A.It.U.N. MEETING

12th

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DEPARTMENT OF PHARMACY AND BIOTECHNOLOGIES

10-11 May 2018

Aula Prodi, San Giovanni in Monte, Bologna

Medicines for older people: advances in drug delivery

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Artwork by Anna Vasileiou

Medicines for older people: advances in drug delivery

May 10-11, 2018

Aula "Giorgio Prodi", piazza San Giovanni in Monte 2

Bologna, Italy

Scientific committee

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Thursday, May 10th, 2018

12:00- 14:00 Registration

14:00- 14:15 **Opening session**

Serena Bertoni, A.It.U.N. Chair, University of Bologna

Nadia Passerini, A.It.U.N. Faculty advisor, University of Bologna

Santi Mario Spampinato, Head of Department of Pharmacy and Biotechnology, University of Bologna

Session I: The older patient population: characteristics & needs

Chairs: Serena Bertoni, Angela Abruzzo

14:15-15:15 **Are patients the better healthcare professionals? Following through the drug therapy from a patient perspective**

Sven Stegemann, Capsugel and Graz University of Technology, Austria

15:15-15:45 **Geriatric pharmacology: a clinical approach**

Fabrizio Imola, Operative Units "Geriatria Calogero f.f", S. Orsola Malpighi Hospital, Bologna.

15:45-16:15 **Issues and challenges in the proper pharmacological management of elderly patients**

Andrea Bedini, Department of Pharmacy and Biotechnology, University of Bologna

16:15-17:00 Coffee break and poster session

PhD student oral presentations:

17:00-17:20 "*Can community pharmacy manage therapy adherence in older people to increase therapy success?"*

Irene Pignata, Department of Pharmaceutical Science and Technology, University of Torino

17:20- 17:40 "*PT(IV) prodrugs-loaded luminescent solid lipid nanoparticles as theranostic brain vehicles"*

Ilaria Arduino, Department of Pharmacy-Drug Sciences, University of Bari

20:00 Social dinner at "Cantina Bentivoglio", via Mascarella 4/b, Bologna

Friday, May 11th, 2018

Session II: Oral drug delivery

Chairs: Greta Adorni, Karthik Neduri

9:10-9:40 **Oral drug therapy in elderly with dysphagia**

Giulia Bonacucina, School of Pharmacy, University of Camerino.

9:40-10:10 **Application of slippery film coating for easy swallowing of solid dosage forms**

Alberto Genovesi, Colorcon Inc., UK.

PhD student oral presentations:

10:10-10:30 "*Administration of solid drugs for dysphagic people: comparison among different commercial gelified vehicles"*

Serena Logrippo, School of Pharmacy, University of Camerino

10:30-10:50 "*From Bitter to Sweet: a preliminary study towards a patient-friendly Praziquantel dosage form"*

Debora Zanolla, Department of Chemical and Pharmaceutical Sciences, University of Trieste

10:50-11:20 *Coffee break*

11:20-11:50 **Can orodispersible films contribute to the improvement of treatment adherence in the older population?**

Umberto Musazzi, Department of Pharmaceutical Sciences, University of Milan

11:50-12:30 **Fixed dose combination products**

Alessandra Rossi, Food and Drug Department, University of Parma.

Session III: Alternative route of administration and future perspective

Chairs: Laura Tiozzo Fasiolo, Roberto Baggio

12:30-13:00 **Nose-to-brain delivery of potential therapeutic agents for Alzheimer's therapy**

Giovanna Rassu, Department of Chemistry and Pharmacy, University of Sassari

13:00-14:50 Light lunch and poster session

14:50-15:20 **Development of new formulations for Ostheoporosis patients**

Silvia Panzavolta, Department of Chemistry G. Ciamician, University di Bologna

15:20-15:40 **Topical ophthalmic drugs in older people: present and future**

Marco Albasini, CoC Farmaceutici, Italy

15:40-16:00 **Innovative drug delivery systems for the treatment of bed sores**

Barbara Vigani, Department of Drug Sciences, University of Pavia

PhD student oral presentations:

16:00-16:20 "*Escin-based nanovesicles to improve berberine topical delivery"*

Giulia Vanti, Department of Chemistry, University of Firenze

16:20- 16:40 "*Biosurfactant loaded vesicles for the local treatment of Staphylococcus aureus skin infections"*

Barbara Giordani, Department of Pharmacy and Biotechnology, University of Bologna

16:40- 17:00 "*PCL/Collagen electrospun nanofibers as polyphenols drug delivery system"*

Dalila Miele, Department of Drug Sciences, University of Pavia

17:00- 17.15 Poster Awards and Concluding Remarks

Annual A.It.U.N. Assembly

INVITED LECTURES

Are patients the better healthcare professionals? Following through the drug therapy from a patient perspective

Sven Stegemann

Capsugel and Graz University of Technology

Human behavior is often not rational. This applies to patients as well as healthcare professionals. This presentation summarizes the learning from several years of patient research, providing insight into the psychology and capabilities of patients when being diagnosed and prescribed to medicines. With increasing age, disease and therapeutic complexity, older patients often have long trajectories of drug use and experience, which provide them with real world expertise of drug therapy. This also includes to overcome administration issues in their own way and using information from sources they trust more than a healthcare professional. Understanding the "unspoken" in patients mind and behavior, is a unique source to develop patient centric drug products, building on their intuition and logic.

*Prof. Dr. **Sven Stegemann** is director, pharmaceutical business development at Capsugel, and professor of patient centric drug design and manufacturing at the Graz University of Technology, Austria. Over the course of his 20-year career at Capsugel, Dr. Stegemann has worked as an advisor to major pharmaceutical companies on ways to improve the design, development and manufacture of pharmaceutical products so they better address the individual needs of patients. In his academic role, Dr. Stegemann's focuses his research on the rational development of patient centric drug products and their associated manufacturing technologies, as well as education and training of students and young scientists. Dr. Stegemann is the founder and chair of the AAPS Focus Group on Patient-Centric Drug Development, Product Design, and Manufacturing as well as the founder and President of the Geriatric Medicine Society.*

Geriatric pharmacology: a clinical approach

Fabrizio Imola

Operative Units "Geriatria Calogero f.f", S. Orsola Malpighi Hospital, Bologna.

Polypharmacy is common among the elderly and optimizing drug therapy is an essential part of caring for an older person. Because of multiple morbidities and geriatric syndromes, elderly are generally underrepresented in clinical trials; therefore the applicability of the guidelines to the geriatric patients remains controversial and prescribing for older patients presents unique challenges. Various tools have been developed to help doctors although none of these criteria can replace clinical judgment. In conclusion we can state that only comprehensive geriatric assessment, which always considers needs and priorities of the fragile patient, it proved to be effective to guarantee the best care for the elderly.

***Fabrizio Imola**, Medical Doctor, graduated in Medicine at the University of Bologna in 2009 and he achieved his specialization in geriatrics at the University of Bologna in 2015. He is currently working at the Operative Units "Geriatria Calogero f.f", S. Orsola Malpighi Hospital, Bologna.*

Issues and challenges in the proper pharmacological management of elderly patients

Andrea Bedini

University of Bologna

The use of medicines in older people (over the age of 65 years) has been described as the single most important health care intervention in the industrialized world. Comorbidity is in fact highly prevalent in the elderly, thus requiring the administration of multiple medications. This polypharmacy, although often clinically appropriate, may be dangerous for patients as it significantly favors the onset of drug-drug interactions, which in turn may lead to adverse drug reaction and the subsequent detrimental consequences on patients' health. Moreover, ageing is accompanied by several changes affecting the pharmacological effects of a drug, including remodeling of biochemical composition of tissues and mass distribution, modifications in adsorption, metabolism and excretion of xenobiotics, altered sensitivity to drug acting on cardiovascular or central nervous system. Furthermore, the prevalence of polypharmacy in the elderly make them more prone to altered hepatic drug metabolism, thus increasing the likelihood to develop drug-drug interactions. The inter-individual genetic variability regarding drug targets and/or metabolic enzymes may further contribute to such vicious cycle; other age-related factors potentially influencing drug metabolism are inflammation, circadian rhythms, gut microbiota, epigenetics. Last but not the least, elderly patients may display significant physiological alterations hampering their ability to take drugs through the common routes of administration (e.g.: oral); thus further complicating their proper pharmacological management. Within this multifaceted scenario, developing novel methods for drug administration (e.g.: orally disintegrating tablets, pulmonary, nasal, transdermal delivery) may represent promising strategies to optimize polypharmacy and reduce drug-related adverse effects in elderly patients.

*Dr. **Andrea Bedini** hold a PhD in Molecular and Cellular Biotechnology attended at Alma Mater Studiorum-University of Bologna. From 2008 to 2014, he worked as a researcher at Molecular and Cellular Pharmacology Unit, Department of Pharmacology, University of Bologna. He is currently a confirmed researcher and assistant professor of pharmacology at the University of Bologna.*

Oral drug therapy in elderly with dysphagia: between a rock and a hard place!

Giulia Bonacucina

University of Camerino

Demographic indicators forecast that by 2050, the elderly will account for one-third of the global population. Geriatric patients require a large number of medicines, and in most cases, these products are present on the market as solid oral dosage forms. However, this population tends to suffer difficulties with swallowing, defined as dysphagia. In this contest, caregivers in hospital geriatric units routinely compound solid oral dosage forms by crushing tablets or opening capsules to facilitate their administration. This practice requires a manipulation of original formulation making necessary to consider different issues: decrease of drug efficacy, increase in toxicity, problems of instability, lowering of palatability, cross-contamination and loss of drugs. The present work deals with the possibility to improve dysphagic patient compliance under therapy with a cholesterol-lowering drug, pravastatin sodium salt, a widely prescribed molecule traded on the market just as immediate-release tablets. Chemical-analytical and microbiological stability of an aqueous solution of pravastatin starting from tablets has been investigated with the aim to administer the solution orally by using syringe directly in feeding tube. The objective was to formulate a hydrogel for oral admistration having a suitable consistency and a release kinetic comparable to that of immediate-release tablet. Therefore, patient might switch pharmacological therapy from original solid form to the gelified formulation assuring compliance to treatment. This work demonstrates the possibility to reformulate pravastatin tablets as liquid pharmaceutical formulation or gel with the aim of improving life quality and safety in drug administration.

*Dr **Giulia Bonacucina** received her degree in Chemistry and Pharmaceutical technology in 1999 and her PhD in Pharmaceutical Sciences in 2004 from the University of Camerino. After graduation she spent a period at the "Bristol Colloid Centre" University of Bristol (UK) and during PhD she was visiting student at the laboratory of Prof. Duncan Q. M. Craig, at the "Queen's University of Belfast in 2001 and at the Physical Pharmacy laboratory of Prof. Jean-Louis Grossiord, Faculty of Pharmacy, Université Paris Sud, in 2002. Currently she works as a researcher at the School of Pharmacy of the University of Camerino where she is lecturer in Pharmaceutical Technology. The research activity of Giulia Bonacucina mainly concerned the preparation and characterization of colloidal systems (micelles, microemulsions and nanoparticles) intended for drug administration.*

Application of slippery film coating for easy swallowing of solid dosage forms

Alberto Genovesi

Colorcon Inc., UK.

Many people cannot swallow tablets and capsules; this problem is more common in older people. The reason of difficulties could be related to the big shape of solid dosage forms as well as a specific disease of the patient. To make medicine easier to swallow, many people will modify the medication dosage form, for example by. splitting or crushing tablets and open capsules with potential risk on reducing therapeutic effect or wrong absorption. Novel film coating agents like Opadry EZ™ are helping to overcome this kind of problems improving patient compliance and reducing the daily dosage consumption and side effects.

