Project no: STRP 517070

Project acronym: PROTEC

Super Critical Carbon Dioxide Processing Technology
For Biodegradable Polymers Targeting Medical Applications

Final Activity Report

Instrument: Specific Targeted Research Project

Thematic Priority: Framework 6

Period Covered: June 1st 2005 to 30th November 2008

Date of Preparation: December 2008

Start date of project: 1st June 2005 Duration: 3 years

Project coordinators: Regina Santos

Project Coordinator organisation name: University of Birmingham

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1 Project Execution

The Protec project, on Supercritical Carbon Dioxide Processing Technology for Biodegradable Polymers Targeting Medical Applications, ran from June 2005 until November 2008.
Details of the project can be found at http://www.euprotec.eu.

Contract Type	Specific Targeted Innovation Project
Budget	€ 2.16 million
Funding	€ 1.4 million
Duration	42 Months

The thematic priority area addressed by this project is: 3.4.2.2 - "Technologies associated with the production, transformation and processing of knowledge-based multifunctional materials and biomaterials".
In particular the project addresses the topic - "Materials processed by radically innovative technologies".

The overall project aim was to develop a highly innovative 'supercritical fluid' processing technology that would enable European industries to develop and manufacture, in a highly controlled manner, advanced multifunctional biodegradable and/ ore bioabsorbable polymers possessing consistent and well defined physical and mechanical properties, chemical composition, porosity, and degradation profile.
This technological advance was to be realised through addressing the scientific and technological gap between fundamental academic research and industry and through further developing advanced process control methodologies. The processing technology developed within the project was to be designed to enable efficient integration with existing extrusion and injection moulding machines.

1.1 Project Objectives

The key project objectives were:

- The processing of porous biodegradable polymers that demonstrate significant weight reductions, but whilst retain the physical and mechanical properties of the compact material.

- The processing of thermally and shear sensitive polymers, demonstrating significant improvements in the reduction of degradation during processing, without induced foaming.

- To establish the fundamental relationship between the injection moulding variables and the surface and interior properties of the material, and to establish the parameters that lead to process control.

- To achieve process control of the materials biodegradation profile.

- To achieve scale-up and application of the processing technology, with consistent and reliable process control.

- To establish the limitations of material design due to the degradation that occurs during sterilisation, and to identify sterilisation best practice.

1.2 Contractors

The Protec Project was coordinated by Dr. Regina Santos of the University of Birmingham.

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The full consortium is listed in table 1 below.

Table 1: Participant List

Participant				
Role	**No.**	**Name**	**Short Name**	**Country**
CR	1	The University of Birmingham	Rapra	UK
CO	2	Trexel GmbH	Trexel	Germany
CO	3	Smithers Rapra Technology Ltd	Rapra	UK
CO	4	The University of Twente	Twente	Netherlands
CO	5	The Technical University of Lodz	Lodz	Poland
CO	6	S. E. de Carburos Metalicos, S.A.	Carburos	Spain

1.3 Work Performed

1.3.1 Refinement of Target Applications, Process Requirements and Specifications

During the first six months of the project, work was undertaken to identify a series of biodegradable polymer implants that could benefit from the addition of supercritical CO_2 during processing. This was essentially the fine tuning and refinement of the process requirements and specifications to be achieved throughout the project.

This work culminated in an industrial overview of the existing limitations throughout the selected medical implant industries and the identification of areas of most promise for exploitation.

Those applications identified as most promising were:

- Tissue engineering scaffold
- Drug depot
- Multifunctional device (suture tack, plate, mesh, interference screw)

This work also led to the definition of success measures for each application identified. A specification was drawn up, allowing developments to then be undertaken in integrated materials, and process development and characterisation.

1.3.2 Supercritical CO_2 Delivery Systems

One of the main limitations of $scCO_2$ technological transfer is the high cost of the equipment; this means high initial investment, high risk and difficulties in demonstrating the economical viability of the application.

The state of the art equipment currently to deliver $scCO_2$ has a cost greater than €30,000. A development was undertaken to reduce the cost of the necessary equipment, ensuring that this was not going to be a barrier to the introduction of the developed products and processes to the market.

CO_2 delivering systems for an extruder or injection moulding have three main units: a pumping system, cooling to avoid CO_2 gasification in the pump and flow control. Each unit was broken down into its consituten parts, and a market search to identify alternative more cost effective solutions was undertaken.

1.3.2.1 A Turnkey Prototype

A turnkey system for delivering CO_2 to extruder and injection mould was developed for research and demonstration, offering good flow and pressure control at cheapest cost and simplicity. The small prototype is able to feed from 5 to 200 g/min at 325 bars for less than €4,000 (see Figure 1).
Width: 30 cm Height: 70 cm Depth: 30 cm Weight 21 Kg.

