Design and transdermal delivery of indomethacin nanosystem

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Presently, transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation *via* skin. The transdermal route offers several advantages over conventional dosage forms including extended duration of activity, avoidance of first-pass metabolism by the liver, minimization of pain, reduction of side effects, reduction in the fluctuations of drug concentrations in the blood and possible sustained drug release.
Indomethacin was selected as a model since it has been widely used as a non-steroidal anti-inflammatory drug (NSAID) for external pharmaceutical preparations. It works by inhibiting the production of prostaglandins, molecules known to cause symptoms such as pain, stiffness and swelling. In fact, oral therapy with indomethacin is very effective but its clinical use is often limited because of its potential to cause 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 viable and practically effective transdermal system of indomethacin. As well-known, the stratum corneum, the outermost layer of the skin, acts as a barrier. It is therefore necessary to disrupt this function to improve the transdermal delivery of this drug.
Thus, nanoencapsulation technologies were applied in order to enhance bioavailability and reduce toxicity of indomethacin after transdermal administration. Nanoparticles are solid sub-micronic drug carriers of natural, semisynthetic, or synthetic polymeric nature in the nanometer size range. Nanoparticles may or may not be biodegradable and they have many advantages over traditional formulations and this is why the interest about them has increased in the past years. Nanoparticles appear as a very good alternative system to deliver and to protect drugs. As well, a promising strategy in nanotechnology field is the use of multifunctional biodegradable polymers exhibiting permeation enhancing and mucoadhesive properties. The polymer selected was gelatine because it is a non-toxic polymer with broad spectrum of use and easy access.

Methods:
Nanoparticles were produced by two-step desolvation process [1]. Parameters such as mean particle size and zeta potential were studied. The skin permeability of this nanosystem was also studied by using Franz cells. Free-indomethacin in cellulose-based system and indomethacin-loaded nanoparticles were considered. The cumulative amount of indomethacin passing across silicone membrane was calculated using the measured indomethacin concentrations in the receiver solutions. Drug release was determined by ultraviolet–visible spectrophotometer.

Results and Discussion:
Nanoparticles appear as a very good alternative system to deliver and to protect drugs [2, 3]. Gelatine nanoparticles were easily included in cellulose-based system as seen in figure.
Gelatine nanoparticles showed a small mean particle size. Particle size ranges from 290 to 350 nm. The polidispersivity index was lower than 0,199. At the skin surface, molecules contact with other molecules which negligibly affect permeation. The penetrant has three potential pathways to the viable 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 [4]. 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 [5].
Zeta potential was negative (mean -9 mV). Values were between -10 and -6.4 mV. Since the human skin has zeta potential around +23 mV [6], opposite charge may increase time contact between drug and skin.
Concerning permeation studies of indomethacin, this study showed that gelatin nanoparticles led to a better controlled release of indomethacin especially on burst release effect but additional experiments are needed.

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

References

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Figure

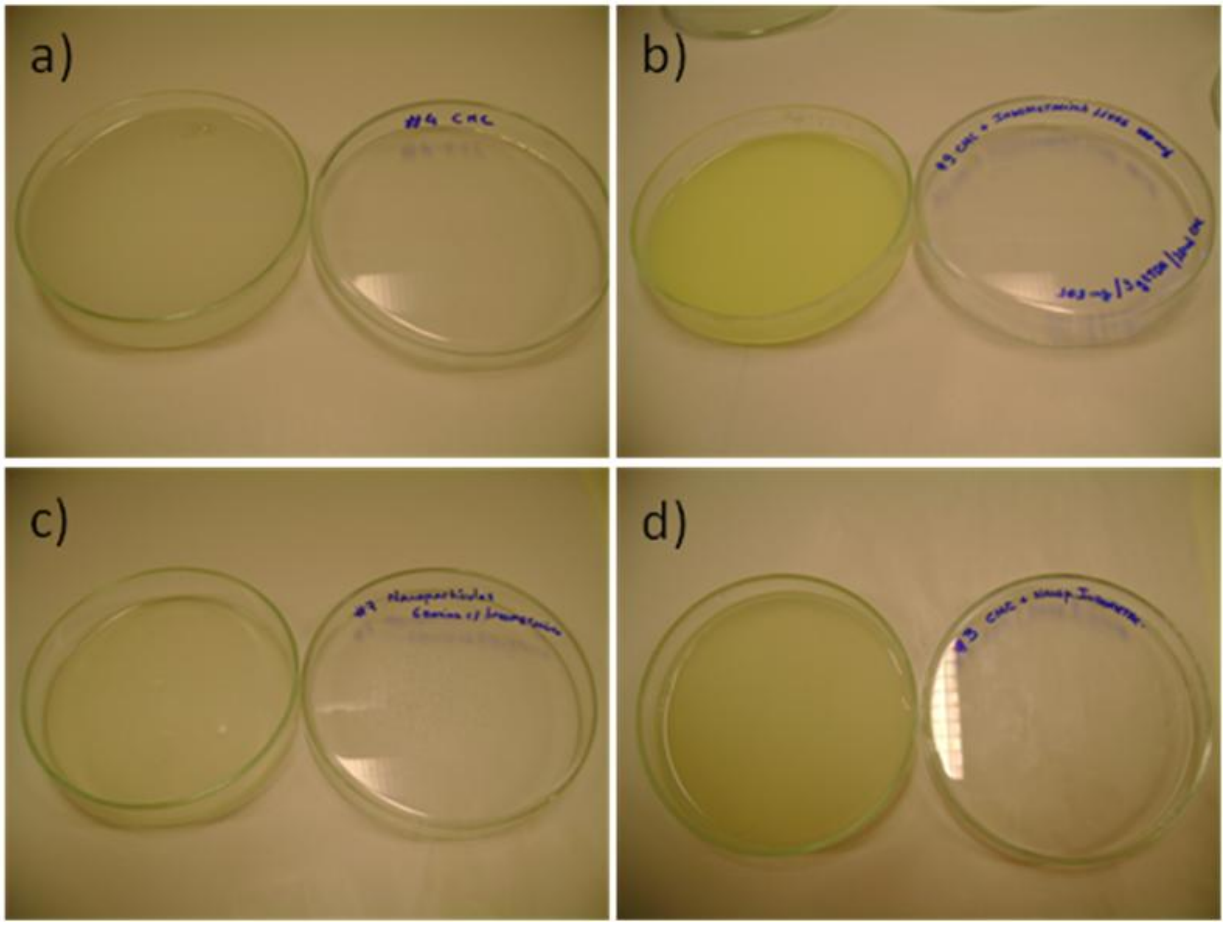

Figure. a) CMC-based system; b) CMC with free indomethacin;c) Indomethacin-loaded nanoparticles and d) Indomethacin-loaded nanoparticles in CMC-based system.