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Abstracts from the

2nd WORKSHOP ON ARTIFICIAL ORGANS, BIOMATERIALS AND TISSUE ENGINEERING

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have been revised and evaluated by a scientific committee

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1.

THE HYPOTHERMIC PERFUSION MACHINE (HMP). APPLICATIONS TO THE PRESERVATION AND/OR THE RESCUE OF LIVERS FOR TRANSPLANT

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The developing demand of donor organs is responsible for an increasing utilization of marginal donor organs (MDO) provided by people suffering from non-beating heart. These organs have a growing vulnerability to ischemia-reperfusion injury and compromised repair mechanisms. Indeed, MDO have been associated with increased rates of delayed graft function and acute rejection rates. HMP offers the possibility of recovering these organs. Principles of HMP are based on controlled perfusion of the organ at low temperature, via the vascular bed which delivers oxygen and nutrients from the perfusate, while waste metabolites are continuously removed. But there are several points to be investigated respect to the methodology involved in the HMP to determine the appropriate practice to perfuse and recover MDO. These points are: 1- perfusion route (portal vein alone, portal vein and hepatic artery, hepatic artery alone, retrograde perfusion via hepatic vein; 2- perfusion pressure and flow (constant flow or constant pressure?, continuous or intermittent flow, pulsatile or not?, flow at 25 or 50% of the normothermic flow?; 3- perfusate oxygenation or not?, how much oxygen may be delivered during HMP?; 4- perfusion temperature, 20, 10 or 5°C?; 5- perfusate composition: the choice of the appropriate colloid and the Na^+ and K^+ concentrations. Is the addition of cytoprotectors, free-radical scavengers and iron chelators relevant during HMP?; 5- could it be beneficial to utilize pharmacological maneuvers as the addition of bioactive gases (CO, NO, or H_2S) during HMP?

2.

QUANTUM DOTS LIGHTING THE INTRACELLULAR WAY

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Continuous cell imaging has been dramatically improved with the introduction of Quantum Dots (QDs), colloidal nanocrystals with unique optical properties for long-term and multicolor imaging. Particularly, emission wavelengths of QDs are size-tunable, ranging from 400 to 1350 nm for nanoparticles cores between 2 to 10 nm in size. QDs conjugated with ligands and antibodies can be delivered to precise cellular targets, detecting biomolecules with a sensitivity extending to single particle. Furthermore, molecular engineering of the QDs surface allows activation of signaling pathways, sensing protein-protein interactions, tracking of membrane receptors in live cells, and long-term *in vivo* animal imaging. An important unresolved challenge is to release monodisperse QDs into the cytoplasm, considering that most of the delivery pathways involves endocytic uptake leading to QDs trapped in endolysosomal compartments. Current strategies point to the embedding of QDs in pH and temperature responsive polymers, liposomes and micelles in order to significantly increase the uptake by cells and to facilitate endosomal escape. The expectation is that QD-based targeted carriers will constitute a new means for the effective delivery of therapeutic macromolecules. However, QD biocompatibility and potential toxicity remain critical issues to employ them in humans, limiting their application in "*in vitro*" systems or in animal models. This presentation summarizes our experience in targeted delivery of QDs into cultured and cold stored rat hepatocytes.

3.

NOVEL Cu^{2+} RELEASING COMPOSITE FILMS FOR BONE TISSUE ENGINEERING

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Biodegradable and bioactive materials with sufficient structural integrity and angiogenic properties based on organic polymer-nanobioactive glass (NBG) composite films were developed. Films were loaded with Cu^{2+}. Morphology features were observed by SEM and the presence of Cu^{2+} was confirmed by EDX. Films bioactivity was analyzed through the growing of hydroxyapatite on the surface of the films, which was investigated by XRD. *In vitro* release of Cu^{2+} was quantified by UV method. Cellular *in vitro* studies were carried out to assess the ability of these films to support the proliferation of human umbilical vein endothelial cells (HUVECs). The incorporation of NBG into the films significantly improved their mechanical properties when compared with films without NBG. In addition, the novel composite films induced an angiogenic effect *in vitro* promoting the proliferation of HUVECs, due to the presence of Cu^{2+}. Cu ions were steadily released, controlled solely by crosslinking the ion with alginate. Biomineralization studies suggested the deposition of hydroxyapatite on the surface of the films, indicating their bioactive nature. Thus, it was shown that the novel composite films possess relevant physicochemical and biological effects, which make these materials promising candidates for bone tissue engineering applications.

4.

SCAFFOLDS FOR BONE TISSUE REGENERATION: STUDY OF CYTOTOXICITY

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A composite of hydroxyapatite (HA) containing poly-ε-caprolactone (PCL)-polydiisopropyl fumarate (PDIPF) (blend) was developed as an alternative for bone tissue regeneration. We have previously investigated the physicochemical, mechanical and biocompatibility properties of the blend using two osteoblast-like cell lines (UMR106 and MC3T3E1). Its properties were compared with a blend without HA and with a PCL/HA film. Based on these results the blend was proposed to be used for bone tissue regeneration. However, one important concern about biomaterials is to demostrate low toxicity properties. The aims of this study is to evaluate the toxicity of the films (PCL, PCL+1% HA, blend and blend+1% HA) in a model of macrophage in culture. To evaluate the production of proinflammatory cytokines IL-1 and TNF (by ELISA) and NO (Greiss´ method), RAW 264.7 cells were cultured on films for 24, 48 and 72 hours. Cells grown on culture dish were used as control, while 0.1 ug/ml LPS was added a positive control. Both NO and cytoquines levels produced by RAW 264.7 growing on PCL, PCL+1%HA, blend and blend+1%HA films shoved no significant differences when compared to cells cultured on plastic control plate along time. On the contrary, a significant increase in NO and cytoquines production was observed after the incubation with LPS. The films evaluated showed a low level of cytokine and NO production suggesting no cytotoxic effect.

5.

IN VITRO ENDOTHELIAL CELLS' RESPONSE TO BIOACTIVE GLASS IONIC DISSOLUTION PRODUCTS

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The aim of the present study was to evaluate the direct response of endothelial cells to the ionic dissolution products (IDPs) of bioactive glasses (BGs). Human umbilical vein endothelial cells (HUVECs) seeded on 96-well tissue culture plates were treated with conditioned media (CM) containing the IDPs of BGs that were prepared by soaking 1% w/v 45S5 BG particles (< 5 μm) of composition (in wt %): 45% SiO_2, 24,5% Na_2O, 24,5% CaO, 6% P_2O_5 or 45S5.2B BG containing B_2O_3 (2% wt) in complete endothelial basal medium M199 in a orbital shaker at 37°C for 24 h. The elementary content of Ca, Si, B, P and Na in the medium were determined by ICP. Cell proliferation was quantitatively assessed using the [^{3}H]thymidine incorporation assay. The migratory capacity of cells was evaluated by the wound healing assay. Cytokine expression was measured by an ELISA assay. Compared to controls, cell proliferation, migration and IL-6 release of HUVECs were statistically significantly increased by CM with BG 45S5.2B. The robust proangiogenic activity of soluble 45S5.2B BG degradation products appears to have promise for future application in tissue engineering and regenerative medicine.