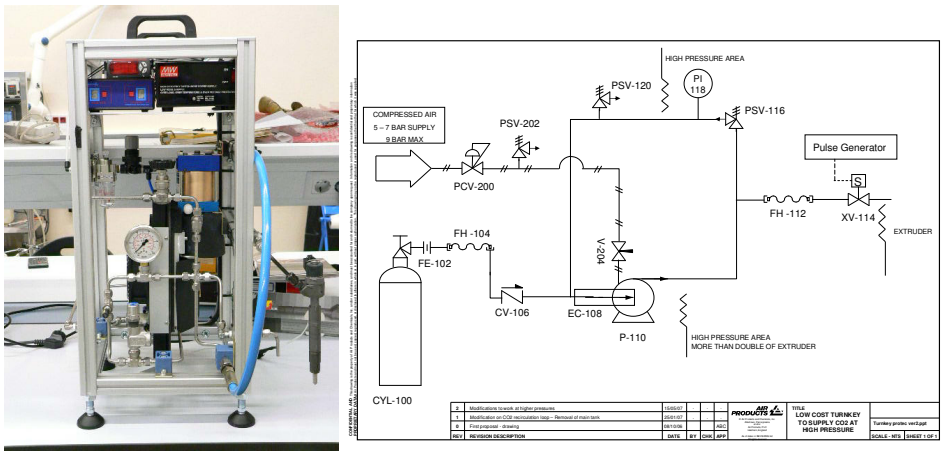

Figure 1: Low cost Turn Key equipment to deliver CO_2 at 550 bars (Right: photo Left: P&I)

1.3.3 Material Characterisation and Analysis

1.3.3.1 Synthesis and Characterisation

Several materials including some based on polylactide, and both polymers and stereocomplexes, were synthesised. These were compared with commercially available alternatives through a thorough characterisation, which included an assessment of:

- composition, using Nuclear Magnetic Resonance (NMR) spectroscopy

- thermal properties, using Differential Scanning Calorimetry (DSC)
- mechanical properties

In an iterative process, the most promising materials were selected for further testing, some of which is detailed in the following sections.

The candidate materials investigated were PLA3051D(Dow Cargill) PLLA, PDLA, poly(LLA-TMC-LLA) and poly(DLA-TMC-DLA) which are all semicrystalline polymers, and poly(TMC), which is an amorphous polymer.

1.3.3.2 The relationship between the bulk and supercritical CO_2, porosity formation and stabilisation

This was investigated using a range of methods including Golden Gate Infra Red (IR) and DSC, and foaming studies carried out in excess CO_2.

1.3.3.3 Sterilisation investigations using irradiation

Electron Beam (EB) irradiation was chosen as the means of sterilisation, since it is one of the most versatile methods available. Irradiation of PLA3051D, PCL, PLLA, PDLLA and PTMC was performed at room temperature using a linear accelerator, and a range of techniques including GPC and Fourier Transform Infrared Spectroscopy (FT-IR) were used to evaluate the effects.

1.3.3.4 Degradation studies

In vitro degradation studies were carried out according to the relevant ISO standards. (13781 and 10993-13).

1.3.3.5 Results

This body of work led to a fundamental understanding of the relationship between the selected polymers and the supercritical carbon dioxide, resulting in greater control and optimisation of the conditions required for

polymer processing, the limitation of temperature dependent degradation and the formation and stabilisation of porosity.

Further to this, the characterisations determined the material taken forward to the next stage of the project.

1.3.4 Laboratory Trials – Process Control

A body of work was undertaken to develop the basic processing principles for both extrusion and injection moulding PLA with the addition of supercritical CO_2.

1.3.4.1 Investigations in Extrusion Systems

This work was designed to provide a greater understanding of the relationship between the processing conditions, polymer chemical and physical structure, and the final foam properties and pore stabilisation, leading to greater process control.

1.3.4.1.1 Rheological Studies

A range of investigations were carried out on a 25 mm extruder setup with a Cavity Transfer Mixer (CTM), custom built rheometer and a 2 mm diameter die. Each part of the equipment can be heated independently of the other parts allowing temperature ramps.
These looked at:

- CO_2 Addition
- Nucleating Agents
- Controlling Product Structure using Temperature

1.3.4.1.2 Injection of ScCO2 into a Vented Extruder System

A vented system was developed, based on a 50mm diameter Bone Craven Extruder fitted with a two part vented Barrel Assembly and a two stage 36 L/D screw.

