and when < 3 μm they penetrate follicles and stratum corneum alike (Schaefer and Redelmeier 1996). Limited literature of nanoparticles penetrating the skin is available but some conclusions can already be drawn. Like previously described, the penetration of the skin barrier is size dependent and thus nanoparticles are more likely to enter more deeply into the skin than larger particles. Our study showed that gelatin nanoparticles were very small (in nano scale) and may potentially penetrate the skin. On the other hand, diffe-

rent types of particles were found in the deeper layers of the skin in the previous studies (Hoet el al. 2004) but it is difficult to predict the behaviour of our particles in the skin. Finally, materials, which can dissolve or leach from a particle or break into smaller parts, can possibly penetrate the skin (Hoet el al. 2004). In this case, gelatin showed very good physical characteristics.

On the other hand, zeta potential of gelatin nanoparticles was negative (mean value was -9 mV). Values were between -10 and -6.4 mV. Since the human skin has zeta potential around +23 mV (Morykwas, Thornton and Bartlett 1987), opposite particle charge may increase time contact between drug and skin.

Concerning permeation profiles of indomethacin, this study showed that gelatin nanoparticles led to a better controlled release of indomethacin but additional experiments are needed.

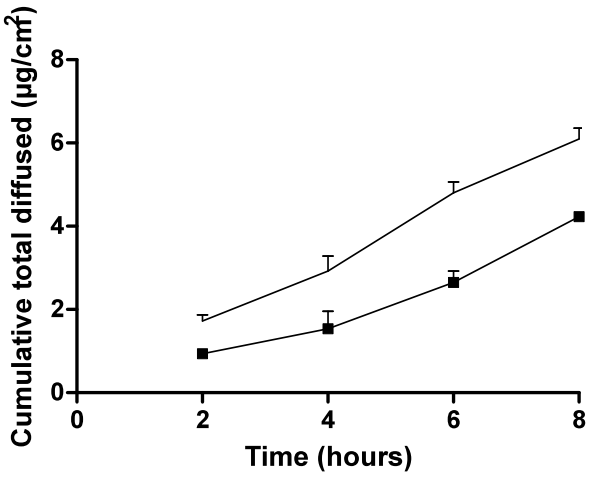

Figure 2: Permeation profiles of free (line) and encapsulated (full squares) indomethacin (mean value, n=3)

CONCLUSIONS

The present data confirmed the feasibility of developing indomethacin transdermal nanosystem. Further studies, now in progress, will deal with the application of the presently reported findings to human skin permeation, involving *in vivo* testing.

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