6.

PRIMARY STABILITY OF IMPLANTS IN CEMENT CALCIUM PHOSPHATE: CLINICAL, RADIOGRAPHIC AND HISTOLOGICAL ANALYSIS

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The calcium phosphate cement (CFC) has been used as filling material for bone defects by offering osteoconductivity properties, bioactivity and biocompatibility. Recently studies, mostly in animals, indicate its use as adjunct treatment with dental implants. Thus this work aims at reporting the case in which post-extraction socket was grafted with CFC and after four months, the implant was installed amid the cement has not reabsorbed. Female patient, underwent surgery for extractions of teeth (12,21) convicted of fracture. Peri-operatively, the test socket was filling with CFC (tooth 21) and the other served as a control socket us and the other served as a control socket (tooth 12). After four months, a second surgery was performed for to install two external hex implants. Upon reopening of the implants after six months, the clinical appearance of peri-implant region was considered normal. Radiographically, there wasn't more radiopaque appearance of CFCs in the alveolar region of the test. The histological results demonstrated remaining CFCs in direct contact with bone without intervening fibrous tissue. The CFC has proved to be osteoconductive direct link between the calcium phosphate cement and bone. The material was shown to be an acceptable option for filling the post-extraction alveolus in order to maintain the bone volume. The results indicate that the CFC could have other applications in dental implants as the treatment of perimplantitis, graft exposed threads of the implant and the maxillary sinus, which, however, more research was needed to generalize the indication.

7.

ASSESSMENT OF NANOSIZED BIOACTIVE GLASS/COLLAGEN COMPOSITES AGAINST STAPHYLOCOCCUS AUREUS CELLS VIABILITY

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The aim of this study was to assess the possible anti-bacterial effects of new composite materials developed from collagen and inorganic bioactive glass nano-particles. For the first time for this end, we employed coating techniques based on stable colloidal suspensions of nano-particles (20-60nm) of bioactive glass (n-BG) from the SiO_2-CaO-Na_2O-P_2O_5 (45S5) system on type I bovine collagen membranes, as well as incorporating different weight percentages of n-BG to the collagen gel for the subsequent elaboration of membranes. The materials obtained were characterized by SEM-EDS. Anti-bacterial assays were carried out with *S. aureus* (ATCC 29213), because of the importance of this pathogen in failures associated with biomaterial implants. Bacterial suspensions of *S. aureus* ($1x10^4$ a $1x10^8$ cfu/mL) were prepared and then put in contact with the biomaterials at 37°C. After 0, 2, 3, 24 and 48h of incubation, their viability was determined by counting in Mueller-Hinton agar plates. Plates were incubated at 37°C for 48h in order to count colonies. The membranes were prepared for observation under SEM. Our results revealed the presence of bacterial cells on the surface of the collagen membranes with or without coating and/or incorporation of 45S5 n-BG. Furthermore, counting in plates did not show significant inhibition of the *S. aureus* strain analyzed.

8.

PRODUCTION OF MONOCLONAL ANTIBODIES FROM HYBRIDOMA CELLS IMMOBILIZED IN 3D SOL-GEL SILICA MATRICES

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The immobilization of mammalian cells in suitable matrices that can retain their viability and capability to produce certain metabolites has gained attention in recent years. In this work, hybridoma cells were immobilized in sol-gel silica matrices for *in vitro* production of monoclonal antibodies. For that purpose, different matrices were evaluated in terms of cell viability, antibody diffusion to surrounding media and physicochemical properties of the polymeric material. Tetrakis (2-ethoxyethyl) orthosilicate (THEOS) matrices were found to be the best option for hybridoma immobilization. The concentrations of the silica precursor as well as the number of immobilized cells were also optimized. Three hundred mM of THEOS precursor and 5×10^5 hybridoma cells appear to be the most suitable alternative. Hybridoma cells immobilized in THEOS matrices were able to produce monoclonal antibodies to the same extent as free cells, thus introducing the possibility of using them in the design of bioreactors for large-scale production.

9.

NITI WIRE CHARACTERIZATION FOR MECHANICAL ACTUATION APPLICATION IN REHABILITATION DEVICES

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Nickel-Titanium wires are commonly used as active materials for mechanical actuators. It is widely known that NiTi wires are capable of developing an important mechanical work when are subjected to a temperature-driven phase change. This project aims to characterize a particular commercial wire (Flexinol® round wire, provided by Dynalloy). The ultimate goal of this work is to have an accurate description of the wire electric-mechanical behavior. This characterization is essential when considering this technology as a potential solution for certain rehabilitation devices which requires nonconventional actuators. The 150 μm diameter wires are heated by *Joule effect.* A programmable current source was developed to meet this purpose (based on a PWM module). The instrument is connected to a computer via RS-232 serial port. The computer is used as an interface to set the current source program, and to receive a signal from a LVDT displacement sensor, which measures wires deformation. The obtained results indicate that the wire is a suitable material to be used as a light weight actuator. The high output work to weight ratio and fatigue resistance are some of the most important features that these type of shape memory alloy shows.

10.

A CUSTOM-BUILT DEVICE TO MEASURE ULTRA-RAPID COOLING RATES OF BIOLOGICAL SAMPLES

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Preservation at low sub-zero temperatures of biological samples has proved to be a useful technique in a wide variety of disciplines such as Tissue Engineering and Regenerating Medicine. The inmmersion of the sample into liquid nitrogen (LN_2) is a simple method to obtain high cooling rates (larger than 2000ºC/min) on what has been known as ultra-rapid cooling. However measuring such temperature rates is not a simple task with standard laboratory instruments.

We have developed a system for measuring temperatures (Te) at high sample rates (up to 1200 samples . sec^{-1}) using a type T thermocouple as sensor element. An immersion device, allows us to measure the penetration speed (PS) of the sample in LN_2. This device uses gravity to obtain a high reproducible immersion process and an optical system as speed sensor. Both measures (Te and PS) can be obtained simultaneously using a USB based dual channel digital oscilloscope interfaced to a laptop computer. The entire setup allow to achieve multiple determinations of high speed cooling and rewarming rates, to assay different configurations of sample reservoirs, and to test the volume and composition of cryoprotector agents. A standard measure shows a 3507 ± 175ºC . min^{-1} (n=5) cooling rate for a 2M DMSO solution contained in a commercial 0.2 ml polypropilene thin wall PCR tube, and a 92.4 ± 10.5 m . min^{-1} (n= 5) PS for the system.

11.