Trials were carried out to investigate injecting excess $scCO_2$ and then removing the surplus at a vent.

1.3.4.2 Investigations in Injection Moulding Systems

This work involved a study of supercritical carbon dioxide injection into a polymer melt whilst utilising a mini injection-moulding machine, in order to study and apply the fundamental principles developed earlier, and to provide a greater understanding of the relationship between the processing conditions, mould design, and the surface and interior material structure, again leading to greater process control.

1.3.4.3 Results

The laboratory scale trials carried out enabled to project team to gain a much better understanding of the fundamentals required to scale up the polymer/CO_2 system to an industrial application.

1.3.5 Application to Drug Depot Manufacture

The aim of this strand of the project was to develop a drug depot for orthopaedic applications using a biocompatible or biodegradable polymer. Since the consortium lacked the facilities necessary to conform to the strict health and safety regulations in extrusion and injection moulding for this application, it was decided to study and prepare drug depots by supercritical impregnation. Supercritical impregnation consists of solving a target chemical into a supercritical fluid and impregnating it in a non-soluble solid matrix, like a polymer, carbon active, alumina or any other material. Once pressure and temperature is removed, the chemical remains inside the non-soluble solid matrix (in the bulk or on the pores) while the CO_2 leaves the matrix. Supercritical impregnation allowed the partners to simulate the mixing of polymer, drug and CO_2 in a small laboratory scale high pressure vessel, and then extrapolate the results to the production of a drug depot by extrusion or injection.

Market research was carried out to identify polymers and antibiotics of interest, and an experimental plan developed to study the impregnation of an antibiotic into a biopolymer as the basis to develop a drug loaded biopolymer implant.

The results obtained were extrapolated to the production of a drug depot by extrusion or injection moulding using $scCO_2$ as a carrier for the drug. Considering that the CO_2/polymer ratio is between 0.10–0.25 % and a good drug solubility could range between 20-200 g drug/Kg CO_2; the concentration of a given drug that could be impregnated into a polymer could range from 20-500 ppm. This extrapolation limits the production of a drug depot during polymer processing to those drugs that are highly soluble into CO_2 and highly active.

1.3.6 Scale-up

1.3.6.1 Dumbell Samples

During the initial phase of the scale up, a range of dumbbell test specimens were manufactured from Industrial grade PLA under various parameters and their properties optimised to minimise weight whilst still achieving pertinent mechanical properties.
The aim was to duplicate on a large scale the findings observed in the lab and the small scale work performed at Rapra.
The methodology used for these trials was documented, and was used in the subsequent production of the final product.

1.3.6.2 Final Product

The final demonstrator product chosen for testing was a biodegradable rod of the type used for internal fixation in extremity fractures and osteotomies. Industrial scale trials produced a range of these rods in both industrial and medical grade PLA, which then underwent a series of rigorous test protocols including sterilisation, biocompatibility and biodegradation, as well as mechanical properties.

The work performed on the rod was designed to allow a judgement of the technology's usefulness in the production of a drug depot.

1.3.7 Evaluation of Final Product Samples

A full range of evaluations were carried out on the samples generated by the industrial trials. These included:

- Evaluation of porosity, using Scanning Electron Microscopy (SEM)
- Study of the biodegradation profile, again using EB irradiation, over an extended time period
- An investigation of the effect of sterilisation using both gamma irradiation and by e-beam irradiation at different doses and
- Sterilisation best practice
- Effects of sterilization on biodegradation
- Selected biocompatibility tests, as described in ISO 10993 "Biological evaluation of Medical Devices". Before testing evaluating their biocompatibility, the specimens were sterilized by EB (e-beam sterilization).

1.3.8 Economic and Environmental Analysis

In order to evaluate the economic advantages and the impact on the environment of injecting CO_2 at high pressures during extrusion and/ or injection moulding processes, polymer processing was simplified to a black box where energy is applied to give or change the shape of a polymer or polymer system, whilst maintaining its mass. When CO_2 is applied, an inlet of liquid CO_2 and an outlet of gas CO_2 are added to the model.

The economical evaluation of the scCO2 technology has been done by estimating how much the cost of the polymer processing changes when using CO_2. The main costs of polymer processing are:

- Energy
- Polymer mass

- Labour
- Equipment investment

If CO_2 is injected, then the costs for the CO_2 mass and for modifications of the equipment also need to be considered.

The environmental impact evaluation has been focused on the greenhouse effect, in other words on the CO_2 footprint of the processed polymer. The difference in the CO_2 footprint between processing the polymer by conventional routes or by injecting CO_2 is considered to be the impact of our technology on the environment. CO_2 emissions are reduced by 3 major factors:

- CO2 recovery from petrochemical industries
- Reducing electricity consumption through energetic savings
- Reductions related to biopolymer production.

