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Indomethacin release in relation to the concentration of pharmaceutical excipients

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Indomethacin *in vitro* release was investigated in relation to the concentration of the pharmaceutical excipients, such as ethanol and propylene glycol. Drug release was studied from gels containing Sepigel 305 as a gelling agent. Not only the concentration of ethanol and propylene glycol influence the rate of indomethacin release, but also Sepigel 305 significantly increased the amount of indomethacin release.

Gels are suitable dosage forms for drugs with local effects (Vitková et al. 2004). Typical polymers widely used in pharmaceutical gel formulations are natural tragacanth, carrageenan, agar, alginic acid; semisynthetic materials such as methylcellulose, hydroxyethylcellulose, carboxymethylcellulose; and the synthetic polymer Carbopol (carbomer) (Aulton 2007).
Sepigel 305 is a gelling and thickening agent, excellent in the preparation of aqueous gels and emulsions with high stability also at high temperature. Sepigel 305, also known as polyacrylamide, C_{13-14}/isoparaffin and laureth-7, appears as a fluid, gelatinous, opalescent, yellowish dispersion with pH 6.5 in a 2% aqueous solution, and is compatible with most materials used in cosmetic preparations (Anchisi et al. 2001).

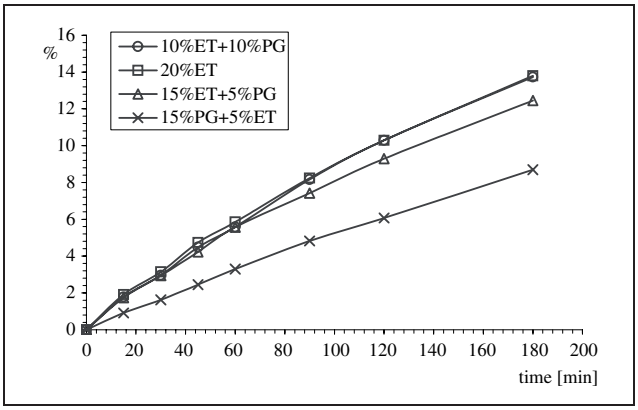

Fig. 1: Time dependent of indomethacin release from 2.5% Sepigel 305 gel in relation to the concentration of excipients (ET-ethanol, PG-propyleneglycol)

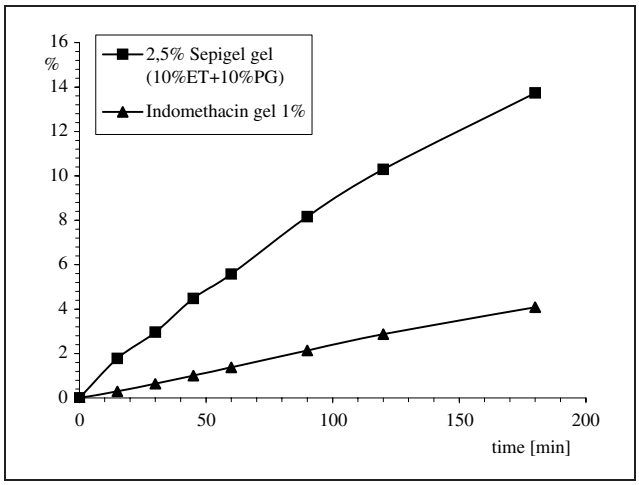

Fig. 2: Time dependent of indomethacin release from 2.5% Sepigel 305 gel compared with the commercial medicinal product named "Indomethacin gel 1%"

Ethanol and propyleneglycol are used as the solvents, extractants, preservatives (Rowe 2006) and chemical penetration enhancers that increase the rate of delivery of a range of drugs (Heard et al. 2006). In the current work, simple formulations were prepared using indomethacin (1%) as the drug, various concentrations of ethanol and polyethyleneglycol (5–15%) and Sepigel 305 as gelling agent.
On the pharmaceutical market in Slovakia there is only one suspension gel containing indomethacin called "Indomethacin gel 1%". Besides indomethacin, it contains Carbopol, ethanol 95%, propyleneglycol, camphor, sodium hydroxide and purified water.
As Fig. 1 shows, drug release from gels depends on the concentration of pharmaceutical excipients. The indomethacin release from the Sepigel gels was best from the formulation containing 20% of ethanol (released 13.8%), but the release of drug from the formulation containing 15% of ethanol and 5% propyleneglycol was similar (released 13.7%).
As Fig. 2 shows, Sepigel 305 (gelling and thickening agent) creates a significantly better gel than the commercially available medicinal product. Indomethacin release after 180 min was 4.1% and 13.7% from the medicinal product and from the Sepigel gel containing 10% ethanol and propylene glycol, respectively.
Based on these results, it could be concluded that ethanol plays a significant role in drug release because of the improved drug solubility, however, the role of the amount of ethanol should be further studied. The gelling and thickening agent Sepigel 305 is a significantly better pharmaceutical excipient for indomethacin release than Carbopol.