*Dr. **Alberto Genovesi** is currently Technical Manager at Colorcon, responsible for the Area comprising Italy, Greece, Malta, Israel, Turkey, Syria, Island, Cyprus, Albania. He graduated in Chemistry and Pharmaceutical Technology at University of Bologna in 1994. His previous professional experiences include roles as Research and Development Scientist at Montefarmaco, responsible for Coating trials using coating pan at GS Coating system and responsible for Coating and Granulation using coating pan, fluid bed and high shear mixer at IMA.*

Can orodispersible films contribute to the improvement of treatment adherence in the older population?

Umberto Musazzi

Department of Pharmaceutical Sciences, University of Milan

The gradual decline of body functions in elderly people results in a higher incidence of dysphagia, trembling hands and reduced hand-eye coordination. Moreover, the altered gastrointestinal motility and hepatic or renal function modify the drug pharmacokinetics, requiring dose and regimen adjustments. In this context, conventional oral dosage forms show a high risk of practical therapeutic problems (e.g., difficult handling and swallowability) and errors that can result in a poor adherence and/or reduced patient or caregiver quality of life. Orodispersible dosage forms (ODXs) permit to overcome these disadvantages. Two main ODXs currently available are Orodispersible tablets (ODTs) and films (ODFs), which have been recently commercialized. ODFs are sheets designed to be placed in the mouth and to disintegrate quickly, giving a fine suspension or solution of drug substance in the saliva that can be easily swallowed also by patients with fear of choking or suffering from dysphagia. Constituted of plasticized water-soluble polymers, ODFs are predominantly produced by solvent casting technique. From a manufacturing point of view, the main advantage of ODF is the possibility to obtain different strengths from the same intermediate laminate by changing the cutting size. The main disadvantage lies in the reduced formulation space, which limits their use to only potent drug substances (< 100 mg) and makes the task masking difficult. Beside such technological limitations, the ODFs seem a very promising dosage form to be used in elderly population since they permit an accurate dosage, an easy handling, a good swallowability, other than a reduced risk of excipient overload.

*Dr. **Umberto Maria Musazzi** graduated in Pharmacy at the University of Milan and received his Ph.D. in "Chimica del Farmaco" in 2013 with the thesis "Transdermal and transmucosal pharmaceutical dosage forms for palliative care in cancer". During his Ph.D., he spent six months at the University of Missouri-Kansas City, Kansas City (United States) working on nanosystems for intratympanic administration of active pharmacological substances. Currently, he works as post-doctoral researcher at the Department of Pharmaceutical Sciences - University of Milan, Milan (Italy). His research areas include transdermal drug delivery systems; oromucosal drug delivery systems and trans-tympanic drug delivery systems*

Fixed dose combination products

Alessandra Rossi

Food and Drug Department, University of Parma

Combination products consist of two or more drugs in a single dosage form. Fixed-dose combinations are designed to simplify the medication regimen and are increasingly shown to be beneficial in many clinical conditions. The knowledge and insights now available concerning the dynamics, kinetics and mechanisms of drug action, along with the variables associated with oral absorption mean that formulation of combination products can be complex. If two or more active principles are present in a single dosage form, the drug release of one or both drugs may be modified, to ensure that plasma levels are aligned with the pharmacokinetics and pharmacodynamics of the individual drug so that clinical effectiveness is optimized. Moreover, a synergistic effect could lead to lower doses with increased efficacy and reduced dose-dependent side effects. Reduced "pill burden" could also aid medication adherence and improved patient compliance, particularly with chronic clinical conditions, such as cardiovascular diseases, diabetes, HIV/AIDS, tuberculosis and malaria. The pharmaceutical industry is facing great challenges in productivity and the popularity of fixed dose combination products is emerging as a big investment opportunity for life-cycle management of marketed drug products. Moreover, a combination product arises not only from the combination of two or more APIs. The innovativeness of the product can be boosted by the technology used to get it with the desired therapeutic schemes for enhancing clinical effects and prolong the intellectual property. Dome Matrix and multilayer technologies can be used in the development of fixed dose combination products. The presentation will show some examples of fixed dose combination products, obtained with these technologies, for the treatment of malaria, helicobacter pylori infection and overactive bladder.

*Prof. Dr. **Alessandra Rossi** is Assistant Professor at the Food and Drug Department, University of Parma. From 1994-1998 she did her PhD at University of Strathclyde (Glasgow, U.K.) in the Department of Pure and Applied Chemistry and in the 1998 she had a Postdoc Research Fellowship from Novartis at Heriot-Watt University, Department of Mechanical and Chemical Engineering (Edimburgh, U.K.). She is Management Committee Member of COST Project MP1404 "Simulation and pharmaceutical technologies for advanced patient-tailored inhaled medicines (SimInhale)" and Leader of Working Group 1 "Particle engineering/processing of inhaled medicines for local/systemic action". The research interests are mainly focused on oral swellable matrices for drug delivery control, Dome Matrix for time and space drug controlled delivery, powder agglomerates, nasal and pulmonary delivery.*

Nose-To-Brain Delivery Of Potential Therapeutic Agents For Alzheimer's Therapy

Giovanna Rassu

University of Sassari

Alzheimer's disease (AD) is a chronic neurodegenerative disease which affects nearly 44 million people worldwide; it is the fifth leading cause of death for adults aged 65 years and older, and the sixth leading cause of death for all adults. AD is the most common type of dementia within the elderly population characterized by memory loss, thinking disorders, impaired communication, difficulties in coordination and eating. This disease affects the normal life of the patients and their families with huge economic consequences. Intranasal delivery is a noninvasive method to bypass the Blood Brain Barrier and directly deliver drugs to the brain due to the unique anatomic connections, provided by the olfactory and trigeminal nerves, that connect the nasal mucosa and the Central Nervous System (CNS). However, due to the mucociliary clearance and the poor mucosal permeability of several drugs, an important requirement for this route is the development of appropriate delivery systems. An attempt to show the potential of this administration route in AD therapy will made; the effect of the drug delivery system and the polymer used will be explain. Furthermore, results concerning hydroxypropyl-β-cyclodextrin, commonly used as excipient, as possible candidate drug for the prevention and treatment of AD, will be presented.

*From May 16th 2011, prof. **Giovanna Rassu** is researcher in Pharmaceutical Technology field at the Department of Chemistry and Pharmacy of the University of Sassari. In April 2017, she obtained National Scientific Qualification for Associate Professor. From 2013-2014 Academic Year, she is Teacher of the Course of "Pharmaceutical Technology, Socioeconomy and Regulations 2" at the Master degree in Pharmacy of the University of Sassari and Teacher of "Systems of Quality Assurance 1" at the School of Specialization in Hospital Pharmacy of the of the University of Sassari. Her research activity has prevalently concerned the preparation and characterization of nasal micro- and nanoparticles for direct transport of active ingredients from the nose to the brain. Furthermore, her research activity includes also In situ forming hydrogels and microparticles for transarterial embolization of hepatocellular carcinoma and the development of "green" formulations containing natural components such as cocoa butter, propolis and milk thistle extract for topical or mucosal application.*

Development of new formulations for Osteoporosis patients

Silvia Panzavolta

Department of Chemistry G. Ciamician, University di Bologna

With the increase in life expectancy millions of people in many countries will be affected by diseases affecting the bones, both acute (fractures) and chronic (osteoporosis, tumors). Osteoporosis has been recognized as one of the most important diseases that afflicts man along with hypertension and diabetes mellitus. The economic impact of osteoporosis is similar to the costs of other major diseases such as stroke, breast cancer, chronic obstructive pulmonary disease and myocardial infarction. Greater attention is needed in understanding the pathology in order to choose which treatment to adopt: it is important to contain the consequences of the pathology with adequate and personalized prevention and treatment. Understanding the detailed mechanism that promotes differentiation of mesenchymal stem cells in the regeneration tissue processes can be useful to the production of new scaffolds able to regenerate bone tissue efficiently and in a short time. Scaffolds used in clinical practice are of various chemical/physical nature, often combining polymers or biopolymers with inorganic phases likely calcium phosphates, due to their similarity to bone tissue composition. These scaffolds must be biocompatible and possess adequate mechanical properties to sustain bone tissue during regeneration. Furthermore, the ability to deliver in situ effective amount of selected drugs represents an additional value for the treatment of a large number of pathologies, included osteoporosis. Different strategies have been pointed out to obtain delivery and sustained release of therapeutic drugs from biomaterials during the bone formation stage: among these, incorporation of Bisphosphonates as well as Growth Factors and Bone Morphogenetic Proteins has been successfully discussed in the literature.

*Dr. **Silvia Panzavolta** graduated in Chemistry cum laude, University of Bologna in 1994 and hold a PhD in Chemical Sciences at the University of Bologna* on *"Biomineralization and models for advanced materials". From 1999, she is working as a researcher at the Faculty of Sciences of the University of Bologna and her teaching activity includes the courses of General Chemistry, 1st level Undergraduate course of Biological Science and Biomaterials, 2nd level degree, course of Photochemistry and molecular materials. Her research involves structural and chemical investigations of biomineralized tissues as model sistems for the design of new materials, design and development of new biomaterials for hard tissue replacement, including calcium phosphates bone cements, calcium phosphates polymer composites, coatings of metallic substrates trough a biomimetic approach.*

Topical ophthalmic drugs in older people: present and future

Marco Albasini

CoC Farmaceutici, Italy

According to the National Eye Institute "as you age, you are at higher risk of developing age-related eye diseases and conditions". So, age is considered a risk indicator for developing eye diseases and conditions for the aging population. Furthermore, with increasing age related vision diseases and conditions there is an increased use of pharmaceuticals as part of ocular therapy. The most common age-related eye diseases are: Macular Degeneration, Cataract, Diabetic Eye Disease, Glaucoma, Dry eye. While there are many effective medications to treat these conditions, the challenge remains to deliver them effectively with a sustained release profile and with minimal side effects. Ophthalmic Preparations are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent (periocular) to the eye or used in conjunction with an ophthalmic device. Problems of poor ocular bioavailability because of various anatomical and pathophysiological barriers prevailing in the eye. Factors affecting drug availability are: rapid solution drainage by gravity, induced lachrymation, blinking reflex, normal tear turnover; superficial absorption of drug into the conjunctiva and sclera and rapid removal by the peripheral blood flow and low corneal permeability. To enhance topical ocular drug delivery, researchers have predominantly focused on two strategies: to increase the corneal residence time using viscosity enhancers, mucoadhesive, particulate, and/or in situ gelling systems and to increase the corneal permeability using penetration enhancers, prodrugs, and colloidal systems such as nanoparticles and liposomes.

*Dr. **Marco Albasini** is Qualified Person and Plant Manager of the pharmaceutical company COC Srl (Sant'Agata Bolognese, Bologna) where, from 2011, he is responsible of both production sites: Sant'Agata Bolognese and Rovereto s / S (Modena), responsible for the release of the specialties for the Italian market, European and Asia. After his graduation in Chemistry and Pharmaceutical Technology at University of Bologna in 1993, he has gained different working experiences in many pharmaceutical companies and in several different positions. He worked in TECRES Spa (Sommacampagna, Vr), ZAMBON GROUP Spa (Lonigo, Vi) and GENTIUM Spa (Villa Guardia, Como) as Quality Control Manager. From 2005 to 2011 he worked as Qualified Person at COSMO Spa (Lainate, Milano).*

Innovative drug delivery systems for the treatment of bed sores

Barbara Vigani

Department of Drug Sciences, University of Pavia

Pressure ulcers, also known as bed sores, are classified as chronic non-healing skin ulcers, that mainly occur in older patients confined to bed or to wheelchair for long time periods. The National Pressure Ulcer Advisory Panel (2014) defined such ulcers as localized injured areas of the skin and/or of the underlying tissue, principally caused by external forces, such as pressure and/or shear stresses. In bedridden patients, a prolonged and unrelieved pressure applied over a small skin area, especially a bony prominence, causes tissue compression, blood flow restriction and, thus, local tissue ischemia and necrosis, with the formation of an open sore. The applied pressure also induces a tissue distortion, resulting in shear stresses particularly negative for older patients, due to the excessive dryness of their skin. Pressure ulcers persist beyond 12 weeks, do not properly heal, mainly due to microbial wound contamination, and often recur. In the last decades, effective therapeutic strategies for the management of bed sores have been proposed: namely, traditional "inert" dressings, aiming only at protecting the wound from infections, have been replaced by modern "bioactive" ones, based on the use of biopolymers able to interact with tissue components and to take part in the healing process. Antibiotic and anti-inflammatory drugs and/or biological agents (hemoderivatives or growth factors) can also be loaded in such wound dressings in order to improve their effectiveness. In this scenario, my research group (Biopharmaceutics and Formulation Development Lab) has gained a consolidated experience in the development of a variety of innovative drug delivery systems intended for the treatment of chronic skin ulcers, comprising thermosensitive gels, sponge-like dressings, films, powders and nanosystems (nanoemulsions, nanocomposites and nanofibers).