These were compared with the increase in emissions related to CO_2 transport from the petrochemical to the polymer processing industries and CO_2 recovering (purification and compressing).

Two study cases were considered:

- The production of a medical device using PLA medical grade in small quantities
- The production of a tray for food packaging using PLA food grade

In both cases, the economical and environmental impacts were controlled by the weight savings obtained by using CO_2; using CO_2 in the polymer processing reduces the production cost by 9%, the CO_2 releases by 9% and energy consumption by 20%.

1.4 End Results

The Project partners have developed an inventive process for biodegradable polymers that overcomes previous issues with material properties. Previous processing routes have led to high degradation, reduced mechanical properties, high costs and poor maintenance of biocompatibility.

1.4.1 Bioabsorbable Polymers

Bioabsorbable polymers (polymers which degrade and are absorbed/ metabolised by the body) are an intensive area of research due to the many benefits that they offer for device design:

- Complete absorption after serving their purpose and thus eliminating interference with natural bone growth
- No requirement for subsequent surgery for removal of the material
- Assistance in the natural healing process (transfer of stress during healing and thus the elimination of stress shielding)
- May be used for the controlled release of drugs or bio-substrates at a specific site
- May be used as structures for the growth of bone/ tissue cells (both in-vivo and in-vitro)

The polymers of greatest commercial importance to industry are: polylactic and polyglycolic acid and their copolymers; polycaprolactone and polydioxanone.

Common applications for bioabsorbable polymers include:

- Wound Closure (sutures and staples);
- Orthopaedic Fixation (pins, rods, screws, plates, tacks and ligaments);
- Cardiovascular Applications (stents and grafts);
- Drug Delivery (implantable devices and hydrogels);
- Surface Coatings

The limitations of current bioabsorbable polymers include:

- Limited mechanical Strength (may not be used for higher-stress applications);
- A lack of accurately controlled biodegradation
- Degradation of polymer during processing and sterilisation
- Late inflammatory/ immune response (for highly crystalline polymers)
- The method of addition of pharmaceutical and bio-substrates during continuous processing

The Protec project has overcome many of these limitations through the application of Supercritical Fluids Processing Technologies.

1.4.2 Supercritical Fluid (SCF) Processing

The high level of interest in SCF Technology first appeared as a result of the environmental benefits associated with the replacement of organic solvents. Supercritical Fluids have since demonstrated a number of unique properties that enhance many types of chemical process operations. By far the most widely used SCF is Supercritical Carbon Dioxide (scCO2), due to its low toxicity, natural abundance, chemical inertness, non-flammability and relative low cost. Important existing applications for SCFs include: polymer synthesis, surfaces and interfaces, lithography, polymer fractionation and extraction, dying, polymer impregnation with small molecules such as pharmaceuticals, waste management and the formation of foams.
The application of supercritical fluids to polymer processing has been successfully demonstrated to enable a wide range of important benefits, including:

- The ability to plasticize the polymer melt (reduce the glass transition temperature), resulting in:
- Reduced Viscosity
- Reduced Processing Temperatures
- Reduced Shear (particularly with regards to injection moulding)
- Foaming of the resulting material (microcellular foaming)
- Elimination of organic solvents (improved toxicology)

- SCFs are inert gases and thus do not require removal steps (time and cost savings)
- Improved control over foam formation and stability
- Enhanced diffusion of molecules or additives through the polymer matrix
- The ability to carry molecules and additives into or out of the polymer matrix

1.4.3 Project Objectives – Were they achieved?

The objectives of the Protec project have been met in the following ways:

The chart below illustrates the Property Retention data for the samples produced during the Munich trials in medical grade PLA. The results of the physical property tests are plotted as percentages, where the upper limit of what is theoretically possible is shown as a black line and the ideal lower limit is shown as a dotted line. Results may fall anywhere below the solid line but ideally should be above the dotted line. All the results from the Protec test bars fall in this range.

