# SYNTHESIS REPORT

# FOR PUBLICATION

CONTRACT N° : BRE 2-CT92-0396

PROJECT N° : CT .1003 /91

TITLE : Development and characterisation of highly stable and rapidly osteointeracting hydroxyapatite, plasma spray coated on prostheses

PROJECT COORDINATOR : Flametal SpA (I- Fornovo Taro Pr)

PARTNERS :

- Cremascoli Srl (I-Milano)
- Biotecnic Sa (F-Toulouse)
- 3C Research Srl (I- Roma)
- CHI-BO Srl (I-Modena)

R&D

- INPT-ENSDC Laboratoire des Materiaux Physico-Chimie des Solides (l?-Toulouse)
- CRITT Centre Regional d' Innovation et de Transfert de Technologies (F-Charleville)
- IOR -Istituti Ortopedici Rizzoli (1-Bologna)
- Chirurische Universitatsklinik und Polyclinic of Wurzburg (D-Wurzburg)

LEMI -Laboratoire d' Evaluation des Materiels Implantables F-Martillac)

STARTING DATE :01.02.93 DURATION :24 MONTHS

PROJECT FUNDED BY THE EUROPEAN COMMISSION UNDER THE BRITE/EURAM PROGRAM ME

DATE : 30/09/95

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# 1 - SUMMARY PAGE

## 1.1 Five keywords on the content of the project

Hydroxyapatite
Coating
Plasma spray
Prostheses
Surface treatment

## 1.2 Abstract of the results and benefit of the project

The aims of this research were to produce highly stable matings to be used in medical devices either by spraying material more stable than regular EIydroxyapatite, such as Fluoridated-apatite, or by treating the surface of an improved Hydroxyapatite to induce the formation of a stable layer.

The innovative aspect of the coating developed in this project is the possibility to produce a more stable " Low Fluoro content Hydroxyapatite material " using a Fluoridated-apatite with only 50% of Fluoro content or treating the surface of an improved regular Hydroxiapatite with a fluoridating agent.

In addition a surface treatment has been developed that produces a bioresorbable highly bioactive layer at the surface of the Fluorided-apatite coating in order to enhance its bone formation capability.

The new coatings coupled with the surface treatment should confer better biological and mechanical properties to the coating and a higher performance to the prostheses, improving in vivo stability and bioactivity combined with a good biocompatibility. They show characteristics of biological compatibility and long term stability better than the uncoated or coated with the standard Hydroxyapatite implant.

The new materials provide to the implant surface with bioactive properties allowing fast bone healing and substantially reducing the failure rate of surgical implantation carried out with uncoated prostheses ameliorating bone attachment, and/or enhancing the resistance to bioresorption and prosthesis longevity and stability in life.

The new surface treated hydroxyapatites are going to have a wide application in coating hip and dental prosteses with subsequent high social benefits, because by means of their enhanced stability and osteointeracting properties medical device substitution could be avoided and accelerating bone healing will greatly reduce the time of hospitalization and the following period of convalescence.

The improvement of osteoconductive properties would allow wide use of these coatings especially in elderly patients with impaired bone activity and they also have opened the way for new clinical application of bioceramic coatings, and it can be stated that if Hydroxyapatites have been introduced in orthopedic surgery to improve the osteointegration of uncemented hip joint prostheses, they could also be more effectively used in fracture fixation to decrease the risk of implant failure, and consequently have a very positive impact on the health of our community

The good results obtained from the new coatings have incited the consortium to protect them by patenting the surface treatment of coatings. It should be pointed out that this treatment can be also applied to all kinds of ceramic biomaterials for orthopaedic use.

## 2- DESCRIPTION OF THE ACHIEVEMENTS

### 2.1 Introduction

Plasma spray coatings of Hydroxyapatite (I-IA) on titanium alloy joint prostheses have been developing for several years. They provide the implant surface with bioactive properties (osteoconductive properties) allowing fast bone healing and fastening of the prostheses by bone in growth, without any use of the polymer cement mainly responsible for the loosening of implant devices. However HA coatings may dissolve and degrade *in vivo* releasing debris in the organism and leaving the metal in contact with the bone tissue. This degradation is one of the major criticisms against this technique.