*Dr. **Barbara Vigani** graduated cum laude in Pharmacy (2013) and obtained her PhD degree in Chemical and Pharmaceutical Sciences (2017) at the University of Pavia. Since April 2017, she is working as Postdoctoral Researcher at the Department of Drug Sciences, University of Pavia. Her current research activities focus on the development of therapeutic platforms for the treatment of spinal cord injuries and the management of skin and mucosal lesions. She is co-author of 19 research papers and 38 proceedings of national and international conferences dealing with pharmaceutical and biomedical sciences.*

PhD STUDENTS ORAL PRESENTATIONS

Can Community Pharmacy Manage Therapy Adherence In Older People To Increase Therapy Success?

I. Pignata[a], L. Ravetto Enri[a], F. Baratta[a], M. Mana[b], P. Brusa[a]

[a] Department of Pharmaceutical Science and Technology, University of Turin, Italy
[b] Federfarma Piemonte, Turin, Italy

Purpose:

Therapy adherence is the extent to which the patient follows medical instructions regarding timing, doses and frequency of taking drugs for the entire therapy cycle. Therapy adherence is very important because greater adherence means greater drug efficacy, lower risk of hospitalization, fewer complications associated with the disease, greater treatment safety. Correct therapy adherence therefore brings undoubted benefits to the patient's health and economic and social gains for the national health service. The patients most at risk regarding adherence are the elderly ones, especially if they are polytreated and “fragiles”. [1]
Community pharmacies, for their widespread diffusion in the territory and accessibility and for the confidential relationship pharmacist-patient may play a key role in adherence management.

Methods:

Therapy adherence, rather than strictly measured, can be estimated with a variety of methods divided into direct tests and indirect tests. In community pharmacy, adherence management can only be performed through direct tests such as questionnaires or pillcount. One of the most used questionnaire is the Morisky test with which is possible to determine, through 4 simple questions with a dichotomous answer, the therapy adherence of a patient. [2-3-4]

Results:

The Morisky test has been used in a survey in 9 community pharmacies of Piedmont interviewing 127 over 65 polytreated patients (taking at least 3 drugs a day). The questionnaire allowed to identify 45 non-adherent subjects.

Conclusions:

The pharmacist can identify people who do not adhere to chronic pharmacological therapies at local level. A questionnaire can therefore be a good method to identify non-adhering subjects even if, being a self report, this tool can underestimate non-adherence. The community pharmacy can thence offer a concrete service on therapy adherence bringing patient’s health benefits and economic savings. [5]

References

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[3] G. Fabbrini , G. Abbruzzese, P. Barone A. Antonini M. Tinazzi Castegnaro, S. Rizzoli,D. E. Morisky, P. Lessi Adherence to anti-Parkinson drug therapy in the “REASON” sample of Italian patients with Parkinson’s disease: the linguistic validation of the Italian version of the “Morisky Medical Adherence scale-8 items” Neurological Sciences November 2013, Volume 34, Issue 11, pp 2015-2022
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Pt(IV) Prodrugs-Loaded Luminescent Solid Lipid Nanoparticles As Theranostic Brain Vehicles

I. Arduino[a], N. Depalo[b], A. Paniello[b], A. Lopalco[a], A. Lopedota[a], A. Cutrignelli[a], F. Re[c], R. Dal Magro[c], N. Margiotta[d], V. Laquintana[a], M. Franco[a], N. Denora,[a,b]

[a] Department of Pharmacy – Drug Sciences, University of Bari Aldo Moro, Italy
[b] CNR-IPCF-Bari Division , Italy
[c] Nanomedicine Center, Neuroscience Center, School of Medicine and Surgery, University of Milan-Bicocca, Italy
[d] Department of Chemistry, University of Bari Aldo Moro, Italy

Purpose:
The aim of this project was the preparation of a theranostic nanocarrier loading Pt(IV)-Prodrugs and quantum-sized-carbon-dots (Cdots) potentially useful for the treatment of glioblastoma, the most frequent and aggressive type of brain tumor. [1]

Methods:
C-dots were synthesized by the thermal carbonization of citric acid as organic precursor, in non-coordinating solvent (octadecene), in the presence of 1-hexadecylamine as coordinating agent. Solid lipid nanoparticles (SLNs) loaded with Pt-(IV)-prodrugs and Cdots were prepared by using an oil-in-water homogenization process at high temperature. The SLNs platinum content was quantified by atomic absorption. In vitro cytotoxic effects and cellular uptake have been assessed in both human cerebral microvascular endothelial cells (hCMEC/D3) and in human glioblastoma (U87) cell line. Moreover, the in vitro brain permeability has been estimated on a human blood-brain barrier (BBB) model using transwell devices with hCMEC/D3 monolayers.

Results:
The prepared nanoformulations proved to be stable in aqueous medium and are characterized by a Z-average under 100 nm, a polydispersity index below 0.2, a zeta potential between −20 and −25 mV and a drug encapsulation efficiency in the range of 30-40%. The cellular uptake studies have highlighted the efficiency of this nanosystem in the delivery of Pt(IV)-prodrugs to the brain. The citotoxicity studies have demonstrated that the antitumor activity of Pt-(IV)-prodrugs is fully preserved upon encapsulation in SLNs. The endothelial permeability values of Cdots/Pt(IV)-prodrugs loaded SLNs through the in vitro BBB model were around 3×10^{-4} cm/min.

Conclusions:
In summary, SLNs have been used as Pt(IV) prodrugs nanovectors in order to maximize brain drug delivery. In this contest, C-dots were used for the realization of optically traceable nanosystems able to visualize the biodistribution and storage of the carriers into the brain.

References

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Administration of solid drugs for dysphagic people: comparison among different commercial gelified vehicles.

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Purpose:
Dysphagia is defined a swallowing disorder of liquids, solids and drugs and is a diffuse condition among older people [1]. Manipulation of tablets is a current clinical practice to manage this condition. Aim of this work was to evaluate commercial gelled products both in terms of rheological properties and of drug release kinetics when used as vehicles to administer tablets [2]. Model drug was Pravastatin sodium Pensa S.p.a. (PraNa) as 20 mg immediate-release tablets (IRT).

Methods:
Samples were prepared extemporaneously by mixing PraNa whole tablets in commercial gelified vehicles of different grades of consistency (conventionally defined 1, 2 and 3) (e.g., Gel Clear, Gel'M and Hydra'Fruit, produced by Nutrisens* Medical, France). Rheological characterization (oscillation and frequency sweep tests) of the products was performed by means of rotational rheometer (Kinexus Lab+, Malvern, UK) with applied C/P geometry 4/40 at 25°C on placebo gels and drug-loaded gels. Afterwards, dissolution tests were performed in a dissolution apparatus II (Sotax). PraNa concentrations were determined through spectrophotometric measurements at 238nm (UV-1800 Shimadzu).

Results:
Rheological results demonstrated different viscoelastic features and viscosities when the same consistency grade of the different vehicles was compared. Gels based on potato starch (Gel'M) presented drug release kinetics comparable to those of the IRT, regardless of the degree of the gel consistency. On the contrary, gels based on maltodextrin and xanthan gum blend (Gel Clear) slowed down the release of PraNa, when the highest degrees of consistency were considered (grades 2 and 3). Hydra'Fruit based gels (xanthan gum, guar gum and pectin blend) showed an intermediate behaviour with only consistency grades 1 and 2 compliant with IRT kinetics.

Conclusions:
Despite of the gelified products available on the market are usually considered interchangeable, these results demonstrated wide variation among the considered gels especially in terms of drug release kinetics.

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From Bitter to Sweet: a preliminary study towards a patient-friendly Praziquantel dosage form

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Purpose:
Praziquantel (PZQ) is an antihelmintic drug used worldwide against Schistosomiasis, despite its low solubility, bioavailability and the disgusting taste. This research represents a preliminary screening of 6 sweeteners in terms of their attitude to form amorphous dispersions with PZQ, towards the development of a patient-friendly dosage form overcoming solubility and taste drawbacks.

Methods:
The cogrounds were prepared with a vibrational mill (MM400, Retsch GmbH, Germany) using zirconium oxide jars and balls (30 min, 25 Hz) with an equimolar amount of PZQ and the sweetener, namely: Mannitol (MN), Xylitol (XY), Aspartame (AS), Sucralose (SU), Maltitol (MT) or Sorbitol (SO). The samples were characterised with Differential Scanning Calorimeter (DSC), Powder X-Ray Diffraction (PXRD), and FT-Infrared Spectroscopy (FT-IR, KBr disc). To analyse the solubility and the Intrinsic Dissolution Rate (IDR, of the best samples) the PZQ content was assessed through a reverse-phase HPLC.

Results:
The PXRD spectra of the cogrounds highlighted a dramatic reduction of drug crystallinity due to the grinding process, except for PZQ: XY system which evidenced the signal of a PZQ polymorph (Form B), recently reported [1]. The same polymorphism was noticed in the corresponding FT-IR spectrum, while the others evidenced the interactions between PZQ and the sweetener. The DSC analyses could only confirm the reduced crystallinity, due to the overlapped signals. The cogrounds had an enhanced PZQ solubility of at least 2 folds, which could be attributed not only to the hydrotropism of the sweetener, but also to a change in the solid state, as evidenced in the IDR of the best samples which was about 2.6 times the one of raw PZQ.

Conclusions:
The grinding of PZQ and the selected sweeteners led to several very interesting products, with prevalent amorphous character, enhanced solubility and IDR, being therefore feasible for future taste evaluations and the development of advantageous dosage forms.

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Escin-based nanovesicles to improve berberine topical delivery

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Purpose:
The study was focused on the development of liposomes based on phosphatidylcholine, cholesterol and escin (ESN) [1], also loaded with berberine chloride (BRB HCl), in order to obtain an anti-inflammatory formulation for dermal administrations [2].

Methods:
Different liposomes were prepared according to the lipid film hydration method, changing lipid mixture. The obtained liposomes were characterized in terms of physical parameters by Light Scattering techniques (DLS, ELS) and Transmission Electron Microscopy (TEM). Moreover the dialysis bag method, followed by HPLC-DAD analysis, was used to define the Encapsulation Efficiency (EE%) and to investigate the *in vitro* release of BRB HCl and ESN. Deformation capability of the vesicles was evaluated by extrusion. Then, liposomes were tested by a system of parallel artificial membranes (PAMPA), miming the *stratum corneum*. Finally the *ex vivo* permeation assay was made on rabbit ear skin, using vertical diffusion Franz cells.

Results:
All liposomes showed an optimal polydispersity index by DLS analysis and spherical shape was confirmed by TEM examination. EE% of ESN and BRB HCl were about 94% and 67% respectively. Furthermore, liposomes had chemical and physical stability during a month storage period. Concerning BRB HCl kinetic release, it was found an early burst effect, followed by a prolonged release. The maximum delivery of ESN was about 25% within 24h. Finally, passive transport through PAMPA, and skin permeability were higher for BRB HCl loaded in ESN-based liposome than BRB HCl loaded in the conventional liposomes formulated with cholesterol and phosphatidylcholine, or respect to the free molecule.