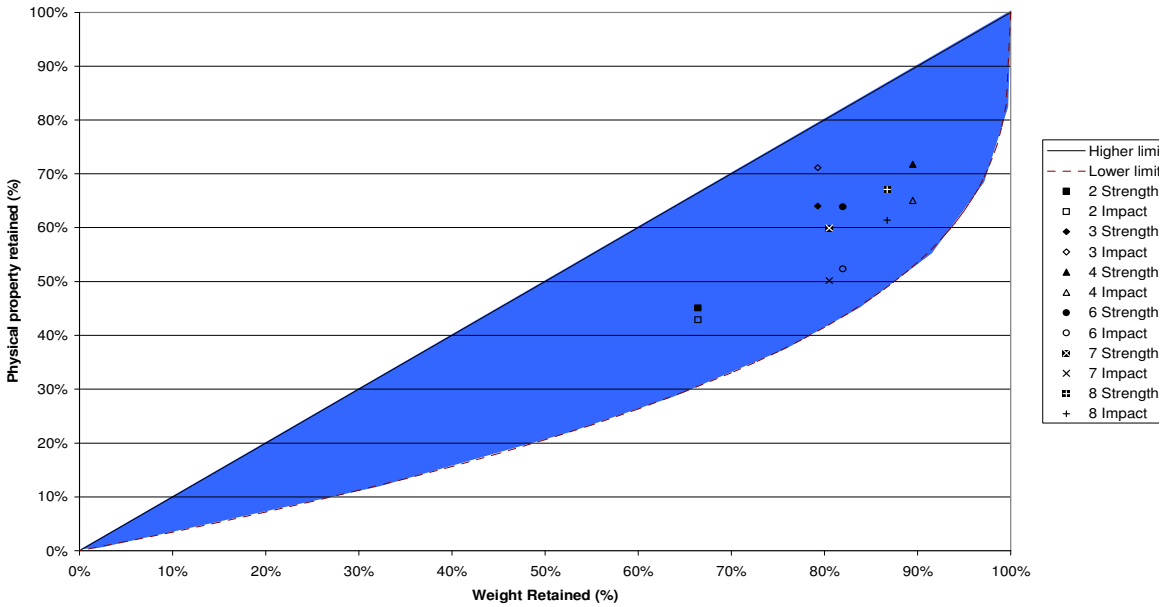

Figure 2: Property Retention Data

The detailed and extensive technical work undertaken as part of the project has led to an increased understanding of the systems involved in the processing of biodegradable polymers, specifically PLA, with $scCO_2$.

The processing and materials engineering characterisation work has pushed forward the state of the art in this area, and a new method of sterilizing polylactides has been developed by the project, which will influence the field incredibly. Patenting discussions are underway.

Materials characterisation and the iterative processes undertaken have allowed the project partners to establish the fundamental relationship between the moulding variables and the properties of the material, and to establish the parameters that lead to process control.
The limitations of the process have also been characterised, allowing the development of best practice guidelines.

Some scale-up work has been undertaken, and has demonstrated the suitability of the process for the production of full-scale products using this technique.

The partners involved in the project have all developed their knowledge and understanding in the filed, and have forged strong links across Europe, which will continue to grow and be mutually beneficial well beyond the end of the Protec project.

1.4.4 Intentions for Use and Potential Applications

The intention for use of the project is to offer the medical technology sector, specifically SMEs in the medical implant and pharmaceutical fields, a new, improved biodegradable polymer system, a sterilisation best practice guide and, moreover, a highly competitive, highly efficient supercritical fluid processing technology that will not only confer advantageous properties to their products – such as increased biocompatibility – but will also reduce

costs, both in terms of the materials and energy consumed. These offering will in turn benefit the health and environment of citizens throughout the EU.

The process may be applied to a variety of materials and applications, which potentially may include:

- Tissue engineering e.g. scaffolds made from poly(DL-lactide-co-glycolide)
- Orthopaedics e.g. Bone fixation devices, cranio-maxillofacial devices
- Sports injuries e.g. Cruciate ligament reconstruction, suture anchors and interference screws
- Guided tissue regeneration and drug delivery
- Automotive applications e.g. recyclable polymer dashboards
- Any plastic products that are required to biodegrade

1.5 Impact

The European Medical Technology industry is dominated by niche market SMEs and employs more than 385,000 throughout the EU in more than 9345 companies, eighty percent of which are SMEs. The technology and materials developments of the project will provide the opportunity for SME manufacturers to move away from traditional low-tech processes, towards more high-tech multifunctional technology and materials, enabling the industry to adapt to changes in market trends, providing both stability within existing employment and the creation of employment in new areas.

The technology will also bring about environmental benefits. Approximately 15 billion kilograms of organic and halogenated solvents are produced each year, most of which are toxic to the environment. The replacement of these solvents in manufacturing and processing has therefore been identified within a range of European policies. A further environmental impact for the use of organic solvents is also realised through the energy used during the removal

of these solvents from manufactured products (for polymer products, this is often the drying steps).

This project directly addresses this issue by replacing organic solvents with supercritical fluids, for a range of solvent intensive processes, such as polymer foaming. The supercritical fluid used is also a gas under ambient conditions and therefore does not require extra drying steps or removal from the product.