This project is aimed at improving apatite coatings with regard to their dissolution and degradation behaviour and obtaining a more bioactive surface.

The achievements can be summarized in the following four points :

- ⇨ **Improved mechanical properties**
- ⇨ **Complete biocompatibility**
- ⇨ **Higher stability after implantation**
- ⇨ **Enhanced osteoconductive properties**

### 2.2 **Achievements**

Improved mechanical properties

Adhesion, Abrasion and Fatigue tests show higher performance of the new coatings, concerning with their higher density and compactness, compared with the standard one.
In addition it was found that the optimised apatite coatings were more adherent to the Titanium substrate than the standard coating.

An abrasion Test has been performed In conformance with an FDA proposal to simulate the abrasion of the surface due to the insertion of the implant into bone during surgery and due to micro motion after surgery.

The method involves rubbing a block of hardened material against the coating. The loss of coating particles removed from the test coupon was measured against the load applied by the hard block.

Annex 2.3_1 shows the abrasion resistance curve of the new coatings (S-T. means Surface Treated) compared with Standard Hydroxyapatite

Complete biocompatibility

To evaluate possible toxicity of new coating and surface treatment an *in vitro* test required for product validation has been performed according to the international 1S010993 standard.

*In vitro* biological testing shows that the Fluoridated-apatite and surface treatments do not reveal any toxicity and can improve both the cellular attachment and cellular proliferation.

The cellular behaviour of the human osteoblast : density attachment appeared higher for the treated samples when compared with untreated one. The citiplasmic effect also appeared better on treated samples.

Higher stability and biocompatibility after implantation

Chemical stability of the coating has been tested measuring the solubility rate of apatite *in vitro* using a simple chemical test that represents the performance of the materials in biological media.

The new coating shows improved properties regarding stability and resistance to degradation compared with the standard hydroxiapatite. Annex 2 .3_2 shows the dissolution test curve of New coating surface treated compared with standard hydroxyapatite.

Concerning in vivo experiments in sheep in both unloaded and loaded conditions the coated implant showed characteristics of biocompatibility which are better than the control coating. This fact is estremely important for the long lasting clinical application.

Statistical extraction torque of samples coated with the new coating at nine months, was from four times to six times higher compared with the corresponding extraction torque measured after two weeks. This improvement was further demonstrated by radiogrphical analisys and histomorphometric assessment which show a very good osteointegration of all samples.

The unloaded study showed that the Fluoridated-apatite coating is less absorbable compared to the regular hydroxyapatite coating.
Attached pictures show the high stability after 9 months of permanence and the osteointegration capability of the new coating compared with standard and with a coating of pure titanium powder with the same surface roughness.

Annex 2.3_3 shows the transverse section of a New Type B surface treated coating after 9 months. The bone appears well integrated all iong the profile of coating. The bone had been perfectly restored

Henhanced Osteoconductive and Osteointegration Properties

Biocompatibility *in vitro* studies concerning evaluation of human osteoblast attachment and growth and study of human osteoblast attachment using Scanning Electron Microscopy according to 1S0 Norms demonstrate that the surafce treated coatings have improved osteointegration properties accelerating the bone ongrowth and bone healing. The same *In vitro* assessment has been confirmed by unloaded and loaded studies in animals.

The progressive enhancement of sample osteointegration of the surface treated coating has been shown by histological and histomorphometric analysis and concerning bio-mechanical assays, extraction torque (that represents the bone-implant interface strength) and percent of bone implant contact results higher in the new coating compared to smooth titanium and a non ceramic coated pure titanium pin with the same surface roughness after 15 and 30 days.

Biomechanical results of loaded tests in animals after six weeks reveal that a statistically significant higher extraction torque was found in the New Type B surface treated coating (Annex 2. 3_4). This result demonstrates that the new coating may achieve a much better stability of fixation compared to standard hydroxyapatite and the smooth stainless steel which is currently used for manufacturing the fixation pins utilized in orthopedic surgery.