Conclusions:
In conclusion, ESN-based liposomes encapsulated with BRB HCl are deformable vesicles, able to cross the skin until the deepest layers of epidermis and suitable for dermatological applications.

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Biosurfactant loaded vesicles for the local treatment of *Staphylococcus aureus* skin infections

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Purpose

Staphylococcus aureus is the major causative agent of skin and soft tissue infections, whose treatment has become more difficult due to the emergence of multi-drug-resistant strains (MDR), especially in elderly population [1]. In this regard, the association of new antimicrobials and appropriate nanocarriers for their delivery is challenging to achieve a synergistic action for the therapeutic treatment. In this study a biosurfactant (Bs) isolated from *Lactobacillus gasseri* BC9 [2] was evaluated for its ability to prevent the adhesion of different MDR strains of *S. aureus* and subsequently loaded in phospholipid vesicles (Vs).

Methods

Bs was investigated for its capability to inhibit adhesion of MDR *S. aureus* strains isolated from patients with sepsis or bacteraemia. The absence of cytotoxic activity of Bs was assessed on human and murine fibroblasts. Bs loaded Vs (Bs-Vs), as well as control Vs containing Tween 80 (Tw-Vs), were prepared by the ethanol injection method. Vs were characterized in terms of size, polydispersity, zeta potential, stability over time, phosphatidylcholine content and anti-adhesion activity against *S. aureus*. Vs suspensions containing suitable excipients (gelatin as polymeric matrix, lactose as lyoprotectant and PEG/glycerol as plasticizer) were lyophilized in blister dies in order to obtain fast dissolving matrices able to restore the antimicrobial vesicles immediately after application.

Results

L. gasseri Bs was not cytotoxic and was able to prevent the adhesion of different MDR *S. aureus* strains. Bs-Vs presented optimal diameter for topical administration, low PDI, negative zeta potential and good stability over time for up 3 weeks. Notably, Bs-Vs were slightly more active than free Bs in the inhibition of *S. aureus* adhesion. Freeze-dried matrices were able to rapidly dissolve upon contact with skin, thus forming a transparent protective film containing the antimicrobial Bs-Vs.

Conclusions

The present study has established the affordable production of fast dissolving matrices containing Bs-Vs and the suitability of these formulations for the treatment of *S. aureus* infections.

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PCL/Collagen electrospun nanofibers as polyphenols drug delivery system

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Purpose:

Curcumin (CUR) and Resveratrol (RSV) are natural polyphenols with significant biological properties; their antioxidant, anti-inflammatory and chemo-protective activities make them beneficial for wound healing. Electrospun nanofibers could represent a useful drug delivery system to improve polyphenol low bio-availability and poor solubility. In this work fibrous structures, constituted by collagen/polycaprolactone (PCL) nanofibers were obtained to mimic the structure of human tissues and to improve tissue regeneration with a decrease of scar formation [1]. The combination of PCL and collagen is aimed at controlling the biodegradability of the nanofibrous membranes and the release of the poorly soluble drugs [2].

Methods:

Native soluble collagen (1% w/v Kelisema S.R.L., I) was dissolved in 90% v/v acetic acid up to a 20% w/w concentration. A 20% w/w PCL (80 000 Mw, Sigma Aldrich, I) solution was prepared in 90% v/v acetic acid. A PCL/collagen solution was prepared by adding a collagen solution in 90% v/v acetic to obtain a 1:1 w:w polymer/protein ratio. Finally, curcumin or resveratrol were added to polymer solution at two different concentrations: 0.5% w/w and 1% w/w. All solutions were electrospun using the basic set up of STKIT-40 electrospinning apparatus (Linari Engineering, I). The membranes were characterized for morphology (SEM, TESCAN Mira 3, CISRiC, Pavia, I), nanofiber size (ImageJ software), mechanical properties (TAX.T Plus Texture analyzer, Stable Micro Systems, UK) in the dry and hydrated state (after 450 μl distilled water addition for 2 min), biocompatibility (MTT-assay) and cell adhesion.

Results:

SEM analysis showed that all the membranes are formed by randomly oriented and continuous nanofibers without beads and having diameters in the nanometric range (from 200 up to 500 nm). The addition of PCL to collagen reduces solubility and improves mechanical properties of nanofibers in comparison with those based on pure collagen. An increase in elasticity with a reduction of maximum breaking strength is observed for all fibers after hydration. The presence of collagen improves nanofiber biocompatibility towards NHDF human dermal fibroblasts, promoting cell adhesion and proliferation.

Conclusions:

Collagen/PCL nanofibers have been successfully prepared by electrospinning technique. The combination of the two polymers allows to modulate solubility and mechanical properties of nanofibers. Further studies are in process to assess membrane biodegradation rate, which is functional to drug release.

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POSTER PRESENTATIONS

1. A. Abruzzo, F.P. Nicoletta, F. Dalena, F. Spedicato, T. Cerchiara, B. Luppi, F. Bigucci. *Freeze-Dried Buccal Matrices For Systemic Administration Of Propranolol*

2. G. Adorni, A. Montepietra, P. Colombo, A. Rossi. *Study Of Formulation And Critical Compression Parameters Of Ibuprofen/Sucralfate Three-Layer Tablets*

3. R. Baggio, H.L.Reimer, V.Lenhart, N. Realdon, P.Kleinebudde, E. Franceschinis. *Evaluation Of Currently Applied High-Shear Mixers Scale-Up Rules Through A Design Of Experiment Approach*

4. C. Bergamini, A. Clementino, E. Botti, F. Sonvico. *Simvastatin-Loaded Lecithin/Hyaluronate Nanocapsules: Development And Optimization Of Novel Statins Nanocarrier*

5. S. Bertoni, N. Passerini, B. Albertini. *Spray Congealed Lipid Microparticles For The Local Delivery Of B-Galactosidase To The Small Intestine*

6. A. Curci, A. Lopalco, A. Lopedota, A. Cutrignelli, V. Laquintana, M. Franco, N. Denora. *Development And Evaluation Of New Pharmaceutical Dosage Forms Of Sodium Dichloroacetate*

7. L. S. Dolci, S. Panzavolta, B. Albertini, N. Passerini. *Injectable Multicomposite Calcium Phosphate Bone Cement As A Drug Delivery System For The Treatment Of Bone Infection*

8. J. Duskey, M. Vandelli, F. Forni, E. Marcolini, B. Ruozi, G. Tosi, R. Chiesa. *PLGA Nanoparticles as Nanoparticle Carriers for Molecules Against Prion Disease*

9. A. Faccendini, G. Sandri, C. Aguzzi, S. Rossi , M.C. Bonferoni, D. Miele, B. Vigani, C. Viseras, F. Ferrari. *Hybrid Nanofibers Combined With Montmorillonite/Norfloxacin Nanocomposite For Skin Reparation*

10. V. Friuli, G. Bruni, L. Tammaro, S. Pisani, L. Maggi. *Electrospun Nanofibers For Drug Targeting To The Colon*

11. SS. Hallan, M. Sguizzato, V. Roncagli, E. Esposito, R. Cortesi. *Design And Development Of Fluorescent And Magnetic SLN For In Vitro/In Vivo Experiments*

12. L. Lequaglie, E. Vettorato, N. Realdon. *Development Of Transethosomes For The Transdermal Delivery Of Cannabinoids*

13. N. Oddone, D. Belletti, M. Vandelli, C. Restani, D. Pinetti, F. Forni, B. Ruozi, G. Tosi. *In Vitro ROS Responsive Study Of TK-Based Prodrug*

14. L. Pavoni, M. Cespi, G. Bonacucina, L. Lucarelli and F. Maggi. *Microencapsulation Of Commercial Essential Oils To Enhance Their Physico-Chemical Properties And Stability*

15. F. Pederzoli, J. Duskey, M.A. Vandelli, F. Forni, B. Ruozi, G. Tosi. *Enzyme Replacement Therapy (ERT): An Open Challenge Of Nanomedicine*

16. V. Piazzini, E. Bigagli, L. Cinci, M. D'Ambrosio, C. Luceri, G. Vanti, L. Risaliti, A.R. Bilia, M.C. Bergonzi. *Development of solid lipid nanoparticles and chitosan-coated solid lipid nanoparticles for silibinin delivery: formulation and in vitro studies*

17. S.Pisani, R.Dorati, I.Genta, E. Chiesa, T. Modena, B.Conti. *Prophylactic Treatment of Hypertrophic Scars: Electrospun chitosan/polylactide-co-polycaprolactone Nanofibre Membrane*

18. M. Saviano, M.D. Filomena, G. Falcone, R.P. Aquino, P. Russo. *Development of innovative FDM-3D-printing technologies for the production of patient-tailored medicines*

19. F. Schmid, R. Baggio, N. Realdon, A.C. Santomaso, E. Franceschinis. *Rheological characterization of wet masses: a tool to predict granules growth*

20. T. Themelis, S. Boschetti, M. Gelli, Rita Gatti. *Simple Determination of 1-Deoxynojirimycin in a New Dietary Supplement by Liquid Chromatography*

21. L. Tiozzo Fasiolo, P. Russo, F. Bortolotti, G. Colombo. *Nasal flurbiprofen powder for Alzheimer's disease*

22. B. Vigani, S. Rossi, G. Sandri, M.C. Bonferoni, G. Bruni, M. Rui, S. Collina, F. Ferrari. *Alginate-based electrospun fibers for the delivery of sigma-1 receptor agonists in the treatment of spinal cord injuries*

23. D. Zanin, E. Vettorato, N. Realdon. *CBD and desoxy-CBD comparison for transdermal delivery of cannabinoids in ethosomes*

Freeze-Dried Buccal Matrices For Systemic Administration Of Propranolol

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Purpose:
In the present study we developed buccal matrices for the administration in paediatric population of propranolol, a non-selective β1 and β2 adrenergic antagonist.

Methods:
Matrices were prepared by freeze-drying of drug loaded polymeric solutions based on gum tragacanth (GT), pectin from citrus peel (PEC), hydroxypropylmethylcellulose (HPMC), sodium hyaluronate (HA), gelatin (GEL) or chitosan (CH). Matrices were characterized for their morphology, water-uptake, mucoadhesion ability, *in vitro* drug release and permeation through porcine epithelium.

Results:
Freeze-dried matrices were characterized by a sponge-like structure. Matrices based on HPMC, CH and PEC showed the best mucoadhesion ability thanks to the polymer hydration ability and molecular weight, and to the different weak polar and electrostatic interactions useful to anchor the polymer to mucus. GEL and PEC provided a quick and complete release of drug within 60 minutes, due to their rapid dissolution. Moreover, a reduction of drug fractional amount released over the time was observed from matrices based on CH, GT, HPMC and HA due to the high viscosity of the polymeric network in the gelled state. Finally, CH showed the highest drug permeation among the polymers, thanks to its ability of interfering with the lipid organization of epithelium [1].

Conclusions:
With freeze-dried matrices, a novel buccal dosage form was developed fulfilling the current demand for child-appropriate formulations, by combining the convenience of solid dosage form and the opportunity to avoid swallowing of a large unit [2]. Moreover, polymers with the best mucoadhesion and permeation properties could be combined in order to design more efficient buccal dosage forms for propranolol administration.

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Study Of Formulation And Critical Compression Parameters Of Ibuprofen/Sucralfate Three-Layer Tablets

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Purpose:

Multi-layer tablets (MLT) are designed for the manufacturing of fixed-dose combination products that simplify the medication regimen and potentially increase the patient's compliance. MLT are heterogeneous systems in which two layers of compacted powders are separated between them by a discrete interface. The hardness and the delamination tendency of MLT depend not only on the layer composition but also on the deformation property of each layer during tableting.