DEVELOPMENT OF A NEW FLAT-PLATE MODEL OF BIOARTIFICIAL LIVER (BAL): ITS ADEQUACY TO LIVER MICROORGANS (LMOS) AS BIOLOGICAL COMPONENT

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BAL devices were designed to "bridge" patients until they either recover or receive a liver transplant. The first prototype developed in our laboratory consist of a simple hollow fiber-based cartridge perfused with blood flowing through the fibers lumen. This device showed an effective ammonia depuration rate using isolated hepatocytes as the metabolically active component. As the "ideal" biological component should contain all liver cell types to obtain the maximum response, we became interested in evaluating the performance of LMOs. LMOs are tissue slices that retain the basic microarchitecture of the liver lobe and its physiological characteristics. The use of LMOs is also attractive because it obviates the stages of cell isolation and cultivation. Adapting the cylindrical shaped model used with hepatocytes did not showed the expected results, so the objectives of this work were to develop a BAL model suitable to use LMOs, and evaluate the performance of rat LMOs in this new model. LMOs were manually cut from rat livers into slices of 338±27 μm thickness, n=25. We constructed a new BAL prototype using a 25 cm^2 culture flask, which offers a flat surface that allows a better bathing and shaking of plane LMOs. LMOs were loaded into the BAL and an ammonia overload (1.06±0.12 mM, n=3) was added to the blood before initiating the system perfusion at 9 mL/min. LMOs detoxify 49.3±8.8 % of the initial ammonia overload at 120 min and the LDH release was 6.1±2.2 %, showing a good maintenance of their viability. In conclusion, the new BAL design is adequate for a good performance of LMOs as biological component.

12.

BIOMIMETIC METHOD FOR COATING MICRO AND MACROPOROUS TITANIUM SUBSTRATES

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Titanium (Ti) surface with calcium phosphate (CaP) coatings has shown to improve osseointegration at the implant-bone interface, because of the high biocompatibility of the mineral. The present work studied a biomimetic method for coating Ti substrates for surgical implant applications. A simplified solution (SS) was used with high calcium and phosphorus ion concentrations. Micro (mTi) and macroporous (MTi) titanium ASTM/grade 2 samples, produced by powder metallurgy, were used as substrates. The samples were pre-treated for surface bioativation using a NaOH solution followed by heat-treating. Then they were immersed for 7 and 21 days in SS, based on $CaCl_2.2H_2O$ and $Na_2HPO_4.2H_2O$ salts. The uncoated substrates characterization was performed by optical microscopy, quantitative metallographic analysis and confocal microscopy. The CaP coatings on Ti substrates was analyzed by scanning electron microscopy, energy dispersive X-ray spectroscopy, high resolution low angle in X-ray diffraction and Fourier transform infrared spectroscopy. Hydroxyapatite and carbonate apatite were observed on mTi and MTi coatings. The results attested that the SS solution is promising for precipitating CaP coating on Ti substrates, although adjustments in the methodology are necessary in order to obtain continuous and thicker coatings.

13.

MECHANICAL PERFORMANCE ANALYSIS BY FINITE ELEMENTS OF A HYDROXYAPATITE POLYMETIL METACRILATE HIP SPACER

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The infection after total hip arthroplasty leads to failure of prosthesis and requires a revision surgery. Before this, it is necessary the antibiotic treatment which can be systemic or local. The last option requires the implantation of a hip spacer, moulded from bone cement (polymethyl methacrylate, PMMA) mixed with antibiotic, with the same shape of hip stem and femoral head. This spacer heals locally the infection by antibiotic release, which is trapped in material pores. This stage requires the mechanical stability of the spacer for two o three months; thus, the strength of the device must be enhanced to avoid the local fatigue stresses. This aim could be accomplished by incorporating a metal core (made of titanium or AISI 316L steel) or by modifying the spacer shape in order to built it using a single material. The material choice is not exploited up to now, so it is analyzed here building a composite made of 60% PMMA - 40% Hidroxyapatite (HA, mineral bone component). In addition, incorporation of HA favors the antibiotic fixation in the spacer. The finite element modeling is applied to both a conventional and a new design of the spacer. The analysis is performed in static conditions, and using material data from bending tests of composite samples and from fatigue tests of PMMA samples (extracted from literature). The results show that local stresses for the new design are up to 34% lower than those of the conventional design. This finding suggests that the new spacer entirely molded with PMMA-HA composite may assure mechanical stability of the device for a longer period of time than that required for the infection treatment.

14.

A MATHEMATICAL MODEL FOR FLOW ANALYSIS OF AN IMPLANTABLE CENTRIFUGAL BLOOD PUMP

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When a cardiac disease affects a patient, we often need a cardiac transplantation or alternative therapies. However, organ's availability doesn't meet the recipients demand and several patients die waiting in the transplant list. Left Ventricular Assist Devices (LVAD) are indicated in these cases as "bridge to transplant". The application of such blood pumps make possible for patients to survive until surgery. The Implantable Centrifugal Blood Pump (ICBP) is been developed in our laboratories as LVAD. Computational Fluid Dynamics (CFD) is a design tool that can predict hemolysis and stagnant flow in blood pumps by numerical analysis. This work presents a mathematical model of a centrifugal blood pump proposed by Motta (1991) and adapted to ICBP project. The model is based on two parallel discs, one rotating and other static. The solution of fluid dynamics Partial Differential Equations (PDE) was performed by a computer program implemented in MATLAB. Preliminary results are similar to the previously calculated by Motta. The model is compared to experimental data in order to propose improvements in the solving method. In future works, the model proposed will consider the non-newtonian behavior of the blood and turbulent flow comparing with other CFD tools.

15.

IMPLANTABLE CENTRIFUGAL BLOOD PUMP DESIGNED FOR LONG TERM LEFT VENTRICULAR ASSISTANCE

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The Implantable Centrifugal Blood Pump (ICBP) is a multicentre project for the design of a Left Ventricular Assistance Device (LVAD) for long term support of patients with severe cardiovascular diseases. LVADs are used in heart transplantation, myocardial recovery and therapy (including regenerative therapy and tissue engineering). The ICBP system includes a centrifugal blood pump with double ceramic pivot bearings, hydraulically-levitated impeller, magnetic passive coupling and rpm-controlled miniaturized actuator. Computational Fluid Dynamics (CFD) models were used to define impeller characteristics. Rapid Prototyping (RP) techniques and Computer Numerical Control (CNC) were used for the construction of physical models. "*In vitro*" tests were performed in order to evaluate wear in pivot bearings, hydraulic performance of different impeller geometries and index of hemolysis with human blood. Results were considered satisfactory. The next step is to evaluate the device performance "*in vivo*".

16.

"IN VITRO" TESTS OF AN IMPLANTABLE CENTRIFUGAL BLOOD PUMP OBTAINED THROUGH RAPID PROTOTYPING PROCESS

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An Implantable Centrifugal Blood Pump (ICBP) is being developed in the Institute Dante Pazzanese of Cardiology to be used as left ventricular assist device (LVAD). The system consists of a centrifugal pump, a driver, a motor, a controller and a power supply. Preliminary tests are important during development of such devices to avoid flaws in operation. Prototyping of LVADs allows the analysis of this operation, identification and correction of flaws. The prototype was constructed in partnership SYCAD (SYCAD Systems Ltda, Sao Paulo, Brazil) through the process of 3D Print using the Polyjet™ technology.
The prototypes were tested in a workbench which consists of an acrylic water reservoir, an ultrasonic flow meter (Transonic Systems, Ithaca, NY, USA), the drive module of the ICBP and a pressure monitor. The prototype was tested in a closed loop using rotation velocities from 1200 RPM to 2200 RPM in order to analyze the pressure and the flow in the ICBP. The process of 3D Print resulted in reliable parts, and it was essential to accelerate the manufacturing and testing of new concepts and different geometries.