This major enhancement of the bone pin interface stability should be considered as a crucial factor for diminishing bone pin loosening and infection. Clinically, the achievement of a more stable boric pin interface is extremely important in the early period of the external fixation fracture treatment, which corresponds to the crucial time of the fracture instability and in the osteoporotic bone. A more rigid bone pin interface could be also particularly useful in the long lasting treatments and when the surgeon decides to dynamize the fixator.

On the basis of the histological results, we state that the very positive biomechanical results reported in this study for the new hydroxyapatite coated pins were mainly due to their better osteointegration. We think that the osteoconductivity of the hydroxyapatite coating facilitated bone remodelling and direct bony coverage of the pin surface.

## 2.3 Remarks

Degradation and dissolution processes of the coating have been carefully investigated and methods for testing coatings and surface treatment which allow a rapid screening of biomaterials saving time and money in long and expensive biological testing have been set-up.

High properties of the new Hydroxyapatite have opened the way for new clinical application of bioceramic coatings, and it can be stated that probably the Hydroxyapatite coatings which have been introduced in orthopedic surgery to improve the osteointegration of uncemented hip joint prostheses could also be more effectively used in fracture fixation to decrease the risk of implant failure. The utilisation of these coatings in fracture fixation could allow the difficulties of the fixation in the osteoporotic bone to be overcome. It is well known that the bone fracture treatment and rehabilitation in the eMer is one of the major problems of the health care system of our country, and in the future the progressive ageing of the population will exacerbate this problem, with a subsequent very strong positive impact on the health of our community

Concerning activities on hip prostheses' we want to state that has been performed a preclinical validation of the " ANCAFIT STEAM " designed by Cremascoli spray coated with the new surface treated coatings has been performed. Endrance trials of a prototype prosthetic steam have been performed in conformance to the ISO standard 7206/7.1993.
Clinical trials are under development.

Referring activities on dental prostheses the fixation after ingrowth and sacrificing the animals was measured by non destructive Dynamic Mechanical Spectroscopy (DMS). The axial movement of the implants under a static preload with stepwise superposed dynamic loads was determined and the complex spring constant was calculated.

The new type of coating confirms the highest spring constant E*, which means the best fixation, which matches with the findings of the best mineralisation pattern.

The combination of dynamic mechanical measurements and microcomputer tomography is the first evaluation strategy that relates the two most important parameters in implant optimisation : The mineralization pattern and the in growth strengths, close to the physiological loading condition.

## 3- EXPECTED ACTION AFTER THE PROJECT END

It is now generally admitted that hydroxyapatite coatings substantially reduce the failure rate of surgical implantation carried out with uncoated hip prostheses , estimated at 25°/0 , for a global market of approximately one million prostheses per year; moreover the use of one month.

The experience accumulated by the enterprises involved in the project provides the opportunity to take a leading position in the field of the cementless titanium based prostheses, from where the introduction on the market of balanced combinations of reliability and innovation would be facilitated.

Making qualified prostheses with well documented coating cohesiveness, high metal-coating interracial strength and bioresorption resistance , together with surface modifications enhancing bone attachment, could be particularly valuable for selling high quality hip and dental prostheses on the major US market, where the use of hydroxyapatite coatings is at its beginning.

The good results obtained from the new coatings have incited the consortium to protect them by patenting the. surface treatment of coatings. They can be easily applied on all kinds of ceramic biomaterials for orthopedic use and are not reserved for plasma coating.

Possibly licensing enterprises in exchange of royalties , to be fairly shared according to each partner contribution to the project. Corsortuim agreement has been made.

The documentation derived from the physical-chemical , mechanical and in vivo studies , would represent a valuable guarantee and advertising support for world-wide customers and the enterprises involved into this project could also provide a valuable contribution from an industrial base using advanced technologies, to the establishment or the verification of the standard tests needed throughout the EEC for qualifying calcium phosphates coated prostheses.