Methods:

Tablets were made with different sucralfate formulations and, by using a compression simulator, it was possible to study the critical parameters involved in the compression process. Based on an experimental design, ten formulations for the two layers of sucralfate have been manufactured, which differ for the percentage of mycrocristalline cellulose, partially pregelatinized starch and lactose but not in the content of the active ingredient (ibuprofen). TLT were manufactured using a Styl'One Evolution Rotary Tablet Press Simulator (Medelpharm, France). This apparatus is a single punch tableting press, in which the displacements of the lower and upper punches are electronically controlled. The tablets were produced using oblong Euro D punches (17.50 x 8.50 mm), at different pre-compression force (0, 2 and 4 kN) and compression forces (10, 20 and 30 kN). The compaction process was performed using Advanced Analysis Software.

Results:

From the analysis of critical compression parameters, for all sucralfate formulations the plastic energy raised as the applied compression force increased. The TLT with the sucralfate layers containing pregelatinized starch, elastic material, showed higher ejection energy, compared to the formulations with microcrystalline cellulose, plastic material, and/or lactose, brittle material. In presence of pregelatinized starch, when the force exerted from the upper punch is removed in the phase of TLT ejection from the die, the friction radial forces increased since the tablet tends to expand in the die and then the ejection energy augmented. Moreover, the sucralfate layers containing microcrystalline cellulose, exhibited a greater tendency to layer separation, due to a reduced interfacial strength between sucralfate and ibuprofen layers. The addition of lactose to the sucralfate formulation was beneficial for the layer adhesion during the manufacturing of the TLT.

Conclusions:

The presence of microcrystalline cellulose, lactose and pregelatinized starch in the sucralfate layers can affect, in different manner, the critical parameters of the manufacturing of ibuprofen/sucralfate three-layer tablets.

Evaluation Of Currently Applied High-Shear Mixers Scale-Up Rules Through A Design Of Experiment Approach

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Purpose:
Scale-up of high-shear granulation is one of the most challenging task in the pharmaceutical industry. The aim of this work is to apply a DoE technique to study the influence of the most critical process parameters (impeller speed and massing time) on target granule properties (size, strength and shape) in order to evaluate the effectiveness of the commonly employed scale-up rules[1].

Methods:
Three mixtures containing Microcrystalline Cellulose and Mannitol (25%) or Sucrose (25% and 50%) were used on a Diosna high-shear mixer with two different bowl sizes (2l and 10l). In the 2l bowl the reference granules were produced while in the 10l bowl, the effects of impeller speed and massing time were studied applying a rotated Doehelert design. The granules obtained for both the scales were characterized in terms of particle size distribution, roundness and strength[2]. Desirability function was finally applied to evaluate which combination of experimental parameters leaded to a successful scale-up of each formulation.

Results:
The PSD and the strength of granules obtained in the small scale mixer were not significantly affected by the different massing time applied for the formulations containing 25% of sucrose or mannitol. Instead for the formulation containing the 50% of sucrose the mean diameter strongly depends on the massing time. Moreover on the 10l scale, the desirability function highlighted that all the formulations studied can be successfully scaled-up using an impeller speed value which differs from the currently applied scale-up rules. In addition it is possible to observe that massing time necessary to achieve a successful scale-up, depends on the binder viscosity and on the amount of soluble material present in the mixture.

Conclusions:
We can conclude that the scale-up rules currently applied are not sufficient to obtain successful results with different formulations. In order to understand if exists a relationship between the formulation's characteristics and the scale-up approach to apply, other mixtures of excipients need to be investigated.

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Simvastatin-Loaded Lecithin/Hyaluronate Nanocapsules: Development And Optimization Of Novel Statins Nanocarrier

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Purpose:
Recently, hybrid nanoparticles composed of polysaccharides and phospholipids have been studied for the delivery of lipophilic drugs. The design of efficient and stable nanocarrier is highly dependent on the selection of its components and their proportions. The aim of this work was to develop and characterize simvastatin-loaded lecithin/hyaluronate nanoparticles, investigating the influence of excipients on manufacturing and physicochemical properties.

Methods:
Nanoparticles were produced through a self-assembling process of an anionic phospholipid(lecithin) with a negatively charged polysaccharide, hyaluronic acid (HA), thanks to a cationicamphiphilic molecule (DODMA). Nanoparticles were obtained by injecting an ethanolic solution of lecithin (2.5%) containing simvastatin (1mg/ml), DODMA (0.5%) and oils (medium chain triglyceride, glyceryl monolinoleate and capric acid) into the solution containing HA, under magnetic stirring. Different HA molecular weights (29.5, 100-400, 750-1000 kDa) and concentrations (1%, 1.5%, 2%) were evaluated for their impact on size and zeta potential. Different percentages of capric acid (from 0% to 30%) were added to investigate the impact of increasing core lipophilicity on encapsulation efficiency (EE%). Nanoparticles were characterized by size and distribution, surface charge, EE% and physicochemical stability over time.

Results:
Nanoparticles produced with 29.5 kDaMW HA, at 1%, showed smaller particle size (242nm) and better stability (PDI 0.214) compared to nanoparticles produced with higher molecular weights, which showed increasing size and reducing EE%, evidencing lack of stability. Moreover, the addition of 30% of decanoic acid to nanoparticles oil core showed good diameter (240nm, PDI 0.191), high zeta potential (-40 mV), and particles were also found to be stable for a week (244nm, PDI 0.173) and to have high EE% (99.86%) which was maintained over time (99.90%).

Conclusions:
The use of extra low molecular weight HA at small concentrations, along with the introduction of capricacid at 30%, has allowed to optimize stability end encapsulation efficiency of the simvastatin-loaded hyaluronate nanoparticles.

Spray Congealed Lipid Microparticles For The Local Delivery Of B-Galactosidase To The Small Intestine

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Purpose:
Oral local delivery of therapeutic biologics is generally limited due to the multiple obstacles of the gastrointestinal (GI) tract, mainly represented by acidic stomach pH and digestive enzymes. The purpose of this study was the development of solid lipid microparticles (SLMs) produced by spray congealing [1] loaded with β-Galactosidase (lactase), an enzyme used for the treatment of lactose intolerance [2], to achieve a local drug delivery to the small intestine.

Methods:
Initially, five excipients were used to prepare unloaded SLMs, which were tested regarding lipase-induced degradation by means of a simplified lipolysis model. Then, lactase was characterized in terms of activity at different pH, kinetic analysis and hydrolysis to digestive enzymes. Two formulations of lactase-loaded SLMs were prepared and characterized by size, morphology, drug loading and encapsulation efficacy. The effect of gastric conditions on the lactase activity was determined by incubating the particles in fasted simulated gastric fluid (FaSSGF) and by measuring the residual activity. Finally, in vitro release studies were carried out in fasted and fed simulated intestinal fluids.

Results:
Among the excipients tested, glyceryl trimyristate was the lipid with highest response, both in terms of speed and total extent of degradation. Spray congealing enabled the preparation of spherical, free-flowing SLMs with extremely good encapsulation efficiency values, always higher than 95%. Incubation of SLMs in FaSSGF suggested that the protection ability of glyceryl trimyristate-based SLMs was correlated to the particle size. The best formulation was able to maintain 65% residual activity of the encapsulated enzyme. Lactase was promptly released in simulated intestinal environment, and an in vitro positive food effect was observed.

Conclusions:
A feasible, non-toxic and inexpensive lipid formulation containing β-galactosidase was successfully produced by spray congealing. The present study illustrated the potential of spray congealed lipid-based formulations to obtain a local delivery a biologic drug by selecting appropriate lipid excipients and particle size.

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Development And Evaluation Of New Pharmaceutical Dosage Forms Of Sodium Dichloroacetate

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Purpose:
The aim of this study was the development of oral formulations of sodium dichloroacetate (DCA) for the treatment of congenital lactic acidosis.

Methods:
Solid-state characterization of the drug was performed using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). The stability of sodium DCA in aqueous solutions was conducted in a pH range 1-9 at 25, 40, 65 and 80°C and monitored by HPLC.[1] Three liquid formulations of sodium DCA (9.5%) were prepared using i) 0.04% sucralose; ii) 0.04% sucralose and 0.04% orange flavoring; iii) 0.02% sucralose, 0.25% hydroxyethyl cellulose, 0.09% citric acid, 0.09% sodium citrate dihydrate and 0.18% potassium sorbate and, their stability at 25 and 4°C was evaluated by HPLC over 3 months. Orally disintegrating tablets (ODTs) were prepared by molding technique mixing sodium DCA with 1% sucralose and moistening the resulting mixture with a hydro-alcoholic solution of PVP 5% (w/w). Tablets were evaluated for different properties (hardness, friability, disintegration time and weight variation) as reported in the Ph.Eur.

Results:
DSC of sodium DCA showed an exothermic peak at ~200°C corresponding to its decomposition. TGA curves of the compound exhibited a weight loss of 9.52% at temperature lower than 100 °C and a second degradation process at ~207 °C. Sodium DCA solutions stored at 25 and 40°C resulted stable over 7 months. The degradation of the compound occurred at 65 and 80°C and could be expressed by a first order rate equation. From the calculated rate constants (k_{obs}) it was possible to generate a pH-rate profile over the pH range 1-9. k_{obs} and $t_{1/2}$ of the compound extrapolated from Arrhenius plot confirmed that DCA was stable at 25 and 40°C. Liquid formulations were prepared using sodium DCA together with sweeteners and flavorings to mask its bitter-salty taste. All the 3 formulations resulted stable at 25 and 4°C. ODTs of sodium DCA were also developed obtaining orodispersible, medium-sized tablets (<10mm) with suitable hardness and friability which disintegrated in less than 1 min at 37°C.

Conclusions:
Solid state characterization of sodium DCA suggested that the compound is hygroscopic. Sodium DCA solutions were stable at 25 and 40°C. No degradation was observed for the liquid formulations. Moreover, a solid formulation (ODTs) was proposed and developed as a more practical alternative to the liquid preparations.

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Injectable Multicomposite Calcium Phosphate Bone Cement As A Drug Delivery System For The Treatment Of Bone Infection

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Purpose:
The post-surgical osteomyelitis infection represents one of the major problems in orthopedic surgery and may results in the removal of the implanted devices, with many limitations for the patients [1]. In this work we investigated a new injectable Calcium phosphate cement (CPCs) as a carrier system for the local delivery of gentamicin sulphate (GS) to bone tissue. This platform should provide an effective bactericidal local antimicrobial treatment, thus limiting the risk of increasing the bacterial drug resistance. In particular, the platform consisted in a biomimetic radiopaque injectable bone cement enriched with Solid Lipid Microparticles (MPs) for the sustained release of GS.

Methods:
Microparticles were produced by spray congealing technology that consisted in the addition of the 20% w/w of GS into the molten carrier to obtain an homogeneous suspension which was then loaded into the feeding chamber of the WPN [2]. CPCs [3] were prepared in the presence of $BaSO_4$ (10% w/w) in order to obtain a radiopaque material.

Results:
The incorporation of GS did not alter the spherical shape of the microparticles, and the encapsulation efficiency was higher than 95%. These results demonstrated that the spray congealing process was a suitable technology for the production of GS-loaded MPs. Successively the influence on the mechanical properties of CPCs as a function of the presence of BaSO4, GS (2,4 and 8% w/w) and MPs-GS (10% w/w) were investigated. The results showed that the presence of $BaSO_4$ positively affected the CPCs mechanical properties. On the contrary the setting times increased as a function of GS content in the powders, evidencing that GS could be added until 4% w/w without a significant delay in setting time. On the basis of these results, a multicomposite platform consisting of a CPCs loaded with both GS (at 2% w/w) and MPs-GS was studied. The results showed values of setting times and mechanical properties in the range of interest for the application of this platform. Finally the injectability was also considered.

Conclusions:
The results of this study demonstrated that the use of gentamicin and MPs as carriers to enrich bone cement formulation, was a successful strategy to develop an injectable cement for the treatment of bone infection. The approach followed in this study allowed to obtain a new injectable CPCs-paste without provoking significant worsening of the mechanical properties.