Experimental

1. Material

Indomethacin — 1-(4-chlorbenzoyl)-5-methoxy-2-methyl-1-*H*-indole-3-acetic acid, propyleneglycol, ethanol, Sepigel 305, KH_2PO_4, cellophane, Indomethacin gel 1% (VULM a.s., SR).

2. Instruments

Spectrophotometer – Philips Pyll Unicam Ltd., Cambridge (United Kingdom); Permeation apparatus – R&D Workshop of the Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava.

3. Preparation of the gels

Sepigel 305 gels were prepared by water addition into Sepigel 305 and after mixing opalescent gels were made at room temperature. Propylene glycol (5, 10, 15%), ethanol (5, 10, 15%) and indomethacin (1%) were added to the gels and the mixtures were homogenized and were left to stand for 24 h.

4. Evaluation of indomethacin release

A series of six permeation chambers was used. In each donor chamber, 3.0 g of the studied formulation was placed and 20 ml of phosphate buffer (pH 6.6) was placed in each acceptor part. The acceptor phase was mixed with a magnetic stirrer. Indomethacin was left to permeate at 37 °C through a hydrophilic membrane into the phosphate buffer. The amounts of released drug were determined spectroscopically at 318 nm after 15, 30, 45, 60, 90, 120 and 180 min.

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Long-term effects of D-003, a mixture of high molecular weight acids from sugarcane wax, on bones of ovariectomized rats: a one year study

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This study was done to determine the long-term effect of D-003 on bones of ovariectomized (ovx) rats distributed in 4 groups: a false-operated and three groups of ovx rats: one treated with the vehicle and two with D-003 (5 and 250 mg/kg). D-003 significantly prevented, in a dose-dependent fashion, the trabecular bone volume (TBV), trabecular number (TbN) and trabecular thickness (TbTh) reduction induced in ovx rats and the increase of trabecular separation (TbSp) osteoclast number (OcN) and osteoclast surface (OcS/BS) increased in the positive controls versus the sham group. It is concluded that D-003 administered for 12 months prevented bone loss and decreased bone resorption in ovx rats, without evidences of impaired bone quality.

D-003 is a mixture of higher aliphatic primary acids isolated and purified from sugarcane wax, wherein octacosanoic, triacontanoic, dotriacontanoic, and tetratriacontanoic acids are the most abundant and other acids (C24-C27, C29, C31, C33, C35 and C36) are at minor concentrations (Más 2004). D-003 inhibits cholesterol synthesis prior to mevalonate formation by regulating HMG-CoA reductase activity (Menéndez et al. 2001), and displays cholesterol-lowering effects (Castaño et al. 2003) and also inhibits lipid peroxidation in rat plasma lipoprotein as in healthy human volunteers (Castaño et al. 2003). D-003 (5–200 mg/kg) administered for 3 months prevented bone loss and bone resorption in ovariectomized (ovx) rats, increasing osteoclast apoptosis (Noa et al. 2004; Mendoza et al. 2005a), and administered for 80 days prevented corticoid-induced osteoporosis in rats (Noa et al. 2004a). D-003 (10 mg/day) for 6 months reduced the urinary excretion of DPD/creatinine, in postmenopausal women with low bone mineral density (BMD) (Ceballos et al. 2005).

The ovariectomized (ovx) rat mimics the increased trabecular bone loss and resorption occurring in postmenopausal women (Mosekilde et al. 1993; Bagi et al. 1997; Glatt et al. 2001). The assessment of the potential effects of any treatment on post-menopausal osteoporosis should include studies in this model, which provides information of the effects on bone quality, difficult to obtain in humans, in a short time, and also the effects after repeated bone remodelling cycles in such species (Thompson et al. 1995). So,