17.

COMPOSITES BASED ON POLY (VINYL ALCOHOL) HYDROGELS FOR WOUND DRESSING

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Wound dressing is an artificial skin that can meet the requirements such as higher vapor or gas permeation and protection of wound from infection and dehydration. Poly (vinyl alcohol) (PVA) hydrogel is one of the well-known polymer gel that due to its good biocompatibility, hydrophilicity and capability of swell in water or biological fluids has been used in several biomedical and pharmaceutical applications.
The main objective of this work was to synthesize, in order to obtain wound dressing with better properties, composite-hydrogels. These composites were prepared using combination of: PVA/bentonite (3 and 7.5wt.%), PVA/cellulose (3 and 7.5wt.%), PVA/Ag nanoparticles, PVA/rosemary extract and PVA /clove extract, via the freezing/thawing method. For this purpose, chemical, thermal, mechanical, swelling analyses and antimicrobial properties studies (using as indicator *Escherichia coli O157:H7* and *Listeria monocytogenes*) were carried out. The results showed that PVA/bentonite and PVA/cellulose had the higher antimicrobial behaviour. In addition, they exhibit the mechanical and swelling characteristics suitable for use as wound dressing.
Their function as barrier against microbe penetration showed that they could protect the wound from further infection; hence it could accelerate the healing process of wound.

18.

FABRICATION OF A POROUS Ti-HAP COMPOSITE

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Titanium and its alloys are considered very good materials for joint replacements. The ideal biomaterial for this application is expected to exhibit properties such as a very high biocompatibility and excellent corrosion resistance with body fluids. Also, a density near that of bone, high mechanical strength and fatigue resistance, low elastic modulus and good wear resistance. It is very difficult to combine all these properties in one material.
Titanium is recognized to have very good properties for biomedical applications. Powder metallurgy techniques allow to introduce pores in solid titanium, lowering the compression modulus by pore collapse.
The need of very good biocompatibility, makes the hydroxyapatite (HAP) an excellent candidate to react with the human tissues. It is widely used to produce porous ceramics and for surface modification of Ti implants. Coating of HAP has some drawbacks: the thoughness is low, and during the coating stage by plasma sputtering interfacial cracks can occur.
In this work we added HAP as a second phase to the Ti with powder metallurgy methods. It was incorporated 5, 10, 15 and 20% of HAP at three treatment temperatures, 1000, 1100 and 1300 ºC. Our results indicate that at the highest temperatures the sinterization process was good but, with more than 10%, HAP discomposed, increase its volume and disaggregate the material.

19.

POLYVINYLALCOHOL / HYDROXIAPATITE HYDROGELS OBTAINED BY TWO DIFFERENTS TECHNIQUES: CHARACTERIZATION AND SWELLING STUDIES

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The applications of Poly (vinylalcohol)/hydroxiapatite hydrogels (PVA/HA) have been extended to the replacement of diseased or damaged articular cartilage due to its good physicochemical and especially tribological properties. The main objective of this work was to obtain and compare PVA/HA hydrogels with “in situ” generated HA by two different techniques: freezing/ thawing (F/T), and ISISA (ice-segregation-induced self-assembly). For this purpose, morphological, chemical, thermal, mechanical and swelling analyses were carried out.
The F/T method consist of: freezing (-18ºC) a solution of PVA with $Ca(OH)_2$ and H_3PO_4 (stochiometric rate to precipitate HA) and thawing this solution (25ºC), repeating the F/T cycle 3 times in order to crosslink the polymer.
The ISISA process involves the submission of an aqueous gel, solution or suspension to liquid-nitrogen temperatures and subsequent sublimation. The controlled ice formation drives the segregation of every solute or colloid originally dispersed in the aqueous phase towards the zones in which the ice is absent, giving rise to areas where the ice resided before sublimation, resulting in an organized 3D scaffold.
The results indicate that PVA/HA by F/T exhibit mechanical and swelling characteristics suitable for the use as articular cartilage replacement. In addition, the scaffold obtained by ISISA revealed the influence of the freezing rate on the final morphology, mechanical and swelling properties. Finally, similar studies were done for scaffolds obtained by the combination of both techniques.

20.

STUDY OF THE NANOFIBROUS MORPHOLOGY OF SMALL-DIAMETER VASCULAR GRAFTS

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Small diameter vascular grafts for cardiovascular applications are still a challenge. The existing grafts present limitations in supply, dimensions (autografts), immunogenic response (allografts and xenografts), thrombosis, stenosis and occlusion (synthetic grafts). Tissue engineering small-diameter vascular grafts are interesting candidates for these applications. In this work, we report the development of poly(L-lactic acid) small-diameter vascular grafts obtained by electrospinning technique. The setup used consisted of a grounded rotocollector small-diameter mandrel, a flow pump, a high voltage power supply and a blunt metal needle. The processing conditions were optimized in order to produce uniform bead-free nanofibrous morphology. In a first approach, random electrospun nanofibrous flat membranes were obtained and a study of the electrospinning parameters influence in the nanofiber diameter was made. Once these conditions were fixed tubular scaffolds were made and the influence of the rotation speed in the nanofiber alignment and morphology was studied. Scanning electron micrographs were processed to obtain the mean diameter, diameter histogram, mean angle of alignment, and angle histogram. Thermal properties of raw and electrospun materials were also analyzed.

21.
NOVEL Ca AND P COMPOUNDS ELECTRO-DEPOSITED ON Ti FOR IMPROVING BIOACTIVITY

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Ti and its alloys present good biocompatibility making them suitable for biomedical applications due to their low toxicity and their ability to promote a positive osseous tissue response after surface modification. The development of a surface film by anodisation would decrease the corrosion rate, minimising metal ion release to the biological media, and facilitating its osseointegration. The incorporation of Ca and P compounds on the anodised film is proposed as a way of improving the bioactivity of the metal implant. The aim of this work is to study the electrochemical properties and film structure of Ti anodic oxides grown in phosphoric acid, followed by the electrodeposition of calcium and phosphorous compounds. The anodisation treatment was performed at a constant potential of 30 V with respect to a counter-eletrode during 1 h. During the electrodeposition a supersaturated $CaCl_2$ and NaH_2PO_4 solution was used, and the treatment was carried out at a constant current density of 3mA/cm^2 for 45 min. The modified surfaces were characterised by Raman spectroscopy and SEM to identify the chemical species present and their crystallographic phases as well as the general morphology of the surface. Phosphate was detected on the anodised samples previous to electrodeposition, indicating its incorporation from the anodising solution. Hydrated calcium phosphate was also identified on the surface after electrodeposition. Finally, electrochemical experiments were conducted in order to study the corrosion resistance of the surface modified samples. The barrier effect is enhanced with the anodising process and it is not further altered by the presence of the electrodeposited compound.