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PLGA Nanoparticles as Nanoparticle Carriers for Molecules Against Prion Disease

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Purpose:

Targeted g7-PLGA nanoparticles are able to encapsulate, protect and target molecules across the BBB[4]. Prion diseases are mainly active in the brain and thus the lack of brain accumulation is a major pitfall for most current prion disease treatments. Therefore, optimizing the loading and stability of anti-prion molecules into G7-PLGA nanoparticles could lead to an efficient brain delivery vehicle against prion diseases.

Methods:

PLGA nanoparticles were loaded with an anti-prion model molecule by a double emulsion technique (w/o/w). The stability of the molecule at various pH, and its loading capacity/efficiency were analysed by using HPLC (UV, Fl, and Ion trap mass analysis) to optimize the NPs formulation in terms of composition. Release studies were performed at both pH 4.0 (citric acid) and ph 7.4 (PBS) to mimic the blood and lysosome microenvironments. Cell uptake and studies were measured in cell lines expressing the prion protein from 6 to 24 hours.

Results:

The molecule was loaded into PLGA forming NPs of ~200 nm with a charge approaching neutral with increasing content (from -16mV to - 6mV). Increasing the initial amount of the molecule in the NP formation leads to an increased payload, but drastically decreased encapsulation efficiency. Furthermore, the molecule remained stable across all pH tested and was only released from PLGA NPs in acidic environments (pH4.0). Finally, nanoparticles were tagged with the fluorophore Cy5 and were shown to enter the cells starting at 4 hours and increasing over 24 hours, arriving in the lysosome.

Conclusions:

PLGA NPs were produced that could encapsulate and protect anti prion model molecules. These particles have previously been shown to cross the BBB into the lysosome where it can release its bound pharmaco. There are numerous anti prion molecules currently on the market that lack the ability to work in vivo. Further testing to ensure their activity after formulation is a critical first step. But even more interesting will be the huge increase in brain accumulation gained by using targeted PLGA nanoparticles leading to a much higher likelihood of disease treatment in mouse prion models.

Hybrid Nanofibers Combined With Montmorillonite/Norfloxacin Nanocomposite For Skin Reparation

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Purpose:
Aim of the present work is the development of a therapeutic platform to treat skin infections and injuries. Glycosaminoglycans as potential polymers mimicing the extracellular matrix, were used to form nanofibers *via* electrospinning. Nanocomposite particles obtained from the interation between montmorillonite and norfloxacin were incorporated into the polymeric nanofibers to control drug release at the site of injury

Methods:
Pullulan (PL) 20% w/w and Hyaluronic acid (HA) 1% w/w or Chondroitin sulfate sodium (CS) 1% w/w were dissolved in distilled water. Three mixtures: PL, PL/HA and PL/CS were obtained and were respectively blended 1:1 weight ratio with Chitosan high MW (CH) 5% w/w dissolved in acetic acid (90% v/v). The nanocomposite based on montmorillonite (MMT) and norfloxacin (NF) has been previously developed [1] and was added to the three mixtures to obtain a final NF concentration equal to 0.16% w/w. All the three formulations were subjected to electrospinning, were characterised by SEM analysis, their mechanical properties were performed and in *vivo* evaluation on human fibroblasts were carried on by MTT test, SEM and CLSM analysis

Results:
SEM analysis showed that all the formulations, presented nanofibers ranged between 400-800nm with knots containing nanocomposite particles. All the formulations showed a decreased stiffness after hydration. Fibroblasts adhesion and proliferation showed that cells grew forming a subconfluent substrates onto the nanofibrous formulations.

Conclusions:
Electrospun nanofibrous scaffolds based on polysaccharides (PL/CH) combined with glycosaminoglycans (CS and HA) and loaded with MTT/NF nanocomposite demonstrated to support fibroblasts adhesion and proliferation especially when CS was used. Such scaffold represents a promising tool to favour skin reparation.

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Electrospun nanofibers for drug targeting to the colon

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Purpose:
The objective of this study was to fabricate and characterize electrospun fibers loaded with budesonide, a synthetic steroid of the glucocorticoid family, with the aim of controlling its release in the gastrointestinal tract. Eudragit® S100 was chosen as polymeric carrier for the drug targeting to the distal portion of the gastro intestinal tract. This polymer dissolves at pH > 7, allowing the release of the drug only in the terminal ileum and colon [1].

Methods:
Budesonide-loaded fibers and fibers of pure Eudragit® S 100 were prepared using the electrospinning method (Apparatus EC-ANL, IME Technologies). The physical mixtures of polymer and drug were prepared by mixing the properly weighted amounts of the components and used for comparison. All the systems were characterized by means of Scanning Electron Microscopy (Carl Zeiss, Germany), X-Ray Powder Diffraction (Karlsruhe, Germany) and Differential Scanning Calorimetry (TA Instruments, New Castle). The in vitro release profiles were studied in two different media: deionized water and pH 7.2 buffer. Furthermore, the samples were analyzed by a pH-change method: at pH 1.0 for 2 h, to simulate the transit through the stomach, and then at pH 7.2, to simulate the distal gastrointestinal environment All the tests were performed using the USP Apparatus II paddle at 100 rpm (Erweka DT-D6, Dusseldorf, Germany). The concentrations of the dissolved drug are determined by UV absorbance, on filtered portion of the dissolution media. The data are processed through a PC software (Lambda 25 UV Winlab V6 software) connected to the spectrophotometer (Perkin-Elmer, Monza, Italy) to obtain the dissolution profiles.

Results:
The results show that the loaded fibers are able to prevent drug release until reaching, pH 7.2 where the full dose of the drug is promptly dissolved in few minutes enabling a local action of the active at the proper concentration.

Conclusions:
The budesonide-Eudragit® S100 electrospun systems could be used for the site specific delivery of the drug to the colon. Electrospinning is a new versatile and effective technique for the drug loading on this polymeric carriers.

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Design And Development Of Fluorescent And Magnetic SLN For In Vitro/In Vivo Experiments

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Purpose:
This work is a preliminary study on the development and characterization of fluorescent and magnetic core containing lipid-based nanoparticles for therapeutic and diagnostic purposes.

Methods:
Fluorophores have been entrapped into lipid matrix by homogenization and ultrasonication method [1]. The formulations were analysed by photon correlation spectroscopy (PCS), by spectrophotometric analysis and their biodistribution was evaluated by fluorescent luminescent imaging after administration in mice. Maghemite magnetic nanoparticles (MN) were obtained by precipitation method and loaded into the lipid with emulsion followed by dilution method [2-3]. The formulations have been characterised by PCS and X-ray diffraction (XRD) technique. The magnetic properties were studied in the 6K-300K temperature (T) range with a superconducting quantum interference device (SQUID) magnetometer. Magnetization loops and magnetization vs. T curves at different applied field, in the zero field cooling (ZFC) and field cooling (FC) modes were measured.

Results:
Three types of fluorescent nanoparticles have been produced, namely solid lipid containing cardiogreen (SLN_{CA}), rhodamine (SLN_{RO}) and their combination ($SLN_{CA/RO}$). They resulted stable in time with mean diameter ranging 250 to 300nm and with no aggregation and no phase separation. The absorption spectra of SLN_{CA}, SLN_{RO} and $SLN_{CA/RO}$, recorded in the visible region with double beam spectrophotometer, were superimposable with those of fluorophores as in solution. The biodistribution of $SLN_{CA/RO}$ administered in vivo to athymic mice, was evidenced by selecting the wavelength for each fluorophore. MN containing SLN showed different mean diameters along with the variation in the ratio of lipid to MN. The lower the lipid concentration the higher the mean diameter. The obtained XRD spectra revealed that the MN nanocrystalline structure did not change upon their inclusion in lipid nanoparticles. At T= 6K, the saturation magnetization of the as-prepared MN is about 40 % of the value of bulk maghemite. ZFC-FC magnetization measurements revealed the presence of interparticle magnetic interactions markedly affecting the magnetic behaviour of the MN.

Conclusions:
The study confirms that the incorporation of fluorescent and magnetic core into lipid nanoparticles is possible without altering SLN inherent properties suggesting their possible use as the efficient therapeutic and diagnostic tools.

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Development Of Transethosomes For The Transdermal Delivery Of Cannabinoids

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Purpose

Transethosomes are soft nanovesicular systems made of ethanol, lecithin, water and a penetration enhancer, suitable for the transdermal drug delivery. In this study the formulation contains Tween 80 which is reported to reduce vesicular size and improve properties, such as the stability, the zeta potential and the flexibility, compared to the classical ethosomes[1]. This favors the penetration of the drug in the deeper layers of the skin. The aim of this study is to investigate the influence of the Tween 80 percentage in the formulation of the transethosomes, for the development of innovative formulations of cannabinoids.

Methods

As described by Touitou[2], the transethosomes were prepared according to the cold method. The organic phase was obtained by dissolving the phospholipids in addition to Tween 80 in ethanol at room temperature. The aqueous phase was added to the organic phase in a fine stream using a syringe and a needle. The mixture was stirred at a speed of 700 rpm using an overhead stirrer for 10 minutes and then treated in an ultrasound bath for 5 minutes to obtain the required ethosomal suspension. Tween 80 was used at 10, 25 and 50% of the total percentage of phospholipid as reported in literature[1]. Lipoid S100 was used at 5%, 4% and 3%. For each formulation, ethanol ranged from used 20 to 50% ethanol. The resulting formulations were analyzed by Dynamic Light Scattering (DLS).

Results

Samples with high concentrations of lecithin (5%), ethanol (50%) and high Tween 80 percentage were micellar systems or very big aggregates. Decreasing the Tween, poly-dispersion phenomena occur, and aggregates are formed with rather high dimensions, above 700nm. They persisted after sterilizing filtration, probably due to surfactant clusters that tend to reform even after filtration. By lowering the ethanol concentration, transethosomes are formed with acceptable dimensions that range from 70 nm to 140 nm. Samples with 4% S100 and 2% Tween 80 were not poly-dispersed and have acceptable dimensions, from 60 nm to 151 nm. 3% S100 samples showed lower PdI, but still with Tween 80 aggregates. Generally, 20% of ethanol in every formulation allowed the formation of the most suitable transethosomal system.

Conclusions

Tween 80 affects significantly the system in terms of aggregates. The most suitable transethosomes are formed at 20% of ethanol, and Tween 80 must be used at higher concentrations when the phospholipid percentage is 5%. The possibility to use low ethanol percentage can be an advantage for the patient safety and compliance.

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In Vitro ROS Responsive Study Of TK-Based Prodrug

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Purpose:
As many pathological conditions, including neurodegenerative diseases, are associated with high levels of reactive oxygen species (ROS), a possible goal is to plan polymer prodrugs which respond specifically to these bio-signals with the activated delivery of drugs in such target sites[1]. Linkers containing Thioketal (TK), are biocompatible and can be excised by ROS[2]. With the aim to confirm the ability of TK based polymers to release drugs under ROS conditions, we study the ROS activated release of Cyanine5 (Cy5) from methoxypolyethyleneglycol-TK-Cy5 (mPEG-TK-Cy5) as a probe of concept.

Methods:
ROS responsive polymer, mPEG-TK-COOH, was synthesized starting from mPEG-NH2, 5.000 Da and TK diacid linker. The responsive mPEG-TK-Cy5 prodrug was prepared by EDC/NHS crosslinking of mPEG-TK-COOH with Cy5-NH2. All the products were purified and characterized by NMR and MALDI-TOF. ROS responsive Cy5 release study, was made by incubating the prodrug with a mixture containing 400 mM H2O2 + CuCl2 for 48 h, 37°C. At determined fixed times, samples for RP-HPLC and fluorometric analysis were taken. This study was also made with mPEG-Cy5 (ROS unresponsive prodrug) as control.

