The effects of the β-cyclodextrin, as a solubility enhancer, on the efficacy and safety of diclofenac and progesterone formulations

C. Scavone[1], A.C. Bonagura[1], S. Fiorentino[1], R. Cenami[1], M. Torella[2], T. Fossati[3], F. Rossi[1]

[1] Dept. of Experimental Medicine – Section of Pharmacology 'L. Donatelli' – School of Medicine – Second University of Naples
[2] Dept. of Woman, Child, General and Specialistic Surgery - Second University of Naples
[3] IBSA Pharmaceutical

Background. According to *Health Technology Assessment* (HTA), patients deserve the better medicine, in terms of *safety* and *efficacy*; this could be made through the production of drug associated to *solubility* e*nhancer*, such as cyclodextrins. Cyclodextrins, cyclic oligosaccharides with a lipophilic inner cavities and hydrophilic outersurface, are very useful in pharmaceutical industry because they can interact with drug molecules to form inclusion complexes, changing drug properties, including enhanced solubility, bioavailability and sometimes reduced toxicity. Different drugs, belonging to class II of *Biopharmaceutics Classification System* II (high permeability, low solubility), are associated with cyclodextrins; example of these drugs are diclofenac and progesterone. When cyclodextrins are associated to diclofenac, they increase its water solubility from 138 μg/ml to 1030 μg/ml; similar effects were observed with progesterone.

Objectives and methods. In order to evaluate data regarding to pharmacokinetic characteristics, efficacy and safety of new medicines containing the associations diclofenac/cyclodextrins and progesterone/cyclodextrins, we performed a review searching articles published to date.

Results. More than 20 clinical studies compared the pharmacokinetics, efficacy and safety of diclofenac and progesterone in inclusion complexes of cyclodextrins in new formulations for subcutaneous administration (Akis®, Lubion® and Pleyris®) with medicinal products containing the same active ingredients but not associated with cyclodextrins. As reported by the results of these studies, nonsteroidal anti-inflammatory drugs (NSAIDs) associated with β-cyclodextrin have a more rapid onset of action after oral administration and better gastrointestinal tolerability. Moreover, the new formulation of diclofenac (25mg/ml) gives a rapid and effective response in acute pain and, furthermore, offers efficacy and safety profile comparable to those of other specialties already marketed. In particular, results from one of these studies confirmed bioequivalence of diclofenac HPβCD with the other diclofenac specialties already on the market. Moreover, based on the parameters of Cmax and AUC, authors of another study concluded that the new diclofenac formulation may be considered bioequivalent to other specialties.Finally, it must be stressed the importance of the lowest dose that suggests that this formulation, especially in patients treated with other medicines, may be more tolerable. Results of studies investigating the characteristics of progesterone and cyclodextrins showed that the new formulation has the same bioavailability of other specialties containing progesterone but because more rapidly absorbed, allows the achievement of peak plasma concentrations in a shorter time. Finally, regarding to the efficacy and safety, the new formulation of progesterone resulted safe and not inferior than other already marketed but not associated with cyclodextrins.

Conclusions. The ability of cyclodextrins to form inclusion complexes with a wide variety of organic compounds has allowed, as regards the development of drugs, to obtain significant increases in the stability, solubility and bioavailability. Thanks to their versatility, the typical structure and the chelating properties, cyclodextrins will play an important role in the pharmaceutical field, by improving the bioavailability and in some cases the tolerability of the different drugs.