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PO-53

Comparison of two methods for assessment of drug-induced intestinal permeability changes

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In the present study, two indices of acute intestinal permeability changes were investigated as measurements of drug-induced gut damage. The first method is based on ^{14}[C]-polyethylene glycol (PEG) 4000 permeability assessment and the second is based on histological evaluation of the intestine. The test compounds were ibuprofen, ketoprofen and naproxen and the alanine, glycine phenylalanine and arginine conjugates of ibuprofen which were synthesised as previously reported [1]. ^{14}[C]-PEG 4000 was obtained from Amersham. UK. Perfusion studies were carried out using a rat model [2]. Liquid scintillation counting was used to measure PEG 4000 permeability coefficients. Post-perfusion, the gut was fixed and tissue changes were assessed and scored as reported elsewhere [3]. Ibuprofen, ketoprofen and naproxen altered the barrier properties of the intestine to PEG 4000 with significantly higher scores ($P < 0.05$) for damage relative to blank buffer. For ketoprofen, PEG 4000 permeability and intestinal damage scores increase with increasing ketoprofen concentration. Ibuprofen amino acid conjugates induce significantly lower ($P < 0.05$) levels of histological damage and less PEG 4000 permeability than ibuprofen, possibly due to masking of the carboxyl group. A correlation coefficient of 0.92 is obtained when intestinal damage scores are plotted against PEG 4000 permeability for all compounds. Histological evaluation of intestinal abnormality is proposed as a useful measure of drug induced acute intestinal damage.

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PO-54

Characterization of the physicochemical properties of a new antidiahetic agent

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ST2518(2-({3-|2-(4-chloropheny|)ethoxy]phenyl}sulfanyl)-2-propionic acid) is a new compound structurally related to the class of fibrates, and selected for development as an antidiabetic agent. Its mechanism of action appears to be related to the dual activation of the α- and γ-isoforms of the peroxisome proliferator-activated receptors (PPARs). The objective of this study is to determine the physicochemical properties of ST 2518 that are relevant to formulation of the drug (e.g. solubility, interaction with excipients, polymorphism) [1]. Solubility in water of ST 2518 at room temperature is 5.85 μg/ml and at pH 7.40 is 0.39mg/ml. In order to improve solubility in water in such a way as to be adequately tested in the preclinical phase and subsequently in the development phase the solubility in an aqueous medium in presence of various excipients was evaluated. The best solubility in an aqueous medium is obtained in the presence of Solutol HS 15, Polysorbate 80, Cremophor and SDS and the resulting solutions are chemically and physically stable for at least 7 days. The DSC of ST 2518 shows the presence of two peaks: one relative to an exothermic and the other to an endothermic transformation. Then we are in presence of polymorphism which could be a problem in the preparation of some pharmaceutica forms. In conclusion this preliminary physicochemical study permitted us to identify different possibilities of solubilizin ST 2518 in water, in relation to which there are no initial problems of compatibility with the principal excipients used.

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PO-55

Formulation and *in vitro* evaluation of bisphosphonat loaded chitosan microspheres for implantation in osteolysis

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Alendronate sodium (AS) is an aminobisphosphonate which inhibits especially the osteoclast related bone resorption [1]. In orthopaedics, in order to make the total joint prosithescs stay in the body for a long time without causing bone tissue loss, chitosan microspheres loaded with AS for implantation were prepared to be applied locally for preventi osteolysis. Therefore, objective of the present study was to design microspheres of AS using chitosan (Med. M.W.) in order to reduce the bone tissue loss. Particle size, drug loading, surface characteristics and *in vitro* release study were examined on prepared formulations. Microspheres containing AS were prepared by emulsion polymerization technique [2]. AS amount in microspheres was determined by precolumn High Pressure Liquid Chromatography method using 9-fluorenylmethyl chloroformate derivatization at 266 nm.