22.
***IN VITRO* AND *IN VIVO* BEHAVIOR OF ANODISED ZIRCONIUM**

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With the aim to evaluate the performance of zirconium as a potential permanent implant material, and the influence of its surface condition on biocompatibility, SBF immersion tests and *in vivo* press fit implantation on Wistar rats were carried out on zirconium anodised at 30 V in 1 mol/L H_3PO_4 solution and unanodised zirconium. After 30 days of immersion in SBF solution, the surface morphology does not present changes on unanodised samples. Meanwhile when observed by SEM zirconium anodised at 30 V, was fully covered with globular aggregates of acicular crystals. Ca and P were the major elements detected with EDS on the aggregates, and according to Raman spectroscopy results, the composition was consistent with hydroxyapatite. These results are an indicative of bioactivity according to the international standard ISO 23317:2007(E); although exists some controversy on such affirmation in the literature. In osseointegration tests, wire samples were implanted on tibia and femur of Wistar rats. The specimens were slaughtered after 60 days of implantation, and histology studies were performed. New formed bone tissue attached to the implant was detected in both surface conditions. However, while on anodised zirconium bone formation was continuous all around the wire surfaces, on unanodised samples, zones with no bone growth were detected. As the amount of bone – implant contact area resulted higher on anodised zirconium; the fixation of this surface modified material presents better perspectives compared to the unanodised metal.

23.
CROSS-LINKED SOY PROTEIN AS MATERIAL FOR BIODEGRADABLE FILMS: SYNTHESIS, CHARACTERIZATION AND biodegradation

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The modification of soy protein isolate (SPI) with different amounts of a naturally and non-cytotoxic cross-linking agent (genipin, Gen) and glycerol used as plasticizer was carried out in this work. In colony-forming assays, the proliferative capacity of cells after being exposed to Gen is approximately 5000 times greater than that of cells exposed to glutaraldehyde. Different films were prepared by casting from heated and alkaline aqueous solution of SPI, glycerol and Gen and then dried in an oven. Total soluble matter, water vapor permeability and mechanical properties were improved by adding small amounts of Gen. These properties were not significantly affected ($P \geq 0.05$) by additions exceeding 2.5% (w/w of SPI). The opacity and cross-linking degree were linearly increased with the addition of Gen, whereas the swelling ratios in water were decreased. All the films were submitted to degradation under indoor soil burial conditions and the weight loss of the films was measured at different times. This study revealed that the film biodegradation time can be controlled or modified from at least 14 to 33 days. The tests performed showed the potential of Gen to improve the SPI film properties. Therefore, the possibility of employing such new films as artificial tissue for biomedical applications was raised.

24.
WAVELENGTH DISPERSIVE X-RAY FLUORESCENCE FOR THE ANALYSIS OF MEDICAL SKIN

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In the absence of studies to ensure the safety of the so-called "medical skins", which are often used in direct contact with the skin of patients, we intend to analyze the chemical composition of the constituent materials of various trade brands of such medical skins. The methodology used is experimental, using the technique wavelength dispersive of X-ray fluorescence, applied to medical skin samples, both natural and artificial. To perform these studies, the selected samples were sent to the Head of Chemistry Atomic Energy Commission, which provided specific equipment and expertise to perform the experimental measurements. In the qualitative semi-quantitative (in ppm) analysis of the spectrograms common chemicals were found in all samples analyzed, among which we can mention the existence of chlorine, calcium, zinc and iron. Also, several other unusual items were identified, that is the case of chromium detected in natural wool. We are currently performing the corresponding quantitative and biochemical analysis in order to determine whether the concentrations of some of the items found may have adverse health effects. Finally, we consider of great importance to introduce this type of analysis in the field of orthoprosthetic and the need for collaborative and interinstitutional work.

25.

OSTEOPLASTY COMPOSITE BONE CEMENT

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The fixation of metal prosthetic devices to bone or the osteoplasty procedure to mimic to substitute loss bone pieces are the frequent uses of bone cements, based on polymethyl methacrylate, PMMA. Also, the local treatment of bone infections by means of antibiotic delivered by this porous polymer may be required. These objectives could be satisfied and improved by means of incorporation of additives into bone cement, as it is shown here with hydroxyapatite, HA (bone mineral phase). The HA particles are obtained from fresh bovine bone, which is sawed, defatted, cleaned from haemoglobin by chemical process, dried, pyrolized up to 900°C milled, and sieved up to a size smaller than 150 µm. These particles are mixed with PMMA in weight ratios up to 70%. The cement is formed by incorporation of monomer, and cast into moulds, where polymerizes. The resulting pieces are subject to mechanical tests (compression and bending) which reveals the increases of failure stress and elastic module up to 40 MPa and 2.8 GPa, respectively, when HA content is close to 40%. This behaviour could be attributed to compression effect of polymer matrix over HA embedded particles, which also stop the fracture propagation into polymer, observed by electronic SEM. These features could improve the resistance of cement under cyclic loading. The presence of porous HA contributes to retention of water in a way much efficient than the porous PMMA particle network alone. This absorption ability increases with HA content, feature relevant to improve drugs realise profile. The moulding ability of composites cement is probed shaping temporary hip prostheses (hip spacers) and costume made cranioplasties.

26.

IN VIVO EVALUATION OF SILICIFIED COLLAGEN HYDROGELS

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Hybrid and nanocomposite silica-collagen materials derived from concentrated collagen hydrogels were evaluated *in vitro* and *in vivo* to establish their potentialities for biological dressings. Silicification significantly improved the mechanical and thermal stability of the collagen network within the hybrid systems. Nanocomposites were found to favor the metabolic activity of immobilized human dermal fibroblasts while decreasing the hydrogel contraction. Cell adhesion experiments suggested that *in vitro* cell behavior was dictated by mechanical properties and surface structure of the scaffold. First-to-date *in vivo* implantation of bulk hydrogels in subcutaneous sites of rats was performed over the vascular inflammatory period. These materials were colonized and vascularized without inducing strong inflammatory response. These data raise reasonable hope for the future development of silica-collagen biomaterials.

27.

BIODEGRADATON AND HISTOLOGICAL RESPONSE OF PHBV POROUS SCAFFOLDS

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Temporary scaffolds for tissue engineering require bioabsorbable materials that degrade into non-toxic substances once the tissue is repaired. Furthermore, these materiales must have suitable mechanical properties to prevent friability, adapt to anatomical contours, facilitate handling by surgeons and last but not least, a proper surface to enhance the adhesion, motility and proliferation of cells and the interaction with the surrounding tissue. Since polyhydroxyalkanoates satisfy these properties, many researchers have focused on them to build up bioabsorbable scaffolds to be harvested with osteoblasts, fibroblasts, vascular cells, among others. One of the drawbacks of these biopolyesters, particularly polyhydroxybutyrate-co-hydroxyvalerate (PHBV), is the slow bioabsorption rate, which affects negatively the formation of the new tissue. Thus, the aim of this work is to evaluate how the degradation rate depends on the meso-structures and the media; measurements include dry weight of samples stored at 37ºC and pH 7.4 in phosphate buffered saline (PBS) and PBS with lipases as well as changes in the molecular weight of PHBV. Furthermore, from H&E-stained sections, the toxicity and inflammatory response after subcutaneous implantation of porous PHBV scaffolds on rats at 1 week, 1 month and 2 and half month post implantation are determined.