Industrial 'partners decided to qualify the hip and dental prosthesis (designed and developed in the project) coated with the best coating validated by the project in conformance with the international standard and apply the EEC mark to the product following " Direttiva 93/42/CEE del Consiglio concernente i dispositivi medici (14 Giugno 1993) and " MEDDEV 14/93 Rev 3 - Demarcation with Directive 65/65/EEC relating to medical products and related directive and Procedure for consultation between Notify' Bodies established under 93/42/EEC and Competent Authorities for medical products.

## 5- **THE CONSORTIUM**

### 5.1 Consortium composition

The program has been carried out by a consortium composed of 5 Industrial Partners a group of **5** Research and Development performers and few external services:

### 5.2 Role of the partners

FLAMETAL SpA - Proposer and Project Co-ordinator (I- Fornovo)

Flametal Spa started its activity in coatings in 1973, and today it is leader in Italy with sixty five people employed ; six of them work in a laboratory with specific equipment for research and development and quality control.
Flametal is specialised in high quality metallic, ceramic and biomedical coatings, produced with "total quality" concepts and ISO 9002 std approval and qualification.

In 1979 Flametal started its involvement in the field of cementless surgical prostheses initially coated with allumina more recently with hydroxyapatite and nowadays it has a well established position on the European market of orthopedic and dental prostheses **through** the company of the Flametal Group : "Biocoatings"

Flametal provided its a contribution to the Project performing the following task :

- Preparation of the powders
- Plasma spray of the coatings
- Morphological characterization
- General management and co-ordination of R& D Performers

CREMASCOLI srl (I - Milano)

Cremascoli has been working for almost 36 years in the hospital market dealing with different medical fields as orthopedics, cardiology , cardio-surgery , urology, general surgery ophthalmology, etc. and its sale network is made up of 75 salesmen who are specialised in different fields and promote and sell to hospitals, private clinics on the whole Italian territory.

Cremascoli manufactured the samples for characterization and it designed and developed a new hip prostheses " ANCAFIT STEAM ", properly tailored to be spray coated with the new product . The prostheses has been pre-clinically validate and it will be used for clinical trialsl.

BIOTECNIC SA (F - Tolouse)

The Biotecnic company was created in 1985 to make surgical implants. Since 1989 it has been trading its prostheses BO3 with or without Hydroxyapatite.
Biotecnic has been involved in specimen manufacturing and prostheses design.

## 3C RESEARCH srl (I - Roma)

3C Research srl, is a young company mainly aimed at design, research, implant production, prosthesis tools and devices for odontostomatology. The company team is made up of expert physicians 'in design, construction and installation of prosthesis on dental implants and mechanical components and devices, plus expert physicians in oral cavity surgery.

3C Research srl designed and developed a dental prostheses suitable to be plasma spray coated in order to ameliorate osteointegration and bone bonding, with a peculiar " sand-glass " shape that provides, after bone regeneration, a strong mechanical axial resistance

Implant configuration has been calculated to receive a suitable coating thickness that will become complementary with it during bone formation, it has been designed without sharp edges in order to increase its coating capability to avoid uneveness in the thickness and coating scaling.

3C Research designed and manufactured dental prostheses that, after being coated, have been implanted in mini pigs at University of Wurzburg.

## CHI-BO srl (I - Modena)

CHI-BO was funded in 1982 with the aim of design and manufacturing dental prostheses to implant in the oral cavity. It developed a dental prostheses design to prevent hollow in jawbone and suitable to be plasma spray coated : " M. D. I?. ( Metal Dental Root ) System ".

The M.D.R. implant consists of a Ti screw in the shape of a frustum of cone which respect the fundamental principle of osteointegration. It has been designed slightly fluted so as to resemble the root of a natural tooth.

The M.D.R. implant, thanks to the fluting of the head, is able to adapt in the cortical housing. The conical shape of the body, with the spiral, is able to deviate vertical force and convert it into oblique force, thus distributing it over the narrow , which thanks to its trabecula, spreads the force over a much greater surface.
Coated Dental prostheses designed and manufactured by CHI-BO have been implanted in mini pigs at the University of Wurzburg.

INPT - ENSDC - Laboratoire des Materiaux-Physico-Chimie des Solides (F - Tolouse)

The "Laboratoire des Materiaux-Physico-Chimie des Solides" has been specialised in research into the synthesis, structure and reactivity of apatite compounds for more than 20 years. Their laboratory has been involved in the drafting of French norms on apatite coatings and is used to analyse such coatings for several companies .

It has been involved in the following activities:

Preparation of FHA and characterization of the powder
Chemical-physical characterisation of the coatings
Surface treatment of coatings
Dissolution test to assess the stability of coatings *in vitro*

Treatment of the coatings invented by Prof. C. Rey and Dr. X. Ranz were patented.

CRITT - Centre Regional d' innovation et de Transfert de Technologie (F - Charleville)

CRITT specialised in materials and coatings was founded in 1984 under the impulse of the Research and Technology Ministry. It was qualified by the Reseau National d'Essai in 1988 and it is approved by the French Ministry of Health for the femoral implants . C.R.I.T.T. is also part of Eurolab Structure (which has 18 European Countries including the 12 of the EEC) of which it is member.

CRITT performed mechanical tests of coating in conformance with the standard ISO norms and FDA Approval Draft for coating on prostheses for implantation.

IOR - Istituti Ortopedici Rizzoli (I - Bologna)

The Rizzoli Institute of Bologna, Italy, is the leader, world wide famous, national research Institution for orthopaedics. The Rizzoli Institute is made up of eight clinical Departments of orthopedic surgery and seven research laboratories.

The Institute performed bio-mechanical and hystogical studies of the new coating, implanting screw shaped metallic coated samples and external fixator pins into the bone of adult sheep in unloaded and loaded conditions. The coatings were evaluated in unloaded conditions after short and long permanence in animals (2 weeks, 1 month, 3 months, 9 months) and in loaded condition in short permanence (6 weeks).
The research involves the Laboratories of Experimental Surgery, the Laboratories of Biocompatibility and the Laboratories of Electron Microscopy.

Additional activities carried out by IOR concerning :

- Pre-clinical validation of the prototype hip prosthesis designed with Cremascoli
- Determination of the accuracy, repeatability and resolution of the computerised X-ray density profile analysis applied to the clinical evaluation of the implant osteointegration process
- Preparation of a detailed planning of the clinical trials that the consortium will use to proceed with the final validation of the product in human subjects.

Chirurgische Universitatsklinik und Policlinic of Wurzburg (D - Wurzburg)

The work of the Wurzburg group covered the field of the mechanical properties of the implant bone interface including macro-biomechanical aspects as well as the correlation with the micro-architecture of the junction. During the last years , new strategies for the determination of a better understanding of interface biomechanics have been developed and they have been applied in this pi-eject.

The Institute performed the implantation ( under the supervision of the Partner's medical dentists ) and the study of dental prostheses in mini pigs and the following mechanical and histological assessment by means of dynamic non destructive push out tests combined with microcomputer tomography to better understand the mineralization pattern.

LEMI - Laboratoire d'Evalutation des Materiels Implantable (F - Martillac)

LEMI carried out Biocompatibility tests following the international ISO standard and *in vitro* study of human osteoblast attachment and growth in order to evaluate the effectiveness of coatings and get a preliminary screening before *in vivo* trials.

External services :

Biotec AG ( CH-Zurich ) as Spray Process Advisor, Inoweep GmbH ( D-Wurzburg ) to perform advanced mechanical testing, Ortofix SpA ( I-Bussolengo ) that provided external fixators, Ing Claudio Lovera ( I-Torino ) as Project Coordinator and Dr Jorge Viera Da Silva of MTA ( F-Paris ) appointed by the EEC to follow the project as Project Technical Assistant.

## 5- REFERENCES

### 5.1 Publications and conferences resulting from the project

The following list of publications was presented at the congress and has been published in conferences proceeding :

. Development and characterization' of highly stable and rapid osteointeracting hydroxyapatite, plasma sprayed on prostheses

Workshop on Biomaterials and medical devices
September 11-14, 1994- Piss (Italy)

- Dinamic Mechanical Spectroscopy. A new way for the quantitative evaluation of implants materials, implant stability and the complex biomechanical properties of human body

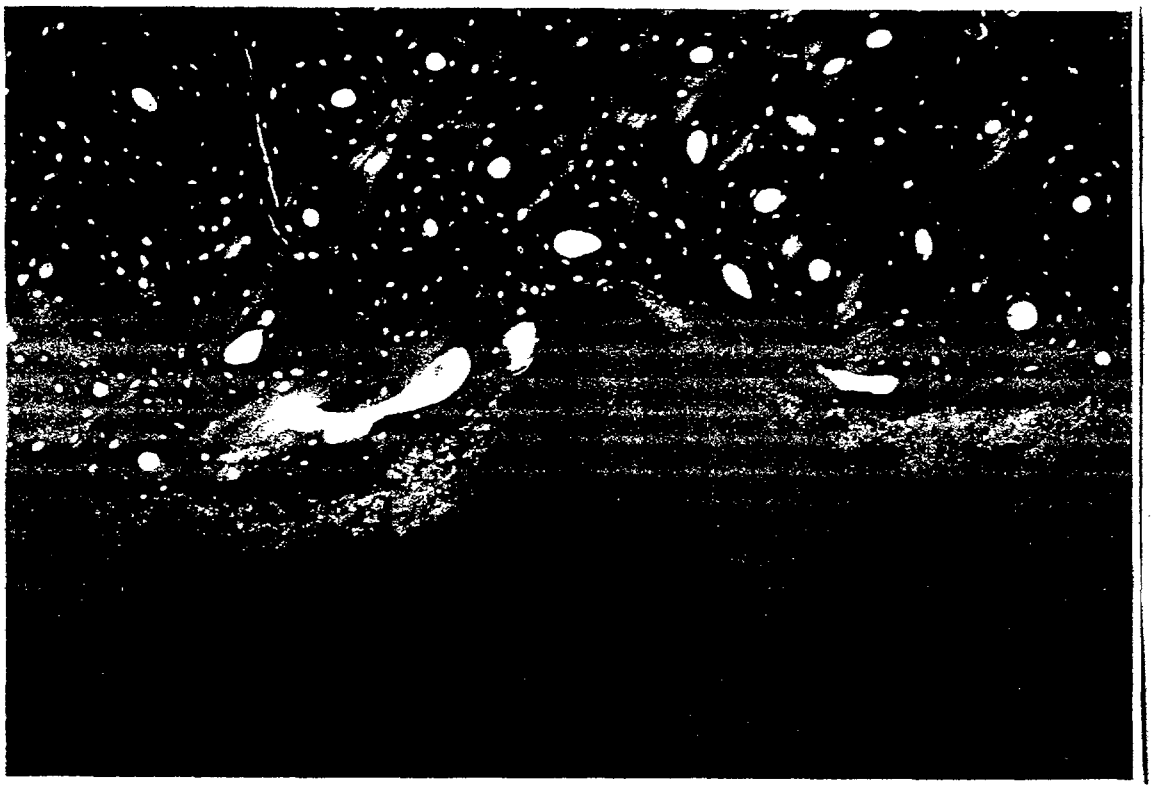
Second International Biomechanic Congress
July [0-15, 1994 - Amsterdam ( The Netherlands )

### 5.2 Patents

Surface treatment of coatings has been patented in the EEC and the USA.

ANNEX 2.3_3

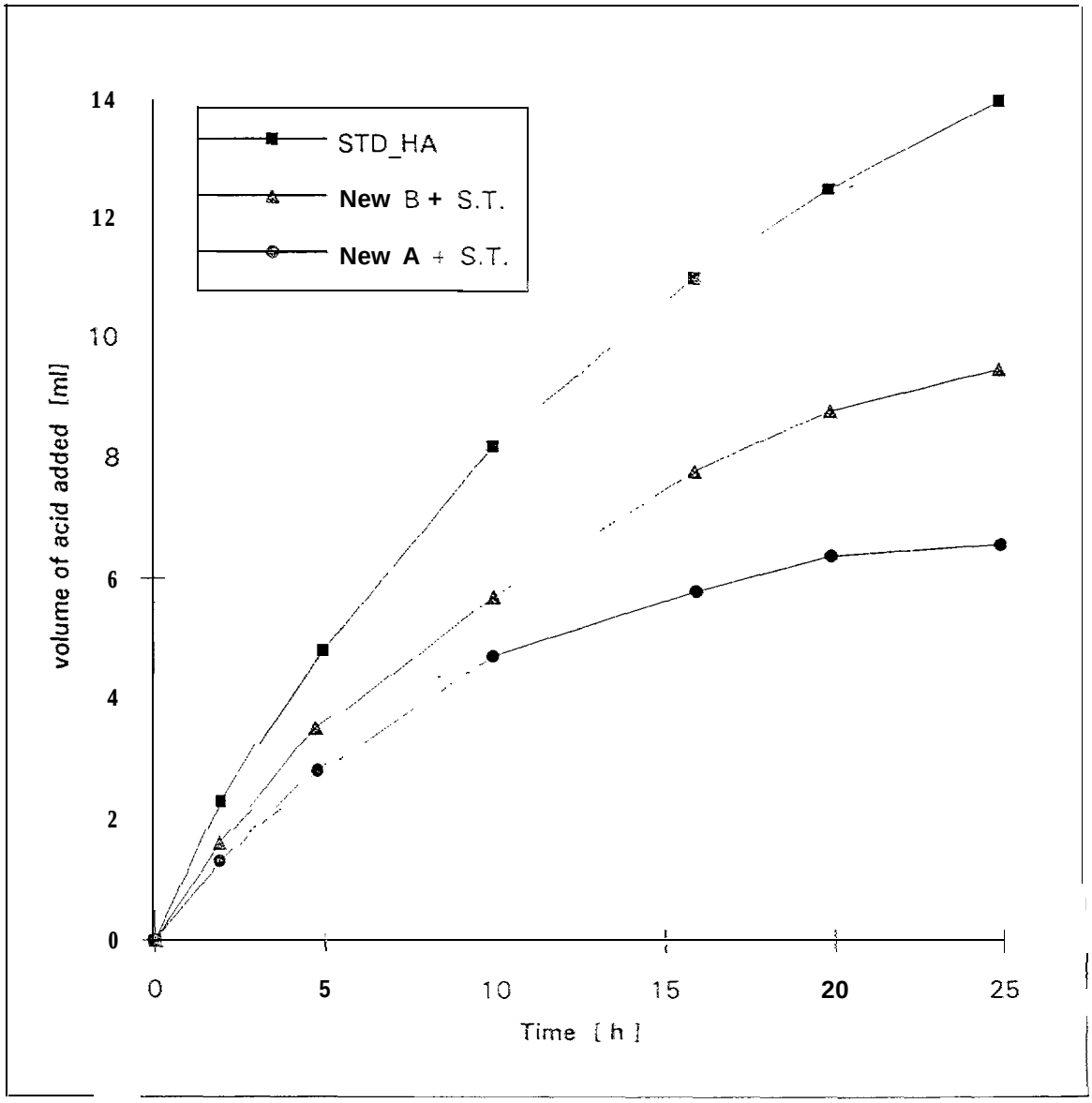
# IN VIVO NOT LOADED TESTING



**Annex 2.3_3 shows the transverse section of a surface treated coating after 9 months in sheep. The bone appears well integrated all long the profile of coating. The bone had perfectly restored.**

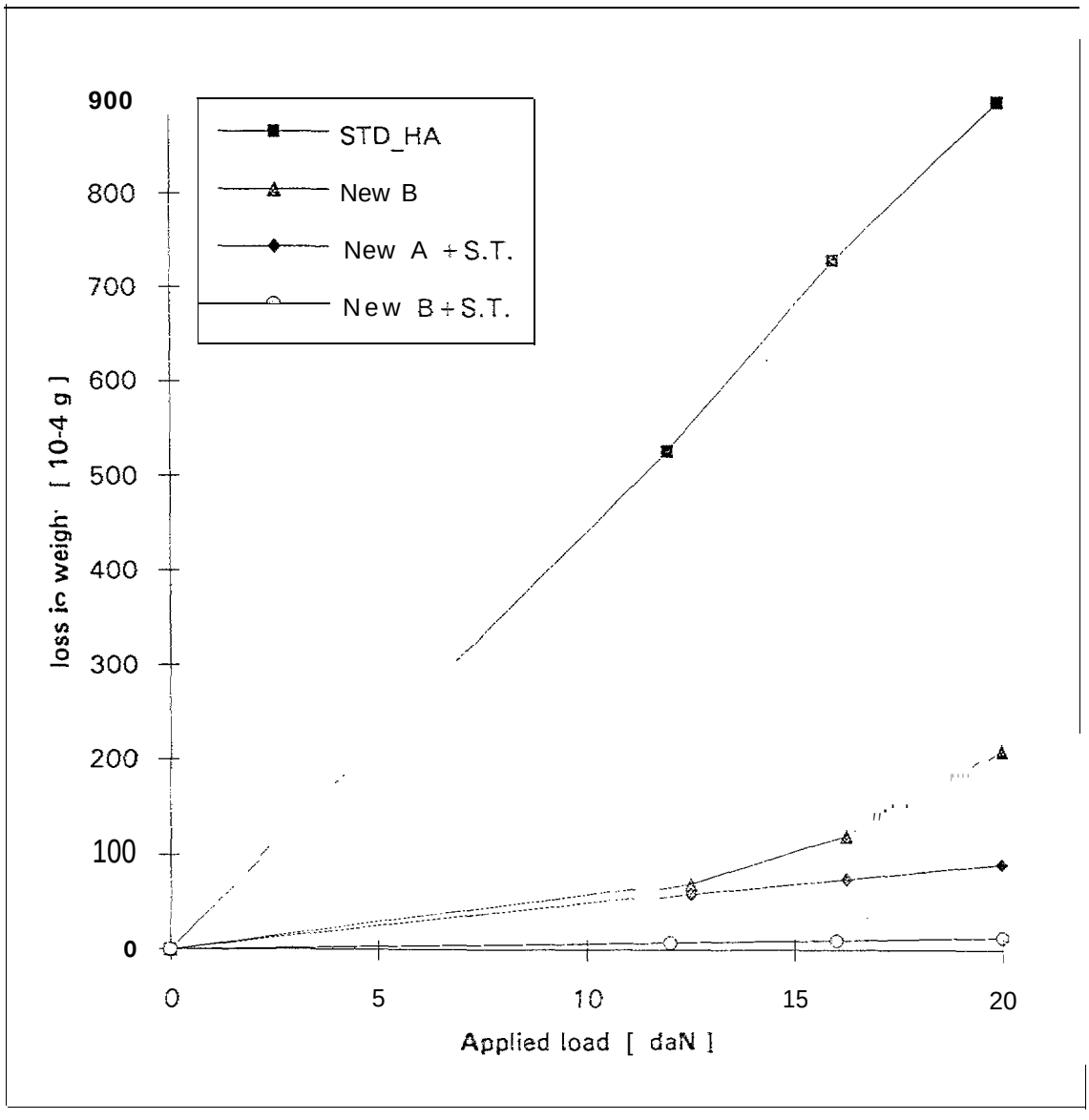
ANNEX 2.3_2

# DISSOLUTION CURVES



## ANNEX 2.3 1

# ABRASION RESISTANCE



## ANNEX 2.3_4

# IN VIVO LOADED TESTING