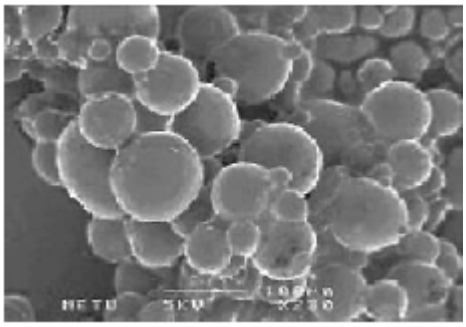

Fig. 1 SEM photograph of drug loaded chitosan microspheres.

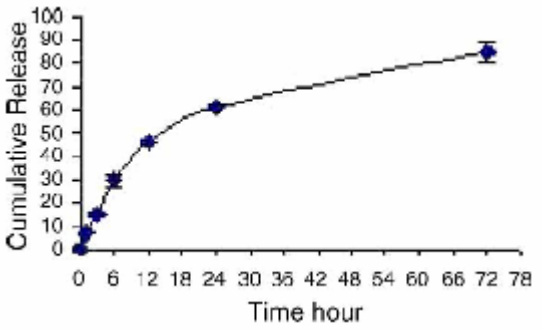

Fig. 2 Release profile of Alendronate sodium from chitosan microspheres.

The encapsulation efficiency of AS microspheres and the average particle size of the microspheres were found 3.3% and 109.28 ± 0.63. respectively. SEM photos revealed that microspheres were homogenous and had a spherical surface (Fig. 1). Release studies were carried out on chitosan microspheres in 0.1 M pH 7.4 sodium citrate solution and it was observed that the 85% of AS had been released from microspheres on the third day (Fig. 2). Prolonged release of AS from chitosan microspheres was observed during *in vitro* release studies. This formulation might be promising for the treatment of osteolysis in orthopaedics.

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PO-56

Novel instrumentation for the design of microspheres for chemoembolization

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The therapeutic efficiency of embolization towards tumoral stuructures is improved by addition of a chemotherapy. The stopped blood flow at the embolization site lead our team to couple drugs to microspheres designed for embolization, taking advantage of the mainly diffusive mass transfer conditions to provide high local concentration and prolonged release of drugs. A critical issue in the manufacturing of drug delivery systems designed for parenteral route is the lack of guidance focussing on *in vitro* release apparatuses. Therefore, we designed a novel *in vitro* apparatus, modelling the particular hydrodynamic conditions encountered at the embolization site. We transformed porous microspheres suitable for embolization into drug delivering microspheres through impregnation by alginate [1]. These novel microspheres were able to transport various hydrophilic tracers (indomethacin [2], FITC-dextran) with molecular masses ranging from 102 to 105 Da, highlighting their high potential as a drug delivery platform. Furthermore, impregnation provided a sustained release of the transported compounds in an *in vitro* continuous flow release system. Release from these microspheres at the embolisation was studied using the novel *in vitro* release apparatus, the "T"-apparatus. Controlled diffusive-convective process similar to mass transfer conditions encountered at the embolization site were reproduced [3], allowing the analytical study of release kinetics. Our novel drug delivering microspheres displayed drug releases over long time scales, highlighting their efficiency as prolonged-release microspheres.

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PO-57

All-trans-retinoie acid microspheres: Preparation and *in vitro* characterization

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Retinoic acid (RA), a vitamin A acid, regulates differentiation, proliferation of epithelial tissues, all important biological process such as growth, development, differentiation. reproduction, morphogenesis. metabolism, homeostasis. It has been used in dermatology, hematology, cancer research and therapy and embryonal development [1]. Antiproliferative effect of RA for retinal pigment epithelium has been reported [2]. It has been proved that RA is effective to reverse the squamous metaplasia in conjunctiva, caused by dry eye syndrome [3.4]. Poly (lactic-co-glycolic acid) (PLGA) microspheres of retinoic acid were prepared by using modified emulsion/solvent evaporation technique. PLGA (50:50) were used in two different viscosities (0.17 and 0.39dl/g). Polyvinyl alcohol or polyvinyl alcohol-sodium oleat mixture (4:1) were the emulsifying agent at the concentration of 0.5 or 1.0% (w/v). For this purpose eight different formulations were repared. The particle size range was obtained