28.

CLINICAL TRIAL DESIGN FOR THE TREATMENT OF RESISTANT VENOUS ULCER USING AUTOLOGOUS DERMOEPIDERMIC DEVICES

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Venous ulcers treatment is based on restoring venous flux and improving scarring mechanisms. During chronic diseases, scarring cell and molecular mechanisms are disturbed, facilitating the development of chronic ulcers. There is a need for better treatments to achieve faster and more efficacious results. Living cells and growth factors and other active molecules, might help to improve healing a chronic non-responding ulcer. Tissue engineered skin substitutes appear as the most appropriate solution to this chronic problem. There are actually many different skin substitutes options developed to improve ulcer healing. Clinical trials have so far proved their efficacy in venous ulcers, reducing pain and time to ulcer scarring, when compared to classical treatments. In this setting we have designed a clinical trial to prove the safety and efficacy of autologous dermo-epidermic devices (DED) in the treatment of chronic non-healing venous ulcers. This device is developed from tissue cultures of autologous skin cells obtained by skin biopsy. We have already developed a DED , and we are now designing a clinical trial, now awaiting approval from the national regulatory agent (INCUCAI). Quality, safety and efficacy are very difficult to obtain, mainly because of the many variables included from the device development to the clinical application. Device development must be uniformed and controlled, assuring good manufacturing practices. Argentina is now developing specific legal regulations according to international standards required to manufacture this products.

29.

THERMOSENSITIVE NANOGELS BASED IN DENDRITIC POLYGLYCEROL AND N-ISOPROPYLACRYLAMIDE

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Stimuli-sensitive nanogels are polymeric particles that consist of a cross-linked three-dimensional network that can respond to local environmental conditions. They can shrink or swell rapidly by expelling or absorbing water in response to external stimuli and are being studied specially for drug delivery and biomaterials applications. In particular, thermoresponsive polymers have shown to have great potential in several fields. Development of temperature-responsive nanostructured water soluble materials using poly (N-isopropyl acrylamide) (PNIPAm) has attracted the attention of both academic and industrial research and is being mostly investigated for potential applications in drug delivery, but also as intracellular temperature sensor, amongst other examples. The use of PNIPAm in the biomedical field, however, has been limited due to its lack of water solubility above the low critical solution temperature (LCST), its non specific protein absorption and its poor biocompatible profile. Here, precipitation polymerization has been used as a convenient synthetic methodology to yield thermosensitive nanogels based in PNIPAm and dendritic hyperbranched polyglycerol (HPG). The incorporation of HPG is aimed to enhance the water solubility and biocompatibility of the nanogels, while at the same time allow tuning the thermoresponsive profile as a function of the nanogel sizes in solution. The thermoresponsive behavior, the enhanced biocompatible profile, and the cell penetrating properties of the nanogels highlight the potential of such constructs for the application as smart, environmental-responsive material.

30.

BIOLOGICAL ACTIVITY OF ELECTROSPUN NANOFIBERS ON POLYMER GELS

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A composite FBG/PLA (fibrinogen/poly-L,D-lactic acid) NFs on a gel obtained from the radical copolymerisation of caprolactone monomers and hydrophilic acrylic units of hydroxy ethylacrylate. Random and aligned electrospun nanofibers (NFs) of FBG/PLA are deposited on gel. Characterization, biocompatibility and cytotoxic assays (NO production, IL-1 and TNF-α) showed good biocompatibility and that not significant release of cytokines or NO was detected in the media of macrophages. Endothelial cells interacted well with the NFs (focal adhesion complexes, actin cytoskeleton), representing higher degree of alignment along their orientation. We also demonstrate the differentiation potential of mesenchymal stem cells on gel-NFs complex to bone or cartilage lineages. Collectively, our data show that the composite PLA/FBG NFs deposited on PLA based gels combine the good cell recognition properties of FBG with the excellent mechanical properties of PLA, which characterizes them as an advanced bioactive and bioresorbable scaffold for tissue engineering application.

31.

BIOLOGICAL EVALUATION OF SCAFFOLDS BASED ON CHITOSAN, FIBROIN AND HYDROXYAPATITE WITH $SAOS_2$ CELLS

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Hybrid composites with chitosan (CHI), fibroin (SF) and hydroxyapatite (HA) are biocompatible and attractive for bone engineering applications. The objective of this work was to evaluate *in vitro* $SaOs_2$ cells behavior in contact with CHI, CHI-SF and CHI-SF-HA composites porous scaffolds. The scaffolds were produced from a chitosan solution (2%wt) in acetic acid (1%). This solution was molded and frozen, then, the scaffolds were freeze-dried, crosslinked with sodium tripolyphosphate (2%). *In vitro* test with $SaOs_2$ cells under static conditions for 7, 14 and 21 days, with an inoculation density of $5x10^5$ cells was performed. SEM analyses were conducted to observe cell growth across the surface of the samples. Cell viability and activity was assessed by MTT reduction and ALP activity detection. Student's t-test was used with a significance at $p<0.05$. SEM analyses indicated cell growth across the surface of the samples and the MTT assay showed an increase of the cell number in all scaffolds. ALP activity presented the best behavior in CHI-SF-HA and CHI-SF scaffolds, since they presented a significant higher rate in 21 days. Further studies are necessary to confirm their potential use as bone substitute biomaterials.

32.

SUPERCRITICAL FLUID-BASED PROCESS FOR PRODUCING POLYCAPROLACTONE SCAFFOLDS IN TISSUE ENGINEERING

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In this work sorption and diffusion coeficients of carbon dioxide in polycaprolactone (PCL) samples are reported. The use of compressed carbon dioxide is discussed for obtaining porous scaffolds from this biocompatible polymer. In order to determine the plasticization effect of carbon dioxide on the degree of foaming it is necessary to relate sorption data of CO_2 in PCL with morphological features of PCL samples in conditions of T and P nearby of the melting point. The amount of carbon dioxide dissolved and the kinetics of the sorption process are found to depend strongly on temperature and pressure. The solubility takes values of up to 25 wt-% being favoured by a melting and glass transition temperature depression which can be observed along with an enhanced mass transfer rate. In general, CO_2 sorption in PCL increases linearly with pressure. When decompressing, microfoaming occurs which enhances the rate of gas release. Changes in morphology and crystallinity occur as a consequence of the pressure treatment. Compared to the melting temperature at atmospheric pressure there is a dramatic reduction observed under pressure where melting occurs already at a temperature of 40°C at 15MPa. Even after pressure-treatment, there is a remaining change in melting temperature and crystallinity observed.