Results:
The ROS responsive mPEG-TK-COOH polymer and mPEG-TK-Cy5 prodrug were obtained with derivatization yields of 83% and 31.5%, respectively. Analysis of ROS incubated mPEG-TK-Cy5 by RP-HPLC, showed a time dependent reduction of prodrug peak, with the concomitant increase of the peak corresponding to Cy5, detected by UV and fluorescence. In the case of mPEG-Cy5, a second peak was not observed. Conversely, the fluorescence intensity of mPEG-Cy5 at 48 h, was reduced 2.17 times respect to initial, while mPEG-TK-Cy5 fluorescence intensity was not changed.

Conclusions:
As expected, mPEG-TK-Cy5 exhibited a ROS responsive behavior by releasing Cy5 along time. Although Cy5 was not released from mPEG-Cy5, Cy5 fluorescence has been quenched by ROS. We conclude that TK may protect Cy5 to be ROS quenched by its ROS buffer capacity. Hence, the design of TK containing prodrugs is very encouraging, due to their ability to specifically deliver drugs in ROS milieu while maintaining drug stability.

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Microencapsulation Of Commercial Essential Oils To Enhance Their Physico-Chemical Properties And Stability

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Purpose:

Essential oils (EOs) are hydrophobic and volatile liquids produced by plants as secondary metabolites. Thanks to their physico-chemical and biological properties, EOs are widely used in several industrial applications, especially pharmaceuticals, cosmetics, foodstuffs and biopesticides [1]. Although many EOs possess interesting perspectives for health, there are several drawbacks that have limited their use; e.g. low water solubility, stability and high volatility [2]. These drawbacks could be overcome by selecting an appropriate formulation strategy to vehiculate EOs. Currently, the nanoencapsulation technology appears to be the most suitable approach.

Methods:

Crithmum maritimum L. (sea fennel) flowering aerial parts, *Trachyspermum ammi* (ajwain) and *Pimpinella anisum* (anise) dry fruits were subjected to hydrodistillation in a Clevenger-type apparatus for 3 h. Once obtained, EOs were characterized by gas chromatography-mass spectrometry (GC-MS) analysis. All the microemulsions were prepared by adding drop-by-drop deionised water to the oil phase under stirring. The oil phase consisted of polysorbate 80, alcohols (ethanol and glycerine) and EOs or EOs-ethyloleate mixture. Microemulsions were characterized through polarizing optical microscopy and dynamic light scattering (DLS).

Results:

After having tested the oil phases at different concentrations, we determined the maximum amount of EOs that could be incorporated in order to obtain stable microemulsions: i.e. 1.5% for *C. maritimum* and *T. ammi*, and 1.15% for *P. anisum* in presence of 0.35% of ethyloleate used as diluted agent to avoid the precipitation and/or crystallization of EO. Moreover, keeping constant the concentration of the oil phase at 1.5%, we prepared binary mixtures at 1:1 and 2:1. The effect of storage time on the droplets size distribution and microemulsion stability have been tested for 5 months.

Conclusions:

The satisfactory results obtained through the nanoencapsulation of EOs with commercial importance in safe and effective microemulsions could represent the starting point for interesting applications in biological and pharmaceutical fields.

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Enzyme Replacement Therapy (ERT): An Open Challenge Of Nanomedicine

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Purpose: Polymeric nanoparticles (NPs) were shown to be promising carriers for protein delivery, due to their potential in both protecting drugs from immunological reaction and modulating drug release at the target site limiting side effects [1]. However, several technological aspects should be considered critical to obtain high loading of active enzyme; the correlation between formulative variables and biologic activity of enzyme with full preservation of the native protein structure during all steps of nanoparticles formulations remains a major challenge to obtain a realistic tool in ERT [2]. In this contest, this research focused on technological variables in NP formulation in order to stabilize enzyme active, thus letting to increase efficacy.

Methods: Poly-lactic-co-glycolic acid (PLGA) NPs were obtained by water-in oil-in water (W1/O/W2) double emulsion preparation protocol. β-glucosidase was used as model enzyme. Taking into account the delicate nature of cargo (sensibility to organic environment, temperature, change of pH etc), but aiming also to preserve the required properties of targeted drug delivery systems that should be iv administered (mean diameter <250 nm, PDI < 0.2, blood stability etc), several pre-formulative studies were carried out i) to drastically reduce mechanical and energetic stressful factors caused by preparative procedures (e.g. sonication), ii) to optimize the volume of liquid phases iii) to choose type of surfactant and concentration. In order to better preserve enzyme integrity, the presence/absence of stabilizing excipients (BSA and tween) were also experimented in enzyme loaded NPs. Spectroscopical (PCS) and microscopical (AFM, STEM) techniques were used for chemico-physical characterization of samples. For each preparation, enzyme loading was evaluated after extraction and analytical quantification by HPLC, and enzyme stability was monitored by enzymatic activity assay.

Results: Preformulative studies suggested that w/o/w emulsion is a very critical step; in particular, these studies defined the limits in terms of power and time of sonication (hypothetical dangerous steps to lead enzyme destabilization), the W1/O/W2 volume ratio and the % of surfactant in W2 in order to keep monomodal and monodisperse NPs (S:60 Watt/ 30''; W1/O/W2 1/2/4; PVA 1%).
On these bases, the different formulation processes designed to allow enzyme encapsulation were planned also taking into account the use of several stabilized agents to preserve the enzyme activity. In particular, the addition of BSA (in the inner water phase) exhibited both an increased rate of encapsulation as well as a stabilizing effect. Moreover, results suggested that other steps required attention; in particular, the optimization of purification process will be needed, also considering that centrifugation does not completely preserved the activity of enzyme loaded into NPs.

Conclusions: In vitro experiments are ongoing to evaluate the release kinetic of enzyme and the stability of these formulations over time. High loading capacity obtained by using enzyme model drugs with preserved enzymatic activity was an important starting point to formulate NPs with optimized conditions for therapeutic enzyme loading.

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Development Of Solid Lipid Nanoparticles And Chitosan-Coated Solid Lipid Nanoparticles For Silibinin Delivery: Formulation And *In Vitro* Studies

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Purpose:
In this study solid lipid nanoparticles (SLNs) and chitosan-coated solid lipid nanoparticles (CS-SLNs) were proposed as nanocarriers to improve the solubility and the intestinal absorption of silibinin (Sb). Sb is the major biologically active component in silymarin, the extract of *Silybum marianum* L. Gaertn. [1]. However, Sb is a low water soluble and low permeable compound, belonging to biopharmaceutical class IV. Thus, to overcome these limitations, Sb was encapsulated into SLNs and CS-SLNs.

Methods:
SLNs and CS-SLNs were prepared by means of emulsion/evaporation/solidifying method. Chemical-physical properties were defined by Light scattering techniques, TEM and HPLC-DAD. In addition, stability studies in simulated gastrointestinal conditions and in a month storage time at 4°C were carried out. The developed formulations were subjected to permeation studies using artificial membranes and Caco-2 cells. Furthermore cellular uptake experiments were performed. In the end, mucoadhesion properties of SLNs and CS-SLNs, were evaluated.

Results:
The developed nanoparticles exhibited particle sizes in the range of 150-200 nm and a ζ potential between -48 and +40 mV. Encapsulation efficiency was greater than 90%. Moreover nanoparticles showed excellent stability in simulated gastrointestinal fluids and in the storage conditions. Permeation studies revealed that the formulations were successful in enhancing the permeation of entrapped compound. Our results suggested a predominant active endocytic process in the absorption of both formulations. Finally, chitosan coating significantly improved mucoadhesion properties of SLNs.

Conclusions:
SLNs and CS-SLNs could be use as alternative oral formulation to enhance bioavailability and, finally, therapeutic effects of Sb.

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Prophylactic Treatment of Hypertrophic Scars: Electrospun chitosan/polylactide-co-polycaprolactone Nanofibre Membrane

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Purpose: Hypertrophic scar (HTs) is a thickened, wide, often raised scar that often develops when skin is injured [1]. HTs is the result of an abnormal response to a trauma or injury and it could cause abnormal sensation, severe functional impairment, psychological morbidity, and costly long-term health-care. On the molecular level, HTs result from imbalanced and excess collagen deposition through irregularities in all wound-healing phases (inflammation, proliferation and remodeling). Current HTs treatments are minimally effective and therefore prophylactics treatments are needed [2 - 4].

The present research project is addressed to develop a platform for the sustained delivery of antifibrotic agents preventing HTs. The success of the present platform would offer a valuable resource for validating new molecules for improving wound healing in animal models.

Methods: Electrospun blend nanofiber membranes were prepared using an automated electrospinning vertical set-up system ready for cGMPs manufacturing (NANON-01A, Mecc Co., LTD). Chitosan powder (CL 113, 7.5% w/v) was suspended in PLA-PCL 20% w/v solution obtained dissolving PLA-PCL polymer in MC:DMF mixture (70:30), following the suspension was electrospun under controlled - environment conditions (28 ± 2°C and 30 ± 2 % RH). The electrospun blend nanofiber membranes were cross-linked into TPP aqueous solution (10 %, w/w) for 5 minutes, lyophilized at – 50°C, 0.01 mbar for 12 hours and stored in sealed aluminum pouch at 4 ± 2°C and 35 ± 2 % RH until the characterization has been assessed.

Nanofibre blend membranes were characterized by SEM and FTIR analysis; contact angle, permeability assay and *in vitro* degradation test were carried out in simulated physiological conditions. Preliminary biological study was performed in order to evaluate attachment and proliferation on surface of electrospun blend nanofiber membrane.

Results: Un-crosslinked PLA-PCL/chitosan membranes show regular fibres with mean diameter of 700 nm**;** while for crosslinked membranes film interconnecting fibres are evident. FTIR spectra of PLA-PCL/chitosan membranes have similar trends as their component polymers. The blending with chitosan led to a slight reduction of contact angle of PLA-PCL/chitosan nanofibre blend membranes; nevertheless, water uptake data collected during *in vitro* degradation study are consistent with the improved hydrophilic features of membranes when chitosan is blended with PLA-PCL copolymer. Permeability data showed that the membranes were completely permeable to 180 Da pullulan standard that freely flows throw the membrane reaching 100 % permeation in 5 hours. Degradation study proved that cross-linked nanofibre blend membranes were stable for 7 days; the percentage of chitosan released from nanofibers was < 5% and no important Mw and Mn reductions were detected during the incubation. PLA-PCL/chitosan nanofibers blend membranes promote good cell growth and cells were homogeneously growing and spreading on surface of electrospun blend nanofiber membrane.

Conclusions: The results obtained clearly showed the potential of PLA-PCL/chitosan nanofibre blend membranes as suitable platform for local delivery of antifibrotic agents into wound bed. Future works are dealing with the incorporation of the antifibrotic agent and evaluation of its release profile.

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Development of innovative FDM-3D-printing technologies for the production of patient-tailored medicines

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Purpose:

From a medical and therapeutic perspective, the fused deposition modeling (FDM) by 3D-printing is a pragmatic tool for producing personalized devices and drug dosage forms [1-2]. One of the main problem to deal with is the lack of availability of biocompatible and biodegradable polymers in form of filaments suitable for 3D-printing. Thus, aim of this study is to investigate the potential of hot melt extrusion for producing drug-loaded filaments to be used for the printing of customized drug delivery systems.

Methods:

Several batches of PVA with different size distributions obtained by milling (i.e. 4-5 mm, 1-2mm, 0.6-1mm, 0.25-0.6mm, <0.25mm) and Ciprofloxacin were prepared varying polymer/drug ratio and then extruded as filaments with the single screw Noztek Touch Extruder. Digital modeling with CAD software Rhinoceros 5 and CAM software Ultimaker Cura 3.1.0 was used for the development of models and scaffolds for FDM-3D printing. Moreover, printer's parameters and operative specifics were refined for an optimal print of the lab-made drug-loaded filaments into the desired dosage forms. Scanning electron microscopy allowed observing the surface interaction between drug and PVA as well as the architecture of the drug-loaded filaments and of the printed products. Finally, the drug content and thermal behavior of mixtures, filaments and *printlets* were monitored.

Results:

The PVA particle size greatly affected the ability of the polymer to load the drug and to form with it homogeneous mixture together with the extrusion process. Coarse or moderately fine PVA powders showed better processability and reduced the drug loss during both the drug/polymer mixture and the extrusion processes. Finally, drug-loaded filaments with different drug concentrations were successfully printed.

Conclusions:

These results can help to fill the gap given by the lack of biodegradable and printable drug filaments moving an important step towards a rapid manufacturing process for personalized galenic formulations.

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Rheological characterization of wet masses: a tool to predict granules growth.

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Purpose:
High shear wet granulation is one of the most commonly used methods for the particle size enlargement in pharmaceutical industry. The growth of granules could be described by growth regime map [1] and material exchange experiments [2]. The purpose of this study was to confirm the ability of a mixer torque rheometer (MTR3, Caleva, UK) to predict the different growth mechanisms of granules produced in a High-shear mixer (HSM) by measuring the maximum torque peak developed by the wet masses.

Methods:
Two formulations were selected for this study, one with pure Microcrystalline Cellulose (MCC) and the other containing 50% (w/w) of sucrose in mixture with MCC. The MTR3 was employed to identify the water amount necessary for the granulation process. Moreover, the MTR3 was employed to study the influence of different parameters (L/S, shaft speed and binder flow rate) on the maximum torque developed by the wet mass. Granulation experiments, planned by a Design of Experiments (DoE) technique, were then performed in a High-shear mixer (Rotolab, IMA, Zanchetta) in order to verify also the ability of MTR3 to predict the critical parameters of the granulation process. Moreover, material exchange experiments, monitoring the dispersion of a colored tracer among the wet granules [2], were carried out to verify if the growth mechanisms predicted by the MTR3 were correct.

Results:
First of all, pure MCC showed for all the parameters studied values of maximum torque that can be related with a steady growth mechanism, which is confirmed by granulation and material exchange experiments. On the other hand, the formulation containing 50% of sucrose showed values of torque peak attributable to different growth mechanisms, depending on the amount of water used for the granulation experiments. The material exchange experiments showed a relationship between the maximum torque measured and the different growth mechanisms, confirming the behavior predicted by the MTR3.

Conclusions:
The rheological characterization of wet masses could represent a tool to predict the growth of granules during the granulation process. This approach could be useful to predict the behavior of a formulation, allowing a better control of the process.

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Simple Determination of 1-Deoxynojirimycin in a New Dietary Supplement by Liquid Chromatography

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Purpose:
The aim of the present work is to develop and validate a HPLC method for the determination of 1-deoxynojirimycin (DNJ) in raw material (Morus Alba extract) and in samples of finished product corresponding to a new dietary supplement of complex matrix. The dietary supplement contains DNJ in association with other ingredients, between them red yeast rise and is used to integrate the diet of patients with high risk of manifesting metabolic syndrome.

Methods:
In the proposed method, 9-fluorenylmethyl-chloroformate (FMOC-Cl) was used as derivatization reagent for the analysis of DNJ and UV-DAD as the detector. The derivatization reaction and chromatographic conditions were optimized appropriately, based on the necessities and problematics that derived from the complex matrix of the product.

Results:
The method was fully validated following the protocol developed in association with the pharmaceutical company and in accordance to the International Conference on Harmonization (ICH) guidelines. The validation parameters (linearity, sensitivity, accuracy, precision, specificity and stability) were satisfactory. Intra-day precision relative standard deviation (RSD) was ≤ 2.23% for peak area and retention time without significant differences between intra- and inter-day data. Recovery studies gave good results (93.59%; n = 15) with a RSD of 2.64% and the derivatized sample solutions remained stable at room temperature for, at least, 24 hours.

Conclusions:
The accurate, simple and universal developed method can be applied for the quality control of finished products in every laboratory equipped with the basic analytical instrumentation. Appropriate and reliable analytical methods of control for even more numerous products on the market are fundamental for the pharmaceutical industry in order to protect public health.

Nasal flurbiprofen powder for Alzheimer's disease

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Purpose:
To develop and characterize a powder formulation in the form of agglomerates of spray-dried microparticles for nose-to-brain delivery of flurbiprofen, a NSAID suitable for Alzheimer's disease treatment.

Methods:
Microparticles of flurbiprofen sodium salt (FB-COONa), were prepared by means of either the Nano Spray Dryer B-90 and Mini Spray Dryer B-290 (Büchi). Agglomerates were then manufactured by first blending the drug microparticles with excipient microparticles previously manufactured by spray drying and made of mannitol (M) and lecithin (L), the latter at 92:8 (w/w) ratio. In the blend, the mass ratio between drug microparticles and excipient microparticles was fixed at 50:50. Two methods of agglomeration were employed. In the vibration method, a weighed amount of the blend was vibrated on a sieve stack (106 and 850 μm sieve's mesh size) at fixed intensity. In the tumbling method, the blend was tumbled in a 100-ml glass pan with deflected wall, at 25 rpm/min for 40 min. All powders were characterized with respect to size, morphology, *in vitro* dissolution rate and *in vitro* flurbiprofen transport across rabbit nasal mucosa (Franz cells).

Results:
For FB-COONa microparticles, small particle size and narrow size distribution as well as high yields were obtained with the Nano spray drier ($D_{v,50}$: 5.7 ± 0.4 μm and 10.4 ± 1.2 μm; yield: 80% and 20% for Nano-SD and Mini-SD, respectively). Moreover, it was possible to process FB-COONa at lower inlet temperature (40-70 °C and 120 °C for Nano and Mini spray drier, respectively). *In vitro* drug transport across rabbit nasal mucosa from Nano-SD FB-COONa microparticles manufactured at 70°C and Mini-SD particles were superimposable (amount per unit area transported in 4 h: 3.4 ± 0.7 μg/cm^2 and 4.0 ± 0.4 μg/cm^2 for Nano-SD and Mini-SD microparticles, respectively). However, the Nano-SD microparticles dried at 40 °C showed significantly higher transmucosal drug transport *in vitro* (5.3 ± 0.3 μg/cm^2). The agglomeration of drug and excipient microparticles caused partial de-mixing of the blend, lowering the agglomerates' actual drug content compared to the initial blend. Agglomeration yields depended on the manufacturing method (80% and 50% by tumbling and vibration, respectively). Drug transport across rabbit nasal mucosa from Nano-SD FB-COONa:ML agglomerate (4.9 ± 1.0 μg/cm^2 in 4 hours) was not significantly different from that of the Nano-SD FB-COONa microparticles used alone.

Conclusions:
Agglomeration of the microparticles improved powder handling without affecting the biopharmaceutical behaviour. Next step of this study will be to administer in vivo flurbiprofen agglomerates by nasal route to study the drug bioavailability in the brain.

Alginate-based electrospun fibers for the delivery of sigma-1 receptor agonists in the treatment of spinal cord injuries

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Purpose: A novel drug delivery system for the sigma-1 receptor-agonist RC-33 [1], based on electrospun fibers, was developed for the treatment of spinal cord injuries. Alginate (ALG), an anionic polysaccharide able to form an electrolyte complex with the cationic RC-33, was selected as the main component of the fiber *core*. Since ALG cannot be electrospun alone, polyethylene oxide (PEO) was identified as adjuvant: PEO at two different molecular weights (MW), high (4000 kDa, hMW) and low (600 kDa, lMW), were blended with ALG.

Methods: Fourteen blends (B), containing 1% w/w ALG, PEO hMW and PEO lMW, were prepared in deionized water with the addition of surfactants; the concentrations of both PEO in each B were defined so that each PEO hMW/PEO lMW combination would show the same viscosity. All B were characterized in terms of rheological behaviour (Rheostress RS600, Haake), conductivity (FiveGo™ F3, Mettler Toledo™) and surface tension (DyneMaster DY-300, KYOWA) and, then, electrospun (STKIT-40, Linari Engineering apparatus) varying the process parameters (applied voltage and needle-collector distance). Fiber morphology was assessed by SEM. For each B, the ratio rH/rL, where r (rH for PEO hMW and rL for PEO lMW) = PEO concentration in B/PEO critical entanglement concentration (CEC) was calculated to appreciate the contribution of polymer grade to the blend properties that were functional to fiber formation. Thereafter, fiber mechanical properties (maximum force of deformation, F_{max}) were also assessed (TA.XTPlus Texture Analyser, ENCO). Moreover, cross-linked ALG/PEO fiber biocompatibility was evaluated *in vitro*: SEM and confocal microscopy analyses were performed to observe cell proliferation (fibroblasts and NSC34 motoneuron-like hybrid cells) within the fibrous network. Finally, ALG binding capacity for RC-33 was defined through dialysis equilibrium studies.

Results: All B were characterized by viscosity (at 1000 s^{-1}) values in the range of 0.32-0.41 Pa·s and by G'' (viscous modulus) values, measured at the frequency of 1 Hz, significantly higher than G' (elastic modulus) ones. All B showed conductivity values significantly lower than a 1% w/w ALG solution, suggesting PEO ability to shield ALG negative charges. SEM analyses revealed that fiber dimensions strictly depended on rH/rL value. Moreover, nano-scale fibers showed a higher mechanical resistance than the fibers with diameters exceeding 10 μm, which were characterized by a plastic behaviour. The biocompatibility of ALG/PEO was verified on both the cell lines considered. ALG maximum binding capacity for RC-33 was calculated as 1.758 mg RC-33/1 mg ALG after 24 hours of dialysis.

Conclusions: Varying blend composition it was possible to modulate fiber morphology. The parameter that better explains the influence of experimental conditions on fiber dimensions was rH/rL. ALG/PEO fibers acted as support of cell growth. Finally, ALG ability to bind RC-33 was confirmed and quantified.

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CBD and desoxy-CBD comparison for transdermal delivery of cannabinoids in ethosomes

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Purpose:

Cannabis and cannabinoids are gaining increasing interest for their role in treating inflammation and neuropathic pain, especially for the targeting of CB_2 or non-CB receptors. Cannabidiol (CBD), one of the main constituent of the *Cannabis* extract, is an antagonist of the cannabinoid receptor CB_1 but a reverse agonist of CB_2 receptors[1]. Desoxy-CBD (DH-CBD) acts on the CB_2 receptor and it also selectively targets the glycinergic system. The aim of this study was to compare CBD and DH-CBD to design a transdermal delivery system of cannabinoids based on ethosomal vesicles as carriers.

Methods:

CBD and DH-CBD were compared after being loaded in binary ethosomes. The ethosomal systems were composed by: 1% drug, 5% Phospholipon 90G as phospholipid, 20% ethanol, 50% propylene glycol, and water to 100% w/w. The loaded binary ethosomes were obtained following the cold method described by Touitou[2]. Size distribution and entrapment efficiency were considered to determine the stability of the two loaded ethosomal suspensions. Size distribution was investigated through the dynamic light scattering (DLS) at T0 and after refrigerated storage, while entrapment efficiency was measured at T0 by dialysis method. Furthermore, the loaded suspensions were incorporated 1:1 in hydrogel with 0,75% Carbopol Ultrez 10. The rheological behaviour was observed using a rheometer with cone plate of 2°.

Results:

The study showed that the two ethosomal suspensions presented significant differences in the size distribution both at T0 and after the storage. Generally, the size of ethosomes loaded with CBD were twice the size of those loaded with DH-CBD. Studies of entrapment efficiency are still under investigation. Moreover, differences were observed in the rheological behaviour of Carbopol hydrogel loaded ethosomes: the CBD formulation showed lower viscosity than the DH-CBD formulation.

Conclusions:

Desoxy-CBD (DH-CBD) resulted a promising molecule that improves the design of transdermal delivery systems as binary ethosomes. The smaller dimensions of DH-CBD ethosomes can be an advantage for the transdermal drug delivery. Further investigations will be performed to analyse the *in vitro* and *ex vivo* diffusion properties.

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