33.
STRUCTURED BIOGLASSES FOR BONE REGENERATION: ALTERNATIVE GREEN AND LOW-COST PREPARATION
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Nowadays, tissue engineering requires novel synthetic materials; bone reconstruction in particular, triggered the creation of a vast family of bioglasses (SiO_2-P_2O_5-CaO). Beyond their composition, their texture plays a key role on their osteointegration ability. However, both their preparation and structuration requires costly reagents. In parallel, the chemical industry claims for novel green procedures of production. In this work we propose to construct novel bioglasses based on low cost and environmental friendly reagents. To this aim, water suspensions containing commercial SiO_2 nanoparticles (LUDOX ®) and milk were structured by freeze drying (ISISA) in a first step. The ISISA process involves the submission of a suspension to liquid-nitrogen temperatures and subsequent sublimation. The segregation of the solute between the ice phases is driven by the controlled ice formation. By drying the porosity appeared where ice crystals originally resides, resulting in an organized 3D scaffold.
In a second step, the scaffold was thermal treated to eliminate the milk-based organic template and trigger the solid state reaction between the milk's inorganic component and the silica phase, giving rise to a structured bioglass. The samples were characterized by XRD, SEM, FTIR and DTA. Finally, the bioactivity was assessed *in vitro* by incubation in simulated body fluid (SBF). The results indicate that the structure can be tuned by variables such as the precursor concentration and freezing rate. The scaffolds showed a bimodal porosity as a result of the removal of the organic template. At least, the chemical homogeneity of the resulting bioglass was enough to ensure a proper *in vitro* biomineralization response.

34.
SYNTHESIS AND CHARACTERIZATION OF NOVEL BIORESORBABLE CATIONIC POLYMERS FOR GENE DELIVERY
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Gene therapy involves the insertion of a functional copy of a defective or absent gene in an individual´s cells and tissues, with the purpose of treating a disease, replacing lost cellular functions or introducing a new function. This therapy has great potential in treating diseases such as cancer and AIDS. To this end, the gene requires a vector to be internalized into the cells and carry out its biological function. The success of this therapy depends largely on the efficiency of the vector. In recent years there has been substantial progress in the development and application of non-viral vectors. However, there are still many problems to be solved before this therapy becomes a standard clinical practice. In this work, we have explored different synthetic routes to obtain bioresorbable polymers suitable for DNA complexation and gene delivery. A polyurethane based on LDI (L-lysine methyl ester diisocyanate), L-tyrosine and TEG (tetraethylene glycol), as well as a polyester based on TEG and L-glutamic acid, were synthesized. Both polymers have protonable amino groups in their backbone for the subsequent complexation. Polymers were purified by dialysis, and characterized by DSC, FTIR-ATR, GPC, NMR and acid-base titration.

35.
GELCASTING PROCESSING OF ZIRCONIA-CALCIUM PHOSPHATE BONE SCAFFOLDS
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The present work analyses the production of porous zirconia-hydroxyapatite composites by gelcasting, GC, in order to mould bone scaffolds. This involved the preparation of two series of hydroxyapatite, HA, and ZrO_2 powder mixtures. CaO was employed as foaming agent and as zirconia stabilizer in 8 and 16 molar %, producing blends with HA up to 50% of total weight. These blends were dispersed in 20% (in wt.) albumin water solutions in order to produce slurries, able to cast into moulds and gelled *in situ*. The wet greens were sintered at 1350 and 1450°C during 90 minutes.
The composite X-ray diffraction analyses show multi-phase microcrystalline structure based on Zr-Ca and Ca phosphates compounds, which include HA thermal decomposition. The relative amounts of each phase are determined in order to understand the solid state reactions. These could be involved in coating procedures on zirconia substrate. The GC allows producing porous scaffolds, containing calcium zirconate due to reaction with zirconia.

36.
SYNTHESIS AND CHARACTERIZATION OF DENDORNIZED CHITOSAN FILMS ON ONE SIDE
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Dendronized polymers represent an alternative with a variety of shapes, core molecules, carbohydrate residues and valences. The incorporation of dendritic structures onto polymeric supports is an effective means for amplifying the number and specificity of functional groups along the polymeric surface. The modification of chitosan with dendritic structures is a novel and interesting path to synthesize highly functionalized and unconventional polysaccharide-based products that may be of interest for various applications, for example, as wound dressing, drug delivery systems and catalysts. Wound dressing is one of the most promising medical applications for chitosan. The adhesive nature of chitosan, together with their antifungal and bactericidal character, and their permeability to oxygen, is a very important property associated with the treatment of wounds and burns. In this work, we have developed dendronized chitosan films on one side (dCh). dCh films were obtained by reaction between crosslinked biopolymer and weiisocianate dendron. We had studied these films by different assays like ATR-FTIR, contact angle and swelling behavior. Our results indicate that these films are two different faces: one is more hydrophobic than the other. dCh films were stable to pH 3.4 at prolonged time. They can be use as wound dressings to maintain a moist environment at the wound interface.

37.

HYDROXYAPATITE/ CHITOSAN COMPOSITE SCAFFOLDS

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Tissue engineering use temporary porous scaffolds which provide mechanical resistance and allow the formation of bone tissue, avoiding a second surgery to extract the implant. The application of a hybrid composite, composted of a biopolymer and calcium phosphate, with similar morphology and properties of natural bone, may be a way to solve the problem of the fragility of ceramics without reducing its mechanical properties, retaining the properties of biocompatibility and high bioactivity. This work aims at the preparation and characterization of a three-dimensional scaffolds hydroxyapatite/chitosan composite, by freeze-drying technique. This involved the study of structural, chemical and morphological frameworks, in order to direct the research suggested the application. The X Rays Diffraction (XRD) and Fourier transform infrared Fourier (FTIR) results confirmed the formation of hydroxyapatite (HA) phase and the presence of characteristic bands of HA and chitosan in all studied compositions. The microstructural study by scanning electronic microscopy (SEM) revealed the formation of longitudinally oriented microchannels with interconnected pores with pores of varying sizes and mostly larger than 100μm, and is therefore considered materials with potential for application in bone tissue engineering.

38.

OPTIMIZATION OF THE MATHEMATICAL MODELING OF DRUG DELIVERY FROM PLANAR POLYMERIC SYSTEMS

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The modeling of the diffusional release of a dispersed or dissolved solute from a polymeric matrix is a problem of special interest in the area of the controlled release of pharmaceuticals or chemicals. The mathematical analysis of the release kinetics is often complicated by the presence of a moving diffusional front separating the undissolved core and the partially extracted region. The aim of this study was to derive an explicit analytical solution based on Refined Integral Method for the case of dispersed–drug controlled release from non–erodible planar matrices. In order to achieve the aim, a new adjusting equation for the dissolved-drug concentration profile in the depletion zone was used. The usefulness and validity of the model were corroborated by comparison of the theoretical predictions with experimental drug release data reported in the literature. A close match between the model and the experimental data was observed. In addition, a comparison with a model reported previously by others authors was also presented. The results showed that our model has a better performance than the previously reported equations in the prediction of the experimental release profiles. Finally, an analysis of the influence of initial drug loading and release time on dissolved-drug concentration profile in the depletion zone was carried out. As conclusion, the obtained results showed that the model can be employed in a broad range of drug delivery systems.

39.

MAGNETIC DRUG DELIVERY DEVICES: CHARACTERIZATION AND SWELLING STUDIES

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The magnetic gels represent a new type of composite and consist of small magnetic particles, dispersed in a highly elastic polymeric matrix. In addition due to their sensitivities to both magnetic field and temperature, thermosensitive polymer magnetic microspheres offer a high potential application in the design of a targeting drug delivery system, which is considered a safe and effective way for tissue-specific release of drugs. The aim of this work was to obtain and characterize ferrogels and magnetic nanoparticles able to respond under magnetic fields sorption or releasing a drug. For this purpose, Ferrogels were synthesized by co-precipitation of iron salt within polyvinylalcohol hydrogel matrix. The nanoparticles were obtained by co-precipitation from Fe^{+2}/Fe^{+3} solution and nanoprecipitation on chitosan (CS). In order to characterize these materials: chemical, thermal, magnetic and swelling analyses were carried out. Ferrogels show dimensional stability, capability of swell in bovine serum albumin (BSA) solution and a superparamagnetic behavior (with a magnetization of saturation =3.6 emu). The nanoparticles sizes are comprised between 95 and 150 nm. The CS incorporation provides biocompatibility and functional groups able to interact with several drugs. The potential of these materials to be used as protein adsorbents was also evaluated by adsorption isotherms from a model protein, BSA. The adsorption kinetic was studied using both ferrogels and nanoparticles as supports.
The preliminary results indicate that materials are very promissory regarding the possibility to be employed as drug delivery devices, biosensors or even in the purification of proteins.

40.

STUDY OF THE RELEASE OF CLOBETASOL PROPIONATE IMMOBILIZED TO POLYPROPYLENE FILMS MODIFIED WITH CHITOSAN

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The formation of biocomposite films of polypropylene (PP) was carried out through the chitosan (CS) immobilization onto the surface of the modified films. Later, the attaching as well as the release of clobetasol propionate (CLO) as substrate was researched. The latter is a corticosteroid used to treat various skin disorders including eczema, psoriasis and dermatitis. Firstly, the PP film surface was modified through a photo-graft polymerization of acrylic acid (AAc) at room temperature, using benzophenone (BP) as radical initiator. The effect of the reaction time on the grafting degree (G) of polyacrylic acid (PAAc) was examined, where the film modified with a 18 G% showed the more suitable properties to carry out the CS immobilization (I). Then, biocomposite films (PP-g-PAAc-CS) were attained through electrostatic interaction between CS´s amine groups and carboxyl groups of the grafted film (PP-g-PAAc). Three techniques were studied for the conjugation of CLO; in one case (A), CLO was attached to carboxyl groups of PP-g-PAAc by hydrogen bond, and then CS was immobilized. On the other hand, the corticosteroid was fixed to a PP-g-PAAc-CS film through its diffusion (B). In addition, CLO was mixed with a CS aqueous solution and anchored to PP-g-PAAc (C). In the three cases, the substrate CLO exhibits controlled release kinetics, which depend on its diffusion through the polymers and its ability to form hydrogen bond. Percentages around 15 wt-% of CLO loaded were released during the first 6 h, and a 30 wt-% after 4 days.

41.
OPTIMIZATION OF CHITOSAN MEMBRANES AS A SUBSTITUTE OF HUMAN EPIDERMIS FOR TRANSDERMAL PATCHES DEVELOPMENT

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Polymeric membranes with skin-imitating permeability properties appear as attractive models in the evaluation of transdermal drug delivery systems. Chitosan is a commercially available inexpensive polymer. Chitosan and its derivatives have been widely explored for pharmaceutical and medical applications. The aim of the current work was to prepare a chitosan membrane as a mimic of human epidermis and evaluate its applicability for the development of a chitosan patch for estradiol delivery. Epidermal sheets were obtained from whole abdominal skin and used in release studies. Estradiol patches commercially available were used as donor compartment. Response surface methodology was implemented for the preparation of the optimized chitosan membrane as a mimic of human epidermis. Chitosan patches for estradiol delivery were prepared by pouring on a polycarbonate Petri dish a solution containing chitosan, glycerol, estradiol and poloxamer; and drying at 30ºC. All release studies were performed according to the USP Apparatus 5 paddle over disk method. Optimization procedure allowed preparing the optimized chitosan membrane; that is, a membrane which reproduced the cumulative amount of estradiol released per unit time of human epidermis. Optimized membrane was prepared with the following experimental condition: 3.76% w/v for concentration of chitosan solution, 5.0% w/v for concentration of sodium tripolyphosphate and 15 minutes of cross-linking time. Optimized membrane was applied to the development of a chitosan patch for estradiol delivery. The release profile of the chitosan patch alone and chitosan patch plus the skin-mimetic membrane were similar to those obtained for commercial patch alone and commercial patch plus the skin-mimetic membrane. The results presented show a successful application of the *in vitro* technology proposed with chitosan mimetic membranes for transdermal patch development.

42.
INTRAUTERINE DEVICES: USE OF BIOCOMPATIBLE CORROSION INHIBITORS TO REDUCE THE BURST RELEASE EFFECT

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Copper-intrauterine devices (IUD) base their contraception effectivity on the copper ions release (CuR). Initially, this CuR is higher (burst release, BR) than the level necessary to ensure contraception and may cause adverse effects in the users. The application of biocompatible corrosion inhibitors is a possible way to reduce this effect. The aim of this study is to assess if purine (P) and thiourea (TU) are biocompatible inhibitors and if they are able to reduce the BR effect.

Firstly, the cytotoxicity of P and TU was evaluated in HeLa line cultures using neutral red and MTT as end points to analyse the lisosomal and mitochondrial activity respectively. Results showed that P y TU in the 10^{-7}-10^{-3} M concentration range (higher than the maximum level that could be in contact with the cells) were not cytotoxic.

Then, the electrochemical behaviour of corrosion inhibitors was evaluated by potentiostatic and potentiodynamic techniques. Results showed a better performance for P treatments after 1 h immersion time than for TU. Consequently, P could be used as a biocompatible corrosion inhibitor to reduce the BR effect.

43.
MICROFIBROUS BIORESORBABLE POLYMERIC MATRIX CONTAINING DISPERSED ANTIFUNGAL AGENTS

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In order to decrease the unwanted secondary effects to systemic levels generated by oral administration of antifungal drugs for fungal epithelium diseases, antimycotic agents loaded polymeric systems were developed and characterized. Polymer meshes were prepared by solubilizing Chalcona 1 (Ch1) and Ketoconazol (Keto) in poly(lactide-co-glycolide) (PLGA 50:50) and Mw 54 KDa. Chalcona 1 is an active natural agent poorly soluble in water which exhibits fungical activity. Ketoconazole is a commercially available drug used to treat fungal and yeast infections. Both agents were selected to prepare drug-loaded fibrous meshes by electrospinning process. The resulting microfibrous meshes were characterized by differential scanning calorimetry, scanning electron microscopy, and ultraviolet-visible spectroscopy. Thermal analysis showed that both Ch1 and Keto were completely dissolved in amorphous PLGA meshes. Ch1 and Keto content incorporated to the PLGA/Ch1 and PLGA/Keto systems was 77.87 and 104.15 mg/g mesh, this load being useful